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1  COCAINE EXPOSURE AND CHILD BEHAVIOR AT AGE 7 YEARS: A GEE PROFILE ANALYSIS

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We estimated influence of prenatal cocaine exposure and recent caregiver cocaine use on parent-reported child behavior problems at age 7, as indicated by the eight domains of the Child Behavior Checklist (CBCL). Methods: Data at age 7 follow-up are from 407 African–American full-term infants (210 cocaine-exposed, 197 unexposed) enrolled prospectively at birth in the longitudinal Miami Prenatal Cocaine Study and their primary caregivers. Recent caregiver drug use was measured by a modified Addiction Severity Index (ASI). Prenatal cocaine use was assessed via maternal self-report and bioassays. A multivariate profile analysis via Generalized Estimating Equations (GEE) was used in lieu of MANCOVA to examine cocaine–behavior relationships because this ‘GEE profile’ method takes into account the interdependent character of the CBCL subscores and avoids violations of MANCOVA assumptions (e.g. compound symmetry). Results: We found greater delinquency scores in a contrast of children without and with recent caregiver cocaine use ($\beta = -0.22; \text{CI} = -0.42, -0.01; P = 0.04$), robust with statistical adjustment for potential confounding influences, and somewhat stronger in a subgroup analysis for boys ($\beta = -0.31; \text{CI} = -0.60, -0.02; P = 0.03$). The GEE profile disclosed no other prenatal or postnatal cocaine-associated elevations on CBCL subscales. Discussion: Subject to limitations of non-experimental clinical studies and parent-report measures of child behavior, the evidence supports an inference of no global deficits in emotional or behavioral functioning in relation to prenatal cocaine exposure. We found a possible increase in delinquency problems at age 7 years for children without cocaine-using caregivers, which may have important developmental implications for early onset drug use. However, future work with multimethod approaches is needed (e.g., direct observation, teacher ratings).

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2  UPDATED STUDIES ON OXYCODONE, THE ACTIVE INGREDIENT OF OXYCONTIN

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Oxycodone was classified as an opioid in 1957. The growing incidence of OxyContin abuse by humans prompted us to scrutinize in more detail its opioid properties. Oxycodone hydrochloride was found to be more active than morphine sulfate, antinociceptively, in mice (mg/kg, s.c.): in the tail-flick (ED50 = 0.94 (0.4–2.2); hot plate ED50 = 1.37 (0.48–3.92); and phenyquinone ED50 = 0.38 (0.19–0.75) tests. It was without activity, as an antagonist, versus morphine. In addition, beta-funaltrexamine antagonized the ED80 of oxycodone [AD50 = 1.23 (0.27–5.56) ug per brain] indicating it was a potent mu-opioid receptor agonist. We did not find evidence that oxycodone, had kappa-opioid agonist properties as reported by (Ross and Smith, 1997). In our hands, nor-BNI, a kappa antagonist, was inactive up to 30 mg/kg. In vivo studies by Spetea and coworkers (1998), indicated high affinity binding at delta-opioid sites and lesser potency for mu- and kappa-opioid sites. In our evaluation, naltrindole, a delta opioid antagonist, was inactive up to 30 mg/kg. In morphine-dependent rhesus monkeys in withdrawal, oxycodone substituted completely for morphine. Onset and duration of actions were equivalent to those of morphine; however, oxycodone was approximately 2 times more potent than morphine. We conclude that oxycodone is a selective mu-opioid receptor agonist.

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3  METHAMPHETAMINE, AND MDMA-INDUCED NEUROTOXICITY: SENSITIZATION TO THE LOCOMOTOR STIMULATING AND DESSENSITIZATION TO THE REWARDING EFFECTS OF PSYCHOSTIMULANTS

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Although many studies had focused on the mechanisms involved in methamphetamine (METH)- and 1,2-methylenedioxyamphetamine (MDMA; ‘ecstasy’)-induced neurotoxicity, little is known about the behavioral consequences of exposure to neurotoxic doses of these substituted amphetamines. In the present study two behavioral paradigms were monitored after the exposure of mice to METH and MDMA, e.g., locomotor activity and the acquisition of conditioned place preference (CPP) as a measure for reward processing. Swiss Webster mice were treated with MET (5 mg/kg × 3) which caused 50–65% depletion of striatal dopaminergic markers. This treatment resulted in long-lasting sensitization to the psychomotor stimulating effect of METH (74 days after the initial exposure to METH). In the CPP paradigm, control saline pretreated mice acquired significant CPP following METH administration (0.5 mg/kg), while the METH pretreated mice acquired very low conditioned response. Following the extinction of CPP, the conditioned response to METH was completely reinstated in the control but not the METH group. The administration of MDMA (30 mg/kg × 2) resulted in 40–60% depletion of striatal and cortical dopaminergic and serotoninergic markers, respectively. This treatment was associated with marked sensitization to the psychomotor stimulating effects of MDMA, METH and cocaine as determined at various intervals after the initial exposure to MDMA. These results suggest that amphetamines-induced neurotoxicity is associated with both opposing behavioral outcomes: (1) sensitization to the psychomotor stimulating effects and (2) desensitization to the rewarding effects of related drugs. These consequences may be relevant to the psychopathology of METH and MDMA abuse.

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4 ADAPTING RESEARCH INSTRUMENTS FOR CLINICIANS: DEVELOPING THE CLINICAL UTILITY OF THE COMPUTERIZED LIFE HISTORY INTERVIEW

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A computerized Life History Interview (LHI) that asks about drug use and drug-related life events for the previous 5 years was developed for the ONDCP-funded Random Access Monitoring of Narcotics Abusers (RAMONA) project to build a mathematical model to estimate prevalence of ‘hardcore’ drug users. Given our experience with the computerized ASI used in the Drug Evaluation Network System (DENS), we recognized that the computerized LHI needed to have relevance for both counselors and patients, to be successfully implemented. This approach of transforming research instruments to have practical clinical use and value can help lessen the disparity often seen between the goals for collection of research data and the delivery of substance abuse treatment and facilitate the data collection process. Prior to the development of the computerized LHI, two focus groups of administrators and clinicians met to assist in the design of the LHI as a clinical instrument and relapse prevention tool. After extensive in-house testing of the LHI program, we field-tested the LHI with five patients at a Veteran’s Administration Medical Center and with 25 patients in a residential recovery program to assure that the LHI collected the necessary data for the RAMONA project and to assess whether the patients felt that it had clinical value and could assist in their treatment. We found that: (1) all patients were able to complete the interview; (2) most found the data relevant to their drug use and relapse and; (3) patients wanted printouts of the graphs to share with their counselors. Following this field-test of the instrument, we held a final focus group with clinicians to share patient feedback, demonstrate the LHI reports, and model use of the reports with patients in treatment. After analyzing the patient and counselor feedback on the computerized LHI, final changes were made to the instrument and a test–retest procedure was undertaken at a local Veteran’s Administration Methadone Clinic. This presentation describes the process of developing the enhancements to the computerized LHI in an effort to make the data gathered clinically beneficial to counselors and patients.

5 EFFECTS OF THE Mu AGONIST BUPRENORPHINE (BUP) ON LOCOMOTOR ACTIVITY, CONDITIONED ACTIVITY AND CONDITIONED PLACE PREFERENCE INDUCED BY COCAINE IN RATS


Neuronal substrates that mediate the conditioned stimulant and reinforcing effects of cocaine are not well characterized. To examine opioid mechanisms, we tested the mu agonist BUP for its capacity to alter the expression of conditioned locomotor activity (CLA) and conditioned place preference (CPP) in male Sprague-Dawley rats. For CLA, 6 conditioning sessions were conducted over a 13-day period; rats received 10 mg/kg ip cocaine prior to activity sessions and saline after; unpaired controls received saline prior and cocaine after. For CPP, 8 conditioning sessions were conducted over a 13-day period; rats received 10 mg/kg ip cocaine while restricted to one of two distinct chambers and, on alternate days, they received saline in the other. BUP was also assessed on cocaine-stimulated locomotor activity for comparison: rats were injected with escalating doses of cocaine (5, 10, 20, 40 mg/kg ip) over a 2-h activity session. Low doses of BUP (0.003–0.01 mg/kg sc, 20-min pretreatment) significantly enhanced the direct stimulatory effect of cocaine on locomotor activity; a higher dose (0.03 mg/kg) was without effect. Conversely, 0.03 mg/kg BUP tended to reduce the expression of CLA, but augmented the expression of CPP at the dose of 1.0 mg/kg. That is, the cocaine-paired environment induced less activity but greater preference in BUP-treated rats compared to saline-treated controls. The highest dose of BUP tested, 0.1 mg/kg, markedly reduced behavior in all three assays. Direct and conditioned effects of cocaine were shown to be differentially sensitive to the mu-opioid agonist BUP. (VA and NIDA support.)

6 SUICIDE ATTEMPTS IN SUBSTANCE ABUSERS: EFFECTS OF MAJOR DEPRESSION IN RELATION TO SUBSTANCE USE DISORDERS

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Little is known about whether the circumstances of depression relative to substance abuse affect the risk for different aspects of suicidal behavior in patients with substance abuse problems. Episodes of depression under three circumstances were investigated. These included episodes predating substance abuse, those occurring during periods of abstinence, and those occurring during periods of substance abuse. The occurrence of any suicide attempt, the number of attempts, and level of seriousness of suicidal intent were studied. Method: The sample included 602 patients aged 18 years and older from inpatient and outpatient settings. All subjects participated in a Psychiatric Research Interview for Substance and Mental Disorders (PRISM) interview. Patients were hierarchically classified as having lifetime diagnoses of major depressive episodes occurring prior to dependence, during periods of abstinence, and during periods of substance use. Logistic regression and linear regression models were used to analyze the data. Results: Being diagnosed with any type of depression increased the risk for suicide attempts. More severe suicidal intent was associated with major depression occurring prior to substance dependence. A higher number of suicide attempts was associated with episodes of major depression occurring during periods of abstinence. Conclusions: The circumstances in which depression occurs relative to substance abuse are related to suicidal behavior when considered on a lifetime basis. Prospective research would clarify the relationships further. Clinical planning should address the possibility of increased risk for suicide attempts in the depressed and abstinent substance abuser.

7 BUILDING BLOCKS OF SELF-CONTROL: INCREASED TOLERANCE FOR DELAY WITH BUNDLED REWARD

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Impulsive choice can be defined as temporary preference for a smaller-sooner reward (SS) over a larger-later reward (LL). Hyperbolic discounting implies that impulsive choices will occur less when organisms choose between a series of SSs versus LLs all at once, than when they choose between single SS versus LL pairs. Eight rats were run in two conditions of an intertemporal choice paradigm using sugar-water as reward. In both conditions, the LL was 150 ml delayed by 3 s, while the SS was an immediate reward that ranged from 25–150 ml across sessions. Preference for the LL was greater when the chosen reward was automatically delivered three times in succession (bundled) than when it was delivered singly. In all eight rats, the estimated indifference point was higher in the bundled condition than in the single condition. Because bundling may be based on the perception that one’s current choice is predictive of future choices, the data presented here may demonstrate an important building block of human self-control.
8 Sub-acute dosing with isradipine modestly decreases pressor response in a phase II lab trials for medications to treat cocaine dependence

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Twelve male cocaine-dependent research volunteers, aged 21–46 years, who were not seeking treatment participated in a study examining the activity of repeated doses of isradipine or placebo to antagonize i.v. cocaine-induced euphoria. Cocaine challenges included an ascending series of cocaine doses (placebo, 0.325, 0.6 mg/kg, i.v.) administered across three successive days. Isradipine effects were examined as a double-blind crossover in two 8-day phases with at least one week between each phase. Each phase began (Day-1) with an initial exposure to 0.325 mg/kg cocaine, i.v. to insure clinical tolerance followed by nightly (qHS) dosing with 30 mg oral isradipine sustained release or placebo. On Days 5–7, an immediate release formulation of isradipine (15 mg) or placebo was administered prior each of the i.v. dose challenges. At repeated time-points before and after the i.v. injection, subjects had automated readings of vital signs (i.e. blood pressure and heart rate). Predictably, cocaine dose-dependently elevated all vital signs. Compared to placebo pre-treatments, isradipine significantly (P < 0.05) decreased systolic and diastolic pressure for low dose but not high dose cocaine. While there was a reflex increase in heart rate, these changes were not statistically significant, and much smaller than previously seen with acute immediate release dosing. Sub-acute compared with immediate release isradipine dosing therefore appears to have a more modest effect on pressor response. These results extend our earlier findings by demonstrating the cardiovascular safety of maximal sub-acute dosing with an L-type calcium channel blocker. Future studies can now be designed to fully explore the dose-response characteristics of sustained release isradipine as a potential therapeutic agent for treating cocaine dependence.

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9 Role of protein kinase C (PKC) in the development of sensitization to methamphetamine in rats

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Repeated treatment with methamphetamine leads to an enhancement in the methamphetamine-induced dopamine release and its related behaviors. This phenomenon is called sensitization or reverse tolerance. The present study was then designed to investigate the implication of protein kinase C in the development and/or maintenance of sensitization to the place preference and to the enhancement of dopamine release induced by methamphetamine in rats. The conditioned place preference paradigm and in vivo microdialysis study were performed to ascertain whether protein kinase C could be involved in the development of the methamphetamine-induced behavioral sensitization. An intra-nucleus accumbens injection of a selective protein kinase C inhibitor chelerythrine chloride abolished the development of sensitization to the methamphetamine-induced place preference. Furthermore, an intra-nucleus accumbens injection of chelerythrine chloride abolished the enhancement of dopamine release and the significant decrease in the major dopamine metabolites, DOPAC and HVA, induced by methamphetamine injection in the nucleus accumbens following repeated treatment with methamphetamine. The present data provide evidence for the implication of protein kinase C in the nucleus accumbens in the development of sensitization to the methamphetamine-induced rewarding effect, dopamine release and inhibition of dopamine re-uptake in rats.

10 Efficacy of atypical neuroleptics in treatment of substance use among schizophrenic individuals


Substance use among schizophrenic patients is a significant public health problem. One of the prevailing theories for substance use in this population is the self-medication hypothesis. In schizophrenic individuals there is a reduction in prefrontal dopamine. Marijuana and cocaine increase dopamine concentration in striatal and prefrontal areas of the brain, and schizophrenic patients may use these drugs to ‘self-medicate’ their psychiatric problems. By using novel antipsychotic medications that bind to D1 as well as D2 receptors, we anticipate improvement in negative symptoms and/or reduction in neuroleptic-induced side effects. This may reduce the desire for illicit substances. Further, antagonism of the D1 receptor may make these illicit drugs less positively reinforcing such that use is reduced. To date, in this preliminary double-blind trial, 11 schizophrenic cocaine and marijuana abusers have been entered. Treatment is separated into three phases: (1) a 2-week assessment phase when baseline data is collected while patients are maintained on their prescribed medication, (2) a 2 week cross-taper phase where patients will be tapered off their previously prescribed medication and onto the study medication (either 15–20 mg olanzapine or 6–9 mg risperidone, taken daily), and (3) a 10-week period in which patients are maintained on the aforementioned doses of olanzapine or risperidone. The blind has not been broken, but initial analyses suggest that some patients receiving atypical neuroleptics in conjunction with relapse prevention therapy have shown a reduction in cocaine/marijuana craving and use. Primary side effects that have been reported include: somnolence (50%), dry mouth (38%), weight gain (13%) and loss of libido (13%), however, despite these side effects, no patients have left the study prematurely. Findings from this study may help guide pharmacologic treatment approaches in schizophrenic substance abusing populations.

11 Facilitation of sexually conditioned behaviors in male quail following cocaine-induced increases in locomotor activity

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It has been demonstrated that repeated administration of n-amphetamines enhances copulatory behavior and anticipatory sexual behavior in rats (Fioreno and Phillips, 1999). According to Robinson and Berridge (1993), this occurs because repeated activation of the mesotelencephalic dopamine transmission by psychostimulants may sensitize this neural system, and thereby increase the ‘incentive salience’ to stimuli associated with activation of the system. The present study was conducted to investigate whether repeated administration of cocaine would increase the ‘incentive salience’ of conditioned copulatory behaviors in birds. Male Japanese quail (Coturnix japonica) were injected with either 10 mg/kg ip cocaine (n = 6) or saline (n = 6) once a day for 6 consecutive days. After a 10 day drug-free period, subjects received conditioning trials in which a red styrofoam block (CS) was lowered from the ceiling and followed 30 s later by copulatory opportunity with a female quail (US). Results indicated that cocaine-treated subjects increased the amount of time they spent near the CS, increased the frequency of activity near the CS, and increased the frequency of contacts with the CS across trials, relative to saline controls (all P’s < 0.05). Copulatory behavior toward the female was also enhanced by cocaine. Cocaine-treated subjects acquired shorter latencies to copulate, more mount attempts, and more clasical contacts with the female than saline-treated subjects across trials. These results indicate that a cocaine-induced increase in locomotor activity may enhance learned sexual responses and raises the possibility...
that incentive-sensitization effects may extend to conditioned aspects of sexual behavior and to nonmammalian species.

12 CANNABINOIDS AND VANILLOID AGONIST SENSITIVITIES OF AMPA GLUTAMATE RECEPTOR SUBUNITS

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The cannabinoid receptor system (CB) is known to be useful in the treatment of pain whereas the Vanilloid receptor system (VR) is involved in the sensory perception of pain. Although agonist cross-reactivity has been reported for CB1 and VR1, the CB1 receptor is activated by Delta9-tetrahydrocannabinol (the major psychoactive compound in marijuana) and the endocannabinoids Anandamide, 2-Arachidonoyl glycerol (2AG) while the VR1 receptor is activated by Capsaicin (the vanilloid compound that makes hot chili pepper pungent) and structural analogs-Arvanil and Olvanil. Because endocannabinoids inhibit cognitive functions and long-term potentiation (an in vitro model of learning and memory) in animals and humans, we compared their effects on AMPA type glutamate receptor (a mediator of long-term potentiation in the CNS) to that of VR1 agonists to further characterize other VR functions in the CNS. AMPA GluR1 & GluR3 receptor currents activated in Xenopus oocytes by two-electrode voltage-clamp were studied for current inhibition by CB agonists 2AG, Methanandamide and VR agonists Arvanil and Olvanil. The order of potency of inhibition of receptor current by 100 mM of drugs for GluR1 is Arvanil > 2AG > Olvanil > Methanandamide and for GluR3, the result is 2AG > Arvanil > Methanandamide > Olvanil. This result may suggest similar roles for cannabinoid and vanilloid receptor systems in long-term potentiation and substance abuse tendencies in animals and humans.

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13 DISTINCT RESPONSES OF EXTRACELLULAR NEUROTENSIN (MEASURED BY MICRODIALYSIS) TO LOW AND HIGH DOSES OF METHAMPHETAMINE

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Neurotensin (NT) is a neuropeptide primarily associated with the regulation of the nigrostriatal and mesolimbic dopamine (DA) pathways. In previous studies, we demonstrated that this neuropeptide system is differentially affected by treatment with low or high doses of methamphetamine (METH). The present study employed microdialysis to examine the effect of a single administration of a low or high dose of METH on the extracellular levels of NT in the substantia nigra and globus pallidus. Sprague–Dawley rats received a single injection of METH (0.5 or 10.0 mg/kg, s.c.) in the presence or absence of a selective dopamine receptor antagonist (D1, SCH 23390; or D2, eticlopride). The low dose of METH significantly increased the extracellular content of NT in both the substantia nigra and globus pallidus. In contrast, the high dose of METH did not affect extracellular NT concentration in any examined structure. The extracellular changes induced in nigra by 0.5 mg/kg of METH were prevented by pretreatment with either dopamine D1 or D2 receptor antagonists, while the pallidal changes were only antagonized by the D2 blocker. These data demonstrate different responses of the basal ganglia NT systems to low and high dose of METH and suggest that dopamine D1 and D2 receptors activity contribute to these effects.

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14 CHARACTERIZING CHANGES IN NICOTINE WITHDRAWAL AND RELATED MEASURES ASSOCIATED WITH INITIAL ABSTINENCE IN CIGARETTE SMOKERS

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An initial period of drug abstinence is often predictive of future abstinence in clinical settings, but there has been little rigorous experimental investigation into early abstinence and concurrent processes that may elucidate this predictive relationship. We experimentally varied the amount of cigarette smoking abstinence achieved in thirty-four smokers not seeking treatment by offering incentives contingent on smoking abstinence (carbon monoxide (CO) < 4 ppm; n = 17) compared to a yoked control group (n = 17). Participants were monitored 3 x per day for 12 days. In addition to 3 x per day CO measures, nicotine withdrawal, mood states, confidence in one's ability to abstain, and related measures were assessed daily. Most individuals in the contingent group were abstinent for 12 consecutive days. Reports of nicotine withdrawal, negative affect (e.g., anxiety) and craving peaked Day 1 – 2 in the contingent group. These symptoms steadily declined to control group levels by either Day 5 (negative affect and craving) or Day 12 (Nicotine withdrawal). In general, confidence in future abstinence and ease of abstinence steadily increased through Day 12 in the contingent group. Ratings of ease of abstinence were not increased relative to controls, however, until after negative affect and craving had resolved to control group levels (Day 5), perhaps indicating a time after which continued abstinence becomes more probable.

15 METHAMPHETAMINE PSYCHOSIS: DOES ANYONE RECOGNIZE AND TREAT THE ASSOCIATED SUBSTANCE ABUSE AND DEPENDENCE?

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Psychosis has been recognized as a complication of chronic amphetamine use since the 1930s. 32 inpatients admitted to psychiatric hospitals in South Australia with methamphetamine-induced psychosis were interviewed within 2 weeks of admission to identify adverse health, social and psychiatric symptoms and their management. Participants’ mean age was 26 years, 78% were male, and were most likely to live with parents. 75% were unemployed. Prior to admission, methamphetamines were used on average 4 days per week (mean daily use 4 g), and most commonly were injected. Almost 70% injected in the preceding month, but only 16% reported reusing others’ needles. The most common psychiatric symptoms were delusions (66%) and hallucinations (38%). Depression and anxiety were prominent in 25%, and flattened/incongruous affect in 16%. Mean SF-12 Physical and Mental Summary Scales scores were 45 and 30 (local norms of 93 and 78, respectively). Methamphetamine abuse and dependence was found in 97 and 91%, respectively. Methamphetamine abuse appears associated with considerable adverse health and social outcomes. The average inpatient stay was 15 days, where treatment typically included antipsychotics, antixiolytics and/or sedative medications. D&A services were rarely provided. Upon discharge, 59% were prescribed psychiatric medications, 61% were offered outpatient psychiatric care while only 35% were offered outpatient D&A services. Twenty percent of patients left hospital with residual psychiatric symptoms. Despite high levels of methamphetamine abuse and dependence there was no systematic intervention or follow up for their methamphetamine use, highlighting the urgent need to develop clinical guidelines for effective interventions.
16 Effect of the competitive NMDA receptor antagonist, LY235959, in combination with cocaine in the conditioned place preference procedure


Experimental evidence suggests that N-methyl-D-aspartate (NMDA) receptor antagonists can prevent the development of conditioned place preferences to some drugs of abuse. The results presented here represent some initial work with the competitive NMDA receptor antagonist, LY235959, when administered alone or in combination with cocaine using a conditioned place preference procedure. Briefly, male Sprague–Dawley rats (n = 40) received drug/environment pairings in a place conditioning apparatus that consisted of three distinct compartments: a neutral center compartment and two distinct drug compartments. L-C. Maas, B.K. Madras, S.E. Lukas, P.F. Renshaw, and M.J. Kaufman, Brain Imaging Center and Behavioral Psychopathology Research Laboratory, McLean Hospital, Belmont and Division of Neurochemistry, NERPRC, Southborough, MA

Lobule VIII of the cerebellar vermis is selectively enlarged in carnivorous versus herbivorous mammals, and enriched in dopamine transporter (DAT) immunoreactivity. This region may be critical for the complex sensory-motor integration required for tracking prey. We investigated localized stimulant and cue-induced craving activation of the vermis. The response of high (H) and low (L) DAT-containing vermis subregions to oral (0.5 mg/kg) methylphenidate (MPH) was examined in drug-free controls (6M:7F) using magnetic resonance relaxometry (T2-RT) to assess blood flow. Repeated measures ANOVA indicated robust effects on T2 in H-DAT (F1,12 = 43.3; P < 0.0001) but not L-DAT regions (F1,12 = 0.24; NS), 45 min following administration. The vermis BOLD fMRI response to brief segments of alternating neutral/cocaine-related scenes and sounds was studied in crack-cocaine-dependent [6M:4F] versus normal subjects [3M:5F]. A two-group × three-region repeated measures ANOVA with Scheffe post-hoc analysis identified DAT-rich lobules II–III and VII, but not DAT-poor VI–VII, as having greater average pixel ROI activation during cocaine-related segments in cocaine-dependent, but not normal subjects (F1,16 = 4.95; P < 0.05). Scheffe mean differences for II–III vs. VI–VII = 0.51; P < 0.006; VIII vs. VI–VII = −0.49; P < 0.009). These findings suggest that DAT-rich lobules of the vermis, and particularly lobule VIII, could play a role in mediating both the acute and persistent effects of stimulants.

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17 Predictors of initial abstinence in smoking cessation

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Among the most significant predictors of initial smoking cessation are nicotine dependence, smoking self-efficacy, and readiness to quit. However, there has been little investigation of the relative contribution of these three variables in predicting a person’s quitting. The present study examined the relative contribution of these predictors of initial abstinence. Participants were 90 individuals smoking at least 15 cigarettes per day and planning on quitting in the near future. Data for the present study were gathered as part of their 10-day baseline participation in a smoking cessation study. The variables measured at baseline included: (1) participant characteristics; (2) stage of change (i.e., University of Rhode Island Questionnaire [URICA]); (3) self-efficacy (i.e., confidence in ability to be abstinent 1 day before intervention began); and (4) nicotine dependence (i.e., Fagerstrom Test for Nicotine Dependence [FTND]). Logistic regression analysis revealed that age (R2 = 0.05, P < 0.05), salary (R2 = 0.15, P < 0.05), FTND (R2 = 0.12, P < 0.01), and self-efficacy (R2 = 0.05, P < 0.05) were predictive of abstinence (CO < 4 ppm) on Day 1 of 10 baseline days. Multiple regression analysis revealed that only self-efficacy (R2 = 0.08, P < 0.01) was predictive of the number of baseline days of abstinence (CO < 4 ppm). Forward stepwise multiple regression revealed that self-efficacy (R2 = 0.06 P < 0.05) but neither FTND nor the URICA scales were predictive of the number of days abstinent. Our findings suggest that teaching self-efficacy may hold promise as a component of effective cessation interventions.

18 Activation of lobule VIII of the human cerebellar vermis by oral methylphenidate and cue-induced cocaine craving

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The generalized matching law predicts that the relative rate of behavior maintained by different reinforcers will match the relative rate of reinforcement. It has previously been shown that responding maintained by either food or cocaine under concurrent variable-interval schedules is well described by the generalized matching law. However, the generality of this conclusion to the choice between a drug and a non-drug reinforcer has not been well established. The objective of the present study was to determine the extent to which the generalized matching law could account for choice between cocaine and food. Four male rhesus monkeys lever pressed under various pairs of concurrent VI schedules with food and/or cocaine injection as the maintaining event. Two doses of cocaine (0.025 and 0.05 mg/kg per inj) were selected to provide information about reinforcer magnitude. As has been found in a context of choice between identical reinforcers, the generalized matching law accounted for most behavior. As in earlier studies with identical reinforcers, there was less responding apportioned to the alternative with the greater reinforcement frequency than predicted by the generalized matching law, i.e. undermatching was observed frequently. There was a tendency for more responding to be emitted toward the food alternative when the lower dose of cocaine was available and toward the drug alternative when the higher dose of cocaine was available. These results suggest that, as proposed by the generalized matching law, relative reinforcement rate is an important determinant of choice between a drug and non-drug reinforcer.

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20 Provision of hepatitis C education in a nationwide sample of drug treatment programs

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The prevalence of Hepatitis C virus (HCV) has reached epidemic proportions among drug users, a population at great risk for both contracting and transmitting the virus. Yet, many individuals who use drugs lack information or are misinformed about the routes of transmission, the testing procedures, the medical treatment, and the progression and consequences of HCV infection. Drug treatment programs are in a unique position to respond to the hepatitis C epidemic by providing each of their patients with HCV education, for both primary and secondary HCV prevention. Using data collected from a random nationwide sample (N = 431) of drug treatment programs in the United States, we report on the results of a logistic regression analysis that examined differences in programs that provide HCV education to all of their patients versus programs that do not. Fifty-four percent of the programs provide HCV-related education to all of their patients. Drug treatment programs were more likely to provide basic HCV education to all of their patients if they (1) conducted HIV testing on-site, (2) were a residential program (as opposed to outpatient) (3) educated most or all of their staff about HCV, (4) dispensed methadone, and (5) had a smaller client/staff ratio. As only half of drug treatment programs are providing HCV education to all of their patients, there is a clear need to increase HCV-related services in drug treatment programs in the US.

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21 High morphine concentrations do not provide antinociception to methadone maintenance patients

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Methadone maintenance patients are cross-tolerant to the antinociceptive effects of clinically used analgesic concentrations (60 ng/ml) of morphine. This study utilised a double blind placebo controlled design to examine antinociceptive responses at two pseudo-steady-state plasma morphine concentrations (93 ± 7 S.E. and 200 ± 14 ng/ml) that exceed those used in a clinical setting. Eleven patients on stable, once daily doses of methadone were tested. Three methadone dose ranges were studied: 11 – 45 (n = 4), 46 – 80 (n = 3), 81 – 115 (n = 4) mg. Testing commenced approximately 20 h after methadone dosing and the next methadone dose was administered 1 h after cessation of morphine or saline. Nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)) were used to measure pain detection (PD) and pain tolerance (PT). Blood samples were collected concurrently with nociceptive responses and analysed by HPLC for plasma morphine and R(-) methadone concentrations. There was no difference in antinociceptive responses between morphine and saline administration periods irrespective of daily methadone dose. Significantly decreased respiration rates occurred at peak plasma morphine concentration (12 ± 0.6 breaths per min vs. 14 ± 0.7 at baseline P = 0.01) and 2 h after methadone administration (12 ± 0.6 P = 0.01). There was a significant cold pressor antinociceptive effect of methadone on both morphine (PD 7 ± 0.6 vs. 9 ± 0.9 P = 0.06), PT 17 ± 1.5 vs. 16 ± 1.8 P = 0.008) and saline days (PD 7 ± 2.6 vs. 9 ± 2.9 P = 0.0005) (PT 13 ± 1.4 vs. 15.8 ± 1.6 P = 0.003). Methadone maintenance patients are cross-tolerant to the antinociceptive effects of high plasma concentrations of morphine, but these concentrations significantly decrease respiration rate. However, rising plasma methadone concentrations provide antinociceptive effect. Up to 200 ng/ml of morphine is unlikely to provide pain relief in this population, and higher concentrations may produce unacceptable respiratory depression.

22 Confirmation of provisional QTLs for methamphetamine-induced chewing stereotypy in selected mouse lines

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At high doses, methamphetamine induces repetitive stereotyped behaviors in both rodents and humans. One stereotypic behavior that mice display is repetitive paw-to-mouth chewing. Mice of 25 different BXD recombinant inbred strains were previously tested and genotyped for this trait (Grisel et al., 1997). B6D2F2 mice were then tested for methamphetamine-induced chewing stereotypy, and we selectively genotyped 152 of the 400 mice tested at markers where provisional QTLs for this trait were found in the BXD mice. Also, mice were selectively bred for high and low methamphetamine-induced chewing stereotypy, and we genotyped 47 breeders from the third selected generation and 124 mice of the fourth selected generation at markers where provisional QTLs were identified in the F2 mice. We initially looked at mid chromosome 5, proximal chromosome 8, distal chromosome 9, and proximal chromosome 17 in the selection lines, since these were the four areas that looked most promising for containing a QTL in the F2 analysis. Upon combining data from BXD and F2 mice, we saw that QTLs may also exist on mid chromosome 2, proximal chromosome 4, and mid chromosome X. The QTL on chromosome 9 appears the most promising. The provisional QTLs on chromosomes 8 and 17 can probably be discounted, since direction of the QTL did not agree in all populations for either. Next, mice that are congenic for the areas containing the QTLs of interest will be tested and backcrossed to their background strains in order to reach higher mapping resolution.

23 Prospective evaluation of alcohol consumption among opiate-dependent patients six months after inclusion in a methadone maintenance program. The CASMe Study

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Poor prospective data is available about the modifications of alcohol consumption of patients involved in Methadone Maintenance Programs (MMP). This study describes how alcohol is used by heroin dependent patients at inclusion in an MMP and at 6 months later. Thirty DSM-IV opiate dependent patients (19 males, 11 females, 35.3 average age) recruited at three addiction treatment centers have been evaluated by the same investigator at inclusion, 3 and 6 months after induction of methadone treatment. Evaluation: Alcohol consumption during the previous week, alcohol craving (visual analogical scale), frequency of drunkenness (during the last month), DSM-IV criteria diagnosis, Addiction Severity Index (ASI). At 6 months follow-up, 23 patients (76.6%) were evaluated; seven dropped-out. The analysis was done with the ‘intention to treat’ method. Mean number of standard drinks consumed during the past week increased from 31.9 (S.D.: 47.6) at inclusion to 43.2 (S.D.: 59) at the 6 month follow-up (Wilcoxon test for paired samples P = 0.06). The frequency of patients who declared having had a drunken episode during the last month increased from 30 to 52.2% (χ², P < 0.05). Subjective effects of alcohol intoxication were
described ‘less intensive than usual’ by respectively 4.8% of patients at 1 month follow-up, 15% at 3 months and 40% at 6 months (χ^2 for trend, P < 0.01). Craving score for alcohol increased from 3.6 (S.D.: 3.5) to 5.2 (S.D.: 4.7) at the 6 month follow-up (Wilcoxon test for paired samples, P = 0.03). 33% of the patients encountered the DSM-IV criteria for alcohol dependence after 6 months. ASI alcohol severity sub-scale increased from 2 at inclusion (S.D.: 2.5) to 2.9 (S.D.: 2.8) at 6 months. Alcohol use prospectively assessed by validated instruments among MPP patients seems to increase during the first 6 months after methadone induction. Both the quantity of drinks and the level of craving for alcohol increased. Subjective tolerance for alcohol increases, producing a related elevation in the amount of alcohol consumed and, probably, the frequency of drunkenness by a hypothetic high seeking process.

24 DOES MARIJUANA USE AFFECT CIGARETTE SMOKING TOPOGRAPHY IN TOBACCO-DEPENDENT ADOLESCENTS?


Adolescent tobacco smokers have higher rates of marijuana (MJ) use than non-smokers. Because MJ smoking typically involves deeper inhalation and longer breathholding than tobacco smoking, we hypothesized greater puff volume, longer puff duration and puff interval, and higher puff velocity in MJ-using teens. Sixty-one (61) tobacco dependent adolescents presenting for smoking cessation treatment (70.1% female, 80.6% European American, mean age 15.33 ± 1.30 years, mean smoking rates at study entry were 18.81 ± 7.26 cpd, mean Fagerstrom Test of Nicotine Dependence score 7.18 ± 1.33, mentholated cigarette preference 83.6%) underwent one tobacco smoking topography session at study entry. We compared topography and associated physiological measures among 24 (39%) tobacco dependent teens who had smoked MJ at least once during the 2 weeks preceding enrollment (and a mean duration of MJ smoking of 2.63 ± 2.00 years) with 37 non-MJ smoking teens. Preliminary results indicate no difference in tobacco smoking topography between MJ users and non-users. MJ smokers also did not have lower smoking rates or tobacco dependence levels than non-users at baseline. Our findings in adolescent smokers are consistent with results from adult studies in which MJ smoking history did not produce changes in tobacco smoking topography.

25 OFFICE-BASED BUPRENORPHINE- AND METHADONE-TREATED HEROIN-DEPENDENT INDIVIDUALS. A CROSS-SECTIONAL STUDY OF MEDICAL INSURANCE DATA

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Buprenorphine and methadone are available in France for Private Practice Office-based treatment of heroin-dependent individuals. Buprenorphine prescriptions may be initiated by General Practitioners (GP), methadone may be prescribed by GPs after inititation and stabilization in a State-approved Treatment Center. Most French residents, regardless of nationality are covered by compulsory medical insurance. Buprenorphine and methadone delivered by private pharmacies are reimbursed to patients. This is a unique opportunity to study this special population, especially regarding issue of access to unlimited prescribers and prescription of added psychotropics. Objective: to describe in a defined region office-based buprenorphine and methadone treated individuals. Methods: cross sectional study among the 3 Million inhabitants of Aquitaine (France, Europe), to determine those that have had at least one reimbursement for a prescription of buprenorphine or methadone from January to June 1999. Results: 2445 individuals where found (2341 buprenorphine (9 mg/day), 102 methadone (73 mg/day), 11 both). Seventy-two percent males mean age 32. Ten percent had only one prescription. During the 6 month period, over 77% of patients had one or two prescribers and two or one pharmacies. Ninety-six percent prescribers where GPs (23% of all GPs), and 84% had 5 patients or less. Half the patients had no other psychotropic prescription during the 6 month period. Ninety percent of those that had prescriptions had benzodiazepines, 10% antidepres- sants. Conclusion: The majority of patients in substitution treatment in France are treated by GPs by buprenorphine. Only a small minority of patients seeks prescriptions from more then two prescribers over a 6 months period. Half the patients have added benzodiazepine pres-criptions. These data are of interest for description of patients, their actual significance for quality of treatment are limited.

26 SPIRITUAL AND RELIGIOUS BELIEFS AS COGNITIVE SCHEMA: IMPLICATIONS FOR THE TREATMENT OF ADDICTION

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Spirituality is a potentially important dimension of human experience that has been linked to adaptive coping and recovery from addiction. We describe a program of research currently underway that is examining the potential influence of spiritual and religious beliefs in preventing drug use and other HIV risk behaviors among inner-city drug users. This research is guided by self-regulation theory and a social-cognitive model of perception and behavior that views the Self as composed of multiple self-representations or self-schemas that are hierarchically organized systems of knowledge and beliefs that underlie an individual’s intentions and behavior. Our previous research has shown that cocaine- and opioid-dependent individuals most frequently access an ‘addict’ self-schema that is associated with beliefs and emotions that promote drug use, as well as with thoughts and actions that lead to a variety of other high risk behaviors. Here we present new findings, suggesting the importance of spiritual and religious faith in the lives of inner-city drug users (n = 52) and the value of activating patients’ spiritual self-schema for reducing illicit drug use and other HIV risk behavior (n = 34). We also describe an intervention for elaborating and activating the patient’s spiritual self-schema that is currently showing promise for the treatment of cocaine- and opioid-dependent patients (n = 10) who continue to use illicit drugs and engage in HIV risk behavior while maintained on methadone.

27 RELATIONSHIP BETWEEN STRESS REACTIVITY AND SUBSEQUENT ALCOHOL USE

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The current study represents a preliminary investigation of the relationship between stress reactivity and subsequent alcohol use among 35 participants with (1) alcohol dependence, (2) alcohol dependence and comorbid PTSD, (3) PTSD only, and (4) a control group. Participants completed the cold pressor task in which their nondominant hand was submerged in cold water (4 °C) for as long as they were able to withstand the discomfort or until 2 min had passed. Immediately following the task, participants rated their subjective level of craving, stress, nervousness, pain, and mood using a 10-point Likert scale. Objective measures of heart rate, skin conductance and ACTH were also recorded. The Time-Line-Follow-Back assessed participant’s alcohol use during the 4 weeks post stress task. The findings revealed that individuals with high post-task craving or negative mood
demonstrated significantly more severe alcohol use during follow up (e.g. greater number of total drinks, percent days drinking, percent days heavy drinking) as compared to individuals with low craving or more positive mood. Higher ratings of stress and pain were significantly correlated with lower immersion time. Multiple regression tests indicated that the best predictors of subsequent alcohol consumption were subjective craving and nervousness. A trend for individuals with higher ACTH levels to demonstrate greater craving was observed. The findings demonstrate important links between stress reactivity, craving and subsequent alcohol use, and may have important theoretical and preventative implications.

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28 Cocaine and delta-9-THC enhance HIV replication in a huPBL-SCID mouse model

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Epidemiologic studies identify inhaled substances such as cocaine and marijuana as potential cofactors for the development and progression of AIDS. To evaluate this interaction, we have developed a hybrid human mouse model in which human peripheral blood leukocytes (PBL) are implanted into severe combined immunodeficient mice (huPBL-SCID) and infected with HIV in the presence or absence of either cocaine or delta-9-THC, the principal psychoactive component of marijuana. In huPBL-SCID animals, the concurrent administration of cocaine and HIV resulted in a significantly higher percentage of human PBL becoming infected with HIV in vivo (38.85 vs. 18.5%). The number of CD4+ cells recovered from HIV-infected/cocaine-treated animals was significantly lower than from mice infected with HIV alone (6.5 x 10^4 vs. 19 x 10^4) and associated with a lower CD4/CD8 ratio (2.7 vs. 6.9). RNA PCR confirmed a 200-fold increase in viral load. Exposure to cocaine alone did not affect the implantation of PBL, suggesting a specific interaction between cocaine and HIV infection. In contrast, although treatment with delta-9-THC, results in a 2-fold increase in HIV-infected human cells in infected huPBL-SCID animals, no commensurate CD4+ target cell lysis was observed. Utilizing our current model systems we are currently defining the in vivo effects of both cocaine and delta-9-THC on parameters known to affect HIV replication. In summary, we have developed a hybrid human mouse model that allows us to evaluate the specific interaction between these substances and the human immune system.

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30 Cocaine-induced compulsive foraging (CICF): A drug-induced obsessive compulsive disorder (OCD) hypothesis


Epidemiologic Catchment Area Survey (ECAS) results suggest that cocaine-abusing patients are at increased risk for OCD (Crum and Anthony 1993 58 /id). Some brain imaging studies have reported similar findings in cocaine dependence and OCD (Volkow et al., 1991); cocaine abusers who present CICF also present abnormalities similar to those of OCD patients at a saccadic distractibility task (Rosse et al., 1994). Compulsive foraging behavior has only been observed with stimulants and there are clinical similarities between CICF and OCD such as: realizing that the belief is unfounded, knowing that the compulsive behavior is in vain, and being typically obsessed. The aim of our study is to compare Yale-Brown Obsessive Compulsive Disorder Scale (Y-BOCS) between CICF and OCD patients. Cocaine abusers having been evaluated by Addiction Severity Index (ASI) were compared on the Y-BOCS with a sex, age matched control group, fulfilling DSM IV criteria for OCD. Y-BOCS is made of ten items; total score measures the intensity of OCD; the first five items indicate the intensity of obsession and items 6–10 the intensity of compulsive part of the disorder. Ability to control obsession and compulsion is evaluated by items 5 and 10. The CICF group (n = 22) has a mean total score on Y-BOCS = 26.4 (S.D. 3.7) The significance of these similarities between the groups is discussed.
Objective: To assess the impact of prenatal cocaine (COC) exposure on neuropsychological function in children at age 7 years. Methods: The sample included 399 full-term African–American children (209 cocaine-exposed; 190 unexposed) enrolled prospectively at birth in the longitudinal Miami Prenatal Cocaine Study. Prenatal drug exposure was measured by maternal self-report and biosamples of urine and meconium. At age 7, the NEPSY: A Developmental Neuropsychological Assessment and WISC-III (short-form) yielded a single latent construct with simple structure, ‘neuropsychological functioning’ (NF), found to be well measured by the five NEPSY domain scores (language, attention/executive function, memory, visuomotor, and sensorimotor) and IQ score. Generalized Linear Models (GLM) and structural equations models (SEM) were used to regress NF level on COC exposure (yes/no; level of exposure), to make statistical adjustments (e.g. other prenatal drug use), and to assess hypothesized pathways leading indirectly from COC to NF via intermediate impact on fetal growth (FG) as measured by head circumference, weight, and length. Results: GLM showed evidence of a cocaine-associated deficit in NF in that COC children were an estimated 1/5th S.D. lower on NF level ($\beta = -0.19$; 95% CI $= -0.36$, $-0.02$; $P = 0.03$), as well as 10% S.D. lower on NF level for each S.D. increase in level of prenatal cocaine exposure ($\beta = -0.10$; 95% CI $= -0.20$, $-0.01$; $P = 0.034$). SEM provided support for a mediated pathway model, with the COC-NF relationship mediated by COC-FG impact and otherwise with no substantial direct paths from COC to NF nor from COC to individual NEPSY and IQ scores. Conclusion: With attention to study limitations, the evidence tends to support at least modest impact of prenatal cocaine exposure on neuropsychological function of children at age 7 years, with mediation via a previously described impact of cocaine on manifestations of fetal growth (Bandstra et al., Pediatrics 108: 1309–1319, 2001). Supported by RO1DA06656; T32DA07292; Health Foundation of South Florida, Kenneth A. Lattman Foundation.

32 A TCI-BASED CLUSTER-ANALYTIC CLASSIFICATION OF FEMALE DRUG-DEPENDENT INPATIENTS

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Background: Personality-based classification of drug-dependent patients is a promising strategy for individualized management of this population. Hypothesis: The Temperament and Character Inventory (TCI) could be useful for subtyping female drug-dependent patients. Method: Participants were 103 female drug-dependent patients undergoing detoxification treatment, assessed with the TCI, the SF-36 and ASI. TCI scores were subjected to a cluster analysis using Ward method. A validation of the cluster solution was performed using one-way ANOVA of the ASI and SF-36 scores. Results: The best solution showed three groups of personality profiles. One cluster ($n = 45$) presented high scores in Harm Avoidance, and low scores in Persistence and Self-directedness; a second cluster ($n = 21$) was characterized by a non-extreme personality profile; and the third cluster ($n = 37$) by high scores in Novelty Seeking and low scores in Self-directedness. The non-extreme personality traits group, compared with the other two groups, presented higher SF-36 scores (Physical Functioning: F(2,70) = 4.78, P < 0.02; Role-physical: F(2,70) = 3.41, P < 0.04; Bodily Pain, F(2,70) = 3.77, P < 0.03; Vitality F(2,70) = 4.98, P < 0.01; Mental Health F(2,70) = 4.03, P < 0.02) and lower ASI scores (Drug composite score: F(2,100) = 6.72, P < 0.002; Psychiatric Severity score: F(2,100) = 9.33, P < 0.001). Conclusion: Our results suggest that there are three reliable TCI-based subtypes of female drug-dependent inpatients: High Anxiety/Low Persistence, non-extreme personality profile, and Novelty Seeking. Supported by Catalonia Government.

33 THE ROLES OF MATERNAL DEPRESSION AND CHILD DEPRESSIVE SYMPTOMS ON SUBSEQUENT CIGARETTE SMOKING AMONG ADOLESCENTS

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Maternal depression has been implicated in a number of child psychological outcomes. In this prospective study of 574 mothers and their children, we examined the relation between maternal depression, child depression and child’s subsequent tobacco use. Maternal depression (CES-D) symptoms and child depression (CDI) symptoms were measured when the child was 10-years-old. Women were categorized as depressed at the value of 45 or greater (range: 20–67). Child’s self-reported average daily cigarette use was measured at 14 years. At the 14-year follow-up (mean age 14.79; range: 13.88–16.56), 45.5% of the children had ever smoked cigarettes. Among the smokers, average daily cigarette use was significantly higher among children whose mothers were depressed (average daily cigarette = 3.95) compared with those whose mothers were not depressed (average daily cigarette = 2.05) ($P = 0.017$). Depression symptoms were also significantly higher among the children of depressed mothers compared to those whose mothers were not depressed, (CDI = 47.73 vs. CDI = 45.63, respectively) ($P = 0.015$). Using regression analyses, without the inclusion of child’s depressive symptoms, the following variables significantly predicted the number of cigarettes smoked per day among 14-year-olds: maternal depressive symptoms ($\beta = 1.845$, $P = 0.017$), current peer cigarette use ($\beta = 1.265$, $P = 0.001$), mother’s current cigarette use ($\beta = 0.105$, $P = 0.001$), and mother’s report of child’s school performance ($\beta = -0.868$, $P = 0.009$). Other covariates in the model included gender, race, family income, presence of man in the household, mother’s other drug use, and peers’ other drug use. When child depression was added to the model, the effect of maternal depression did not change and child depression was not a significant predictor of number of daily cigarettes smoked. These results demonstrate that maternal depression has a significant independent effect on child’s tobacco use and that this effect is not mediated by child depressive symptoms.

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34 EFFECTS OF AYAHUASCA ON SENSORY AND SENSORIMOTOR GATING IN HUMANS, AS MEASURED BY P50 SUPPRESSION AND PREPULSE INHIBITION OF STARTLE

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Suppression of the P50 auditory evoked potential and prepulse inhibition of startle (PPI) are operational measures of inhibitory neural mechanisms thought to intervene in the normal filtering of sensory information. These operational measures of sensory (P50 suppression) and sensorimotor (PPI) gating have been found to show abnormal values in a number of neuropsychiatric disorders where a sensory overload is postulated. Current human research with hallucinogens has explored the possibility that drugs displaying agonist activity at the 5-HT2A/2C sites temporally disrupt neural gating mechanisms, an effect which would account for the perceptual and cognitive modifications characteristic of hallucinogen-induced subjective effects. In the present study, the effects of the acute administration of the N,N-diethyltryptamine (DMT, a hallucinogenic 5-HT2A/2C
agonist) containing psychoactive beverage ayahuasca on P50 suppression and PPI in humans was assessed. Eighteen healthy volunteers with experience in hallucinogen use participated in a double-blind placebo-controlled clinical trial in which two doses of encapsulated freeze-dried ayahuasca (0.6 and 0.85 mg DMT per kg body weight) were administered. P50 and startle reflex (pulse-alone and 60, 120, 240 and 2000 ms prepulse-to-pulse intervals) recordings were undertaken at 1.5 and 2 h after drug intake, respectively. Whereas significant dose dependent reductions of P50 suppression were seen after ayahuasca, non-significant increases in the startle response and PPI (120 and 240 ms) were observed. Results indicate a decremental effect of ayahuasca on sensory gating, as measured by P50 suppression, and a mild enhancing effect for the beverage on sensorimotor gating in humans, in line with previous data from serotonergic drugs. The present findings suggest a differential modulation of PPI and P50 suppression by serotonergic hallucinogens in humans.

35 SEX-RELATED DIFFERENCES IN MECHANICAL NOCICEPTION AND KAPPA OPIOID ANTINOCICEPTION IN F344 RATS

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Previous studies indicate that in thermal nociceptive assays, some kappa opioids are more potent and effective in male than female rats. However, few studies have used non-thermal nociceptive stimuli to examine sex differences, and thus the purpose of the present study was to examine nociception and kappa opioid antinociception in male and female F344 rats using a mechanical (paw pressure) nociceptive stimulus. Results indicate that males had a higher threshold for baseline nociception, but sex differences were not observed in the psychophysical relationship between nociceptive stimulus intensity and paw withdrawal latency. Repeated testing did not systematically alter nociceptive thresholds in either males or females. To determine the relative contribution of the endogenous opioid system to baseline nociception, various doses of naltrexone were administered prior to testing. Although naltrexone dose-dependently decreased nociceptive thresholds in males and females, sex differences were not apparent. Spiradoline, enadoline and U50, 488 produced intermediate to high levels of antinociception, and were equally potent and effective in males and females. Whereas the maximal effect produced by U69,593 and ethylketocyclazocine (EKC) were comparable in males and females, sex differences were not apparent. Whereas the maximal effect produced by U69,593 and EKC was slightly more potent in males. Proxorphan and nalorephine produced only low levels of antinociception, with an intermediate dose of proxorphin producing greater effects in females. These data indicate sex differences in mechanical nociception, but a similar psychophysical relationship between nociceptive stimulus intensity and paw withdrawal latency as well as similar involvement of the endogenous opioid system. Furthermore, that sex differences were not observed consistently in kappa opioid antinociception contrasts with findings using thermal nociceptive stimuli, suggesting that stimulus modality should be considered when examining sex differences in opioid antinociception.

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36 THE EFFICACY OF COMMUNITY REINFORCEMENT AND FAMILY TRAINING (CRAFT) FOR ENGAGING RESISTANT ADOLESCENTS INTO TREATMENT

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A major challenge in treating adolescent substance use disorders is poor engagement and retention in treatment. Adolescent drug abusers referred to treatment, but who actively refuse to participate, are particularly at risk for continuing disturbance because of the greater severity of their problems and because these problems go unaddressed. Thus, the very youth for whom treatment is most indicated are the least likely to get it because of their resistance. Community Reinforcement and Family Training (CRAFT), targeting family members as a potential source of influence, is an innovative approach demonstrated to be effective in engaging resistant adults in treatment. The primary goal of this study was to evaluate the efficacy of the model for resistant adolescents. Of the 43 parents who participated in the study, 71% successfully engaged their treatment-resistant youth in treatment. The study also demonstrated significant improvements in parent functioning in depression and other negative moods, physical complaints, and other domains at the post-treatment and 3-month follow-up assessments. In addition, the treatment-resistant youth who participated in treatment had positive outcomes, with significant reductions in drug use from pre- to post-treatment. Further analyses were conducted to identify variables predictive of parents' success in engaging their youth in treatment.

37 POSSIBLE INCREASED SENSITIVITY TO CORTICOTROPIN RELEASING FACTOR IN DRUG-FREE FORMER HEROIN ADDICTS ON STABLE DOSE METHADONE MAINTENANCE

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Altered hypothalamic-pituitary-adrenal (HPA) axis responsivity to stress and stressors has been observed during different stages of the addictive diseases. In this study, HPA response to exogenously administered corticotropin releasing factor (CRF) in normal male volunteers (NV) free of addictive disease (N = 16) and male drug-free former heroin addicts on stable dose methadone maintenance treatment (MM; N = 8). Each subject was admitted to the stress-minimized environment of the Rockefeller University Hospital GCRC for single blind testing with placebo, h/rCRF 0.5 μg/kg, and h/rCRF 2.0 μg/kg infused intravenously over 2 min between 09:00 and 10:00 h on 3 separate days. Baseline plasma ACTH and cortisol were measured each morning 10 min and just prior to the infusion and at intervals over the next 4 h. There was a significant dose response of both ACTH and cortisol to the CRF testing with no significant difference between groups in levels of ACTH or cortisol after placebo or the 0.5 μg/kg dose CRF. There was, however, a significantly higher level of ACTH, but not cortisol, in the MM group after the 2.0 μg/kg dose of CRF (P < 0.05). These results indicate that male drug free former heroin addicts on stable dose methadone may have increased direct pituitary sensitivity to CRF.

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38 PROSPECTIVE EVOLUTION OF ALCOHOL CONSUMPTION AMONG OPIATE-DEPENDENT PATIENTS 6 MONTHS AFTER INCLUSION IN A BUPRENORPHINE MAINTENANCE PROGRAM, THE CAMES STUDY

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Poor prospective data is available about the alcohol consumption during Buprenorphine Maintenance Program (BMP). This study describes how alcohol is used by heroin-dependent patients at inclusion
in an BMP and at 6 months later. Thirty-three DSM-IV-opiate-dependent patients (26 males, seven females, 35.5 average age) recruited among the consultants of general practitioners involved in heroin treatment patients have been evaluated by the same investigator at inclusion, 3 and 6 months after induction of buprenorphine program. Evaluation: Alcohol consumption (previous week), alcohol craving (visual analogical scale), frequency of drunkenness (last month), DSM-IV criteria diagnosis, Addiction Severity Index (ASI). At 6 months follow-up, 21 patients (63.6%) were e

e to the sixth month after the starting of the treatment was obser

e subjects to MA. The analysis was done in intention to treat. Mean number of standard drinks consumed during the past week decreased from 56.4 (S.D.: 86.2) at 6 months follow-up (Wilcoxon test for paired samples, \( P = 0.08 \)). The frequency of patients who declared having a drunken episode during the past month increased from 24.2 to 33.3% \( (\chi^2, NS) \). Subjective effects of alcohol intoxication were described 'less intense than usual' by respectively 10.5% of patients at 1 month follow-up, 25% at 3 months and 16.7% at 6 months \( (\chi^2 \text{ for trend NS}) \). Craving score for alcohol decreased non significantly from 3.3 (S.D. 3.7) to 3 (S.D. 3.4) 28% of the patients encountered the DSM-IV criteria for alcohol dependence after 6 months. ASI alcohol severity sub-scale decreased from 3.1 (S.D. 2.6) at inclusion to 2.5 (S.D. 2.6) at 6 month. Alcohol use prospectively assessed by validated instruments among patients including a BMP seems to decrease during the first 6 months after buprenorphine induction. The small size of the sample limits interpretation of the results. However a trend for decrease of both quantity of drinks and level of craving for alcohol from the third to the sixth month after the starting of the treatment was observed. Subjective tolerance for alcohol seems not to be affected by the treatment but an increased frequency of drunkenness is observed.

39 Methamphetamine-amlodipine interactions: preliminary analysis

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Background: Methamphetamine (MA) abuse is a serious problem for which there are no established pharmacological treatments. Calcium channel blockers (CCBs) such as isradipine and amlodipine have been proposed as putative treatment agents. Isradipine has been shown to reduce MA effects in a human laboratory trial (Johnson, 1999), but amlodipine was not effective for MA dependence in a controlled outpatient trial (Batki, 2001). Objective: This study was designed to examine the subjective and physiological effects of oral \( \alpha \)-methamphetamine after acute premedication with amlodipine. Method: Nine subjects underwent 2-2 day sessions in each of which they received 30 mg of immediate-release oral \( \alpha \)-methamphetamine hydrochloride after premedication with amlodipine 20 mg or placebo. The order of premedication was randomly assigned, and double-blinded. Subjects were six males and three females, all experienced with, but not abusers of or dependent on methamphetamine. Subjective and physiological effects, and plasma MA and amphetamine levels were measured. Results: In this preliminary analysis, MA produced significant increases over time in systolic and diastolic blood pressure (BP), heart rate, ARCI MBG and A scores, and POMS Vigor, Arousal, and Positive Mood scores. Amlodipine pretreatment was associated with significantly lower peak response in systolic BP. However, no other treatment-related differences emerged in subjective responses such as euphoria, craving, and hyperactivity, with the exception of significantly higher POMS Arousal scores in the amlodipine group. MA plasma levels did not differ in the two groups. Conclusions: Amlodipine appears to be more effective in reducing the physiological response than the subjective responses to MA. Therefore, while amlodipine may be somewhat protective against MA-induced hypertension, this study does not appear to support the utility of amlodipine as a treatment for MA dependence.

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40 Neuroendocrine effects of acute and repeated methamphetamine administration in male rats

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Methamphetamine (METH) abuse is a serious health concern, and no treatments for METH addiction are available. A first step toward the development of treatments for METH addiction is the elucidation of basic pharmacological effects of the drug in vivo. Surprisingly few studies have assessed neuroendocrine actions of METH, so in the present work we examined the effects of METH administration on secretion of various hormones in rats. Male Sprague–Dawley rats were fitted with indwelling intravenous (i.v.) catheters prior to treatments and allowed one week to recover. In the first experiment, rats received single i.v. injections of METH (0.1–1.0 mg/kg) and serial blood samples were withdrawn via the catheters. In a second experiment, rats were treated with repeated doses of METH (5 mg/kg, i.p., bid) for 4 days. At 1 and 2 weeks after METH, rats received i.v. METH injections and blood samples were withdrawn. Plasma samples were assayed for prolactin, growth hormone (GH), and corticosterone using radioimmunoaassay methods. Acute METH produced dose-related elevations in plasma corticosterone but did not alter prolactin or GH. After repeated dosing, the ability of METH to increase plasma corticosterone was reduced, and basal circulating levels of corticosterone were elevated compared to control rats. Our data suggest that acute METH administration activates the HPA axis but this response exhibits tolerance upon repeated drug exposure.

41 True and quasiopiate withdrawal in chick embryos increase blood vessel diameter via 5-HT2 receptors

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Hypothesis: Opiate withdrawal during late development alters cardiovascular function via 5-HT2 receptors, manifest as changes in blood vessel (BV) diameter. Vehicle or NLAAM (5 mg/kg egg) was injected into eggs with 4-day-old embryos (E4). Some were pretreated with the 5-HT2 antagonist ritanserin (RIT, 0.9 mg/kg egg) on E17. After recording baseline diameters of large and small BV (LBV; SBV) on E18, naloxone (Nn, 10 mg/kg egg) was injected. Recordings were made for 15 more minutes to quantify changes in BV diameters (N = 12–14 per group). SBV and LBV were significantly dilated (up to 37%) in NLAAM–Nt treated embryos and RIT blocked this effect. RIT or NLAAM on their own had no effect. Isobutylmethylxanthine (IBMX) mimics other manifestations of opiate withdrawal. We administered RIT on E17 and IBMX on E18 (N = 5 per group) to determine if quasiopiate withdrawal led to similar effects. IBMX (10 mg/kg egg) significantly increased LBV and SBV diameter (up to 55%) and RIT blocked this effect also. Thus, a 5-HT2 antagonist (e.g. RIT) prevents adverse cardiovascular effects of prenatal opiate withdrawal.

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42 Drug analysis for dance drug users at free parties: from 1998 to 2001 major improvements in the French market

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Since 1997, ‘Médecins du Monde’ has operated at free parties. In 1998 a national research intervention was developed to consider demographic data, ethno-psycho-social characteristics, drug use prevalence. ... By acknowledging drug users know what they use, two distinct programmes were developed: Drug Analysis on Site (DAS) [using Marquis and Merck Reagents and TLC] and Stationary Drug Analysis in Laboratories (SDAL) [using HPLC and GCMS]. The latter was recognised in 1999–2000 by the French Government as part of a European Community Action for drug assessment. From November 1998 to December 2001 more than 1600 tablets, powders, liquids or blotting papers collected at free parties were documented on site and analysed in laboratories. When necessary and possible, qualitative and/or quantitative results from the laboratories were returned to DU or DUC. By sending results to the ‘Observatoire Français des Drogues et des Toxicomanies’ (OFDT) a contribution was made to the European Early Warning System. On-site warnings were issued from OFDT, EUROPOL, and the European Monitoring Center for Drugs and Drug Addiction. A progress report at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented at such events is presented.

43 The impact of residential treatment on long-term recidivism of felony drug offenders

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A quasi-experimental design was utilized to examine 3-year recidivism outcomes for two groups of serious felony offenders arrested for low-level drug sales: 150 experimental subjects diverted from prison to a community-based, residential drug treatment alternative to prison program, and 130 comparison subjects (matched offenders sentenced to prison terms equivalent to successful treatment completion length). Subjects were tracked for 3 years from treatment completion (experimental or treatment completion length). Multiple measures compare the impact of residential drug treatment on recidivism patterns over time, including rearrest, reincarceration, and time to first rearrest. We hypothesized that treatment reduces the probability of recidivism and increases survival time to first rearrest. Secondary hypotheses were that treatment effects would interact with individual static and dynamic factors to influence recidivism. Analyses include (1) descriptive comparisons of prevalence rates for various time frames, (2) multivariate analyses of prevalence rates using logistic regression, and arrest rates using OLS regression, and (3) Cox proportional hazard models of time to rearrest. Control variables are included from the following domains: demographics, family, social, educational, employment, medical, psychological, criminal, sexual behavior, and drug use and treatment histories. The data indicate a significant overall impact of treatment on recidivism, although the effect decays somewhat over time. Treatment effects are mediated by individual factors. The findings indicate that residential treatment of drug offenders in lieu of incarceration reduces drug use and improves public safety.

44 A possible involvement of cannabinoids in the pathogenesis of fever

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The cannabinoid system affects several physiological functions, including thermoregulation. Two cannabinoid receptors have been identified: CB1, present in the central nervous system (CNS) and to a lesser extent in other tissues, and CB2, present outside the CNS, in peripheral organs. Although lipopolysaccharide (LPS) has been known to induce fever, the mechanisms involved are not fully understood. In this study, we have examined the role of cannabinoid receptors in the fever induced by LPS. Radio transmitters (Minimitter) to measure body temperature (Tb) were used in this study. This method minimizes stress to the animal during the Tb reading. Intraperitoneal (i.p.) injection of Sprague–Dawley rats with 50 μg/kg of LPS (Escherichia coli, 0111:B4) caused a biphasic fever. The febrile response to i.p. injection of LPS was completely blocked by pretreatment with the CB1 cannabinoid receptor antagonist, SR 141716 (2.5 mg/kg) given intramuscularly (i.m.) thirty min before LPS. However, pretreatment with the CB2 cannabinoid receptor antagonist, SR 144528 (2.5 mg/kg), did not alter the LPS-induced fever. The i.m. injection of the CB1 receptor antagonist or the CB2 receptor antagonist alone did not result in significant change in Tb. The present results suggest the involvement of CB1, but not CB2, cannabinoid receptors in the fever induced by LPS and indicate a possible role of the cannabinoid system in the pathogenesis of fever.

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45 Behavioral sensitization following repeated IV nicotine: sex differences and dopamine D3 receptors

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Repeated administration of stimulants, by SC and IP routes, is known to yield behavioral sensitization in male animals. The study at hand investigated whether behavioral sensitization occurs in response to repeated IV nicotine administration, particularly when employing low doses of nicotine; and secondly, if there is a sex difference in the expression of behavioral sensitization. Sprague–Dawley rats (intact male and female) were surgically implanted with an intravenous access port (Mactutus et al., 1994), and habituated to 60 cm diameter chambers for three days with no drug. Animals received 50 μg/kg per ml IV nicotine 1 per day for 21 days, delivered as a bolus injection (30 s). This dose does not affect estrous cyclicity (Booze et al., 1999). On days 1 and 21, observers blind to treatment condition performed observational time sampling of behavior. On the 22nd day the animals were euthanized and their brains were removed and frozen for subsequent dopamine receptor analysis. There was an overall effect of repeated IV nicotine on centrally directed locomotor activity and rearing; i.e. robust sensitization was produced. For both measures, no sex difference was observed after saline or the initial nicotine injection; however, the females were markedly more sensitized than males following repeated nicotine administration. The number of D3 receptors in the dorsolateral striatum was positively correlated with centrally directed activity of sensitized females (R = +0.55) and negatively correlated with centrally directed activity of sensitized females.
males ($R = -0.35$). There was also a relationship between D3 receptors and rearing in the dorsolateral striatum of females ($R = 0.45$) that was not apparent in males. In sum, IV dosing in rats served to (1) produce robust behavioral sensitization, (2) sensitization was noted in two components of behavior, suggesting a commonality of the sensitization effect, and (3) sex differences in behavioral sensitization were not only observed, but related to sex-dependent alterations of D3 receptor number.

Acknowledgments: Support for the longitudinal data collection be aided by greater attention to culture.

Knowledge of Neighborhood Terminology for Marijuana and Subsequent Risk for Use Among Adolescents

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The Problem: The aim was to study whether knowledge of different names for marijuana used by a group of urban youth signifies increased risk for use. Knowledge of words to describe drugs and drug use practices are culturally defined and learned through social interactions. Socially shared characteristics of neighborhoods and communities may influence knowledge of neighborhood terminology for marijuana. To the extent that vocabulary and word usage are manifestations of culture, it is possible that the words used to talk about illegal drugs will help us understand future drug using behavior.

Methods: The participants were from an ongoing longitudinal study and randomized in a controlled trial of pre

Center phase II study. Placebo, lazabemide 100 and 200 mg/day were administered for 8 weeks. Setting: General practices and antismoking clinics in France and Belgium. Participants: Smokers smoking ≥ 15 cigarettes per day and motivated to quit. Main outcome measure: Sustained abstinence during the last 4 weeks of the study. Findings: The study was prematurely discontinued by the sponsor before randomization of the planned 420 smokers because of liver toxicity observed in studies in other indications. Data of 330 randomized subjects could be analyzed. Sustained abstinence during the last 4 weeks of treatment was 9, 11 and 17% in the intent-to-treat population [$P$ for trend: 0.07 (two-sided)]; 11, 14 and 21% in the intent-to-treat population of smokers without those excluded because of discontinuation of the study $[N = 262, P$ for trend: 0.02 (one-sided), 0.049 (two-sided)] and 19, 27 and 35% in completers $[P$ for trend: 0.03 (one-sided), 0.07 (two-sided)] in the placebo, lazabemide 100 mg/day and lazabemide 200 mg/day groups, respectively. Point prevalence abstinence (intention-to-treat population) at the end of treatment (week 8) was 17, 19 and 30% in the placebo, lazabemide 100 mg/day and lazabemide 200 mg/day groups, respectively. Placebo vs. lazabemide 200 mg/day; $P = 0.03$. No treatment emergent major adverse event occurred. More nausea and insomnia were reported with lazabemide than with placebo. Conclusions: MAOB inhibitors are promising treatments as an aid in smoking cessation. Further studies may associate MAOB inhibitors with nicotine replacement therapies to increase therapeutic efficacy.

The EEG of Cocaine Abusers after Another Two Years of Cocaine Use

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EEG alterations in chronic cocaine abusers have been reported by a number of researchers. These alterations have been attributed to either prefrontal factors, comorbid psychopathology or prolonged exposure to cocaine. Nineteen cocaine abusers were tested during an initial session and at then at 2.0–0.9 years in order to determine the longitudinal effects of continued use of cocaine on the EEG. Twenty-one control subjects were tested on one occasion as comparison group. Three minutes resting eyes closed EEGs were recorded from eight electrodes (F3, C3, P3, O1, F4, C4, P4, and O2). The artifacted EEG was converted to six frequency bands (theta, alpha, beta and gamma). Three minutes resting eyes closed EEGs were recorded from eight electrodes (F3, C3, P3, O1, F4, C4, P4, and O2). The artifacted EEG was converted to six frequency bands ($\alpha$, $\theta$, $\beta_1$, $\beta_2$) using a fast Fourier Transform. Absolute power was significantly lower ($P < 0.01$) for the cocaine abusers than the control subjects for theta, $\theta$, and $\beta_1$ bands. Relative power in the cocaine abusers was significantly lower for $\theta$ and higher $\beta_2$ than in control subjects. Absolute power significantly decreased over the period of continued use for theta, $\theta$, $\beta_1$, and $\beta_2$. These findings suggest that prolonged use of cocaine rather than the alterations resulting from prefrontal conditions is responsible for the EEG deficits in this population.

Bivalent Ligands for Kappa Opioid Receptors


Compounds that contain two pharmacophores joined by a connecting spacer have been termed ‘bivalent ligands.’ Such bivalent ligands have attracted interest as molecular probes for opioid receptor, particularly, since opioid receptors may form dimers and oligomers. Our studies have focused on mixed kappa/mu opioids as potential therapeutic targets for treating cocaine abuse. The morphinan (–) cyclorphan and its N-cyclobutylmethyl derivative, MCL-101, had high affinity for the kappa and mu receptors (Neumeyer et al., J. Med. Chem. 43:114 (2000)). This report describes bivalent ligands formed by coupling two
50 THE PROGNOSTIC SIGNIFICANCE OF BASELINE COCAINE USE IN THE TREATMENT OF COCAINE DEPENDENCE


Several problems encountered in substance abuse treatment trials can reduce the efficacy of the trial to detect medication effect. Pre-randomization placebo lead-in periods have been used to identify patients who will more likely respond to treatment. As a part of the current study of gabapentin for cocaine dependence, we are evaluating the prognostic significance of the use of placebo lead-in to select patients based on the level of baseline cocaine use. To date, 50 individuals have completed the trial. During the 2 weeks of placebo lead-in, patients provided at least four urine samples. Patients were then randomized to either the active or control condition, stratified by route of cocaine administration, and level of cocaine use during the 2 week lead-in period. The High Use Group, defined as >1 cocaine-free urines during the lead-in period, had significantly more cocaine positive urines over the 12 week trial than the Low Use Group, defined as >2 cocaine-free urines during the lead-in period. The magnitude of the High versus Low Use Group difference appears to be greater in the intranasal users than smokers. However, there was no difference in 12-week treatment retention between the High and Low Use groups. These interim results suggest that baseline abstinence is a strong predictor of abstinence at outcome, may be a useful tool in patient selection, and is an important covariate to consider in efficacy analyses. The effect of abstinence during placebo lead-in on gabapentin placebo difference in cocaine use outcome will be presented.

51 D-AMPHETAMINE INDUCES DIFFERENTIAL EFFECTS ON Locomotion, Stereotypy and OBJECT RECOGNITION MEMORY IN FEMALE AND MALE RATS

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Since d-amphetamine (AMPH) produces greater scores for locomotion and stereotypy in female as compared with male rats, it is hypothesized that AMPH will also induce gender differences on cognition. We investigated object recognition memory during a withdrawal period following chronic AMPH or acute AMPH administration to female and male rats; and, measured locomotion, stereotypy and neurochemistry changes induced by an AMPH challenge dose after a 16-day withdrawal period. Sprague-Dawley male and female adult rats were treated chronically (N = 8/10 per group), (10 i.p. inj., one every other day; males: 3 mg/kg, females: 2.6 mg/kg), or acutely (N = 8 per group) (one inj., same doses). Locomotion and stereotypy were also quantified. Object recognition memory was evaluated during the withdrawal period and after acute administration. Monoamines in brain areas were measured after a challenge dose on the 16th withdrawal day. Two-way ANOVA (sex × treatment) tested statistical significances. AMPH treated rats showed impairments in visual recognition memory during withdrawal, but no sex differences were found. However, after acute AMPH, treated males showed the lowest performance in the object recognition test. Females treated had higher scores of stereotypy and locomotion after an acute and chronic treatment but no gender differences were found after a challenge dose. In AMPH groups, striatal DA, 5-HT and 5-HIAA were increased (females also had higher 5-HT and less HVA), in substantia nigra 5-HIAA and 5-HIAA/5-HT were also increased. In nucleus accumbens, females had lower norepinephrine levels than males. Thus, both sexes showed memory impairments during the withdrawal period but after acute AMPH, object recognition performance was not impaired in females. Further, an amphetamine challenge dose after a withdrawal period did not amplify gender differences in locomotion/stereotypy or neuroamine levels. This study provides novel information to better understand functional cognitive consequences of AMPH administration and suggests that females may have less/differential cognitive impairments to psychoactive drugs than males. MIDARP (R24 DA12136, NIDA).

52 BLENDING COMMUNITY-BASED PRACTICES WITH RESEARCH SUPPORTED TREATMENT

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Currently, there is a lack of congruence between faith-based community efforts and approaches considered to be more research and theory-driven. This incongruence reflects the dilemma lay-led recovery providers and researchers face in delivering the most effective and appropriate treatment interventions. The growing recognition of the relevance of incorporating spirituality and faith components in substance abuse treatment underscore the importance of this model development. The model entitled Faith Inspired Research Supported Treatment (FIRST) augments and blends a pre-existing residential faith-based community program with research-supported therapeutic interventions. Systematic evaluation of this project will yield new knowledge and data sets on how to blend substance abuse research with faith-based community approaches. FIRST can also serve as a state licensure model for faith-based community groups. FIRST will develop and evaluate the effectiveness of a residential faith-based integrated treatment model located in the community. The cornerstones of this model are the ‘FREE ‘N’ ONE’ Faith-Based Program, established in 1993, and the Matrix Model on Addictions, a comprehensive research-driven and validated treatment approach developed during the 1980s.

53 DISREGULATION OF DRUG-SEEKING BEHAVIOR FOLLOWING LIDOCAINE INACTIVATION OF THE LATERAL PREFRONTAL CORTEX

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Research from this laboratory has sought to determine what role different memory systems play in regulating addiction-related behaviors. We have extended our investigation to the lateral prefrontal cortex (PFC), an area critical for executive functions including working memory, response inhibition, and temporal sequencing of behavior. The effects of lidocaine inactivation of the lateral PFC were investigated during cocaine maintenance, cocaine cue-induced reinstatement, and cocaine prime-cue-induced reinstatement phases. Rats (n = 6) were trained to self-administer 1 mg/kg cocaine under an FI5
min(FR5:S) second-order schedule of drug delivery that measures drug-seeking and drug-taking behavior independently. Following lidocaine, no significant changes in the magnitude of drug-seeking behavior occurred during maintenance or cue-induced reinstatement tests. However, lidocaine produced a significant 2-fold increase in the reinstatement of drug-seeking after cocaine priming. Lidocaine did not affect drug-taking behavior in any test. Cumulative records were generated to examine response patterns. Baseline responding was characterized by a high rate of continuous responding for approximately 15 min followed by a scallop-shaped response pattern, typical of FI-based schedules, for the remainder of the session. With lidocaine, the response pattern during maintenance tests lacked the scallop-shape, and instead showed continuous responding throughout the session. During prime+cue-induced reinstatement tests with or without lidocaine, a similar continuous pattern of responding was observed. However, the slope of the cumulative responses was greater following lidocaine compared with the saline condition. The patterns of continuous high rate responding may indicate a dysregulation of drug-seeking behavior through perseveration or response disinhibition. Therefore, the lateral PFC may regulate the temporally appropriate response pattern engendered by cocaine and cocaine cues, but not the motivational salience of the cues themselves.

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54 An SAB study of bupropion, N-ethylpropion and cathinone analogs

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Bupropion is a widely prescribed anti-depressant/anti-smoking medication sold under the brand names Wellbutrin® and Zyban®, respectively. The structure of bupropion is based on cathinone, the primary active stimulant isolated from the leaves of Catha edulis also known as khat. Bupropion is primarily a dopamine uptake inhibitor while cathinone is primarily a dopamine/norepinephrine dual releaser. In a recent study Rothman et al. have shown that the active component of the anorectic diethylpropion is in fact its metabolite N-ethylpropion, which is also a structural analog of bupropion and cathinone. Interestingly, N-ethylpropion was found to release norepinephrine but inhibit dopamine uptake. These three compounds differ mainly by N-substitution. Cathinone is unsubstituted and is a neurotransmitter releaser. Bupropion has a bulky t-butylamine group and is a neurotransmitter uptake inhibitor. N-Ethylpropion has a much smaller ethylamine group and has mixed activity. These observations point to the need to study related compounds in order to define a structure activity relationship for their activity at the biogenic amine transporters. Such an in vitro study will be described.

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55 Relationship between mother’s substance abuse and mental health problems and children’s behavior among women in outpatient substance abuse treatment

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Research suggests that children of substance abusing mothers are vulnerable to behavioral problems. It has been shown that children of mothers with mental health problems are also prone to behavioral problems. This study examined whether the nature and severity of children’s problems were affected differentially by their mother’s substance abuse and mental health problems. Mothers and children (ages 6–11) were enrolled from four Philadelphia intensive outpatient addictions treatment programs (n = 111 mother/child pairs). The Addiction Severity Index (ASI) measured parent problems, while the Child Behavior Checklist (CBCL) and the Social Skills Rating System (SSRS) measured child’s behavior. All instruments were completed by the mother at baseline. A series of three blocked regression analyses were used to examine the relationship between the severity of mother’s substance abuse and psychiatric symptoms and the target child’s problem behaviors. The same procedure was used to examine the relationship between mother’s problems and child’s pro-social skills. Overall, the findings indicated that mother’s severity of substance abuse and mental health problems were related to child’s problem behaviors. Internalizing behaviors (social withdrawal, somatic complaints and anxious and depressed feeling) in the child were positively related to mother’s psychiatric severity but not substance abuse severity. The severity of mother’s psychiatric symptoms and drug problems was associated with externalizing problems (delinquency and aggression) in the child. Pro-social skills in the child were not related to the severity of mother’s psychiatric symptoms, but mothers with more severe substance abuse problems had children with poorer pro-social skills. These findings lend preliminary support to the premise that a mother’s substance abuse and mental health problems make independent contributions to the problem behaviors of her children.

56 Gender differences in adolescents’ social relationships and drug use context: implications for treatment

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The juvenile justice system relies on residential drug treatment for male and female adolescents, though the latter represent a minority of clients in this modality. In light of gender differences in background characteristics and behavior among adolescent juvenile offenders, we conducted a case study of the Therapeutic Community treatment experience for female adolescents. Data from quantitative interviews with adolescents court mandated to residential treatment (N = 449) and semi-structured interviews with seven boys and three girls attending a co-ed residential treatment program indicate that girls’ and boys’ social support systems and social networks prior to treatment entry differ dramatically. Girls’ drug-using and support networks are comprised of older males who act as ‘protectors,’ as well as sexual partners, while those of boys are comprised of same-sex, same-aged peers. Girls’ relationships with boys are highly sexualized and they express distrust of other girls. These relationship patterns continue during treatment. In addition, girls are more likely to have a history of either sexual or physical abuse, and have more problematic family environments. We discuss gender differences in responses to treatment components as a result of these pretreatment differences.

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57 New method for estimation of tobacco quitting rates using current population survey tobacco use supplement data

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The purpose of this methodological study is to define and estimate population quitting rates among tobacco users. Quitting is usually defined as not using for a certain period of time. Estimation of long-term quitting rates from survey data is complicated because subjects who report being abstinent for a shorter period can possibly relapse at some point in future. We present novel and consistent methodology which uses information about subject’s quitting history to estimate chances of relapse during specified time period. Next, these estimates are utilized to estimate the long-term quitting rates. As an example, we applied our method to the data from nationally representative household sample survey Current Population Survey Tobacco Use Supplement (CPSTUS) conducted during 1995–1996 which includes all persons in the civilian non-institutional population aged 15 years and older (n = 47,000). We analyzed the white population as a first step. We intend to produce estimates for other racial groups. The estimated probability of quitting for 1 month is 0.114 (95%CI 0.107, 0.121) for males and 0.112 (0.105, 0.119) for females. The probabilities of quitting for 1 year are 0.047 (95%CI 0.041, 0.053) for males and 0.040 (95%CI 0.034, 0.045) for females. The largest differences in quit rates among demographic groups occur among age groups and among education groups. Presented methodology could be used for estimation of quitting rates for other drugs if surveys provide quitting history information as in CPSTUS.

58 A KNOCKOUT (KO) OF THE GLUR5 RECEPTOR SUBUNIT PREVENTS MORPHINE TOLERANCE BUT NOT DEPENDENCE, HYPERALGESIA OR ALLODYNNIA

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Antagonist studies suggest the involvement of the GluR5 subunit of the kainate receptor in clinical pain, nociception and morphine tolerance. However, we found that the responses of constitutive homozygous GluR5 KO (Girk1 T1M1SFH) and wild-type (WT) mice are not different in the following behavioral tests: rotorod (motor coordination), von Frey threshold (mechanical sensitivity), intraplantar formalin (inflammatory), partial sciatic nerve ligation (thermal hyperalgesia, and mechanical allodynia) and morphine antinociception (ED50 value). The tailflick withdrawal latencies of the KOs are increased at 52.5 and 55 °C but not at 48 and 50 °C. After repeated morphine, WT mice exhibit a 4-fold increase in the morphine ED50 while this value is unchanged in KOs. The WT and the KOs exhibit the same degree of morphine dependence as measured by naloxone precipitated jumping behavior. At 48 h after morphine pellet removal, both WT and KOs exhibit equivalent mechanical allodynia. Thus, GluR5 KOs are less sensitive to higher intensities of noxious thermal stimuli and do not develop tolerance to morphine. These KOs provide an opportunity to separate the expression of hyperalgesia and allodynia, as well as morphine dependence, from the development of morphine tolerance.

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59 AGONIST EFFICACY AND THE ROLE OF Beta-ARRESTIN2 IN MU OPIOID RECEPTOR REGULATION

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There is a growing literature on the regulation of mu opioid receptors (MOR) in response to agonists of different efficacies. It has been demonstrated that the MOR rapidly desensitizes and internalizes in the presence of high efficacy drugs, i.e. etorphine and DAMGO; yet after morphine binding, it resists rapid desensitization and does not internalize G protein-coupled receptor (GPCR) regulation by GPCR kinases (GRKs) and β-arrestins can lead to desensitization and subsequent internalization. In addition, overexpression of GRKs or β-arrestins permits morphine-induced desensitization and internalization of the MOR in cell culture studies. While it appears that β-arrestins do not play a major role in regulating MOR responsiveness in cell culture, removal of the β-arrestin2 (Barr2) gene in mice leads to enhanced and prolonged MOR mediated antinociception, as well as increased G protein coupling to the receptor. Furthermore, Barr2 knockout (Barr2-KO) mice fail to develop morphine hot-plate antinociceptive tolerance suggesting that the Barr2 protein plays an essential role in MOR regulation in vivo. These observations suggest a paradoxical role of Barr2. In this study, the contribution of Barr2 to the regulation of the MOR was examined in both HEK293 cells and in Barr2-KO mice following morphine or etorphine treatment. A green fluorescent protein (GFP) tagged receptor was used to track MOR internalization in living cells. The interaction of Barr2 with the receptor was visualized by GFP-tagged Barr2 translocation to the membrane following agonist treatment. After morphine treatment, the MOR-GFP did not internalize nor did the Barr2-GFP molecule translocate; however, after etorphine, both events occurred. In vivo, morphine induced greater and longer lasting antinociception in the Barr2-KO mice than in their WT littermates, whereas etorphine induced the same effect in both genotypes. It appears that the agonist can determine the contribution of Barr2 to the regulation of the receptor.

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60 PERSISTENT DOSE-RELATED NEUROCognitive EFFECTS IN 28-DAY ABSTINENT MARIJUANA ABUSERS

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Marijuana is the most widely used illicit drug in the US. In 1999, an estimated 75% of America’s 14.8 million illicit drug users used marijuana alone or in combination with other illicit drugs. As there has been a growing debate about the medical applications of marijuana and an increasing pressure to legalize its use, knowledge of the persistent effects of marijuana on neuropsychological function is critical. We administered a battery of neuropsychological tasks to 23 heavy marijuana abusers (joints smoked/week-mean 47.9 (36.2); duration (years)-mean 5.8 (5.9), after 28-days of verified abstinence in a residential unit. The group was 23 (6) years old, with 11 (2) years of education, Shipley IQ of 95 (11), and consumed 3.6 (4.5) alcoholic drinks per week. Analyses were performed using multiple linear regression. After controlling for age, sex, alcohol consumption, and intellectual ability (Shipley IQ), joints per week smoked and duration of use were associated with decrements on tests of memory, psychomotor speed, and executive cognitive function. The interactions between IQ by joints per week and IQ by duration were significant for a number of tests. These results suggest that marijuana abuse is associated with persistent decrements in cognitive performance that are
most pronounced in heavy marijuana abusers and those with lower intellectual abilities.

61 EVOLUTION OF THE ROLE OF COMMUNITY PHARMACISTS IN THE PREVENTION OF HARM RELATED TO DRUG USAGE AND THE PROVISION OF SUBSTITUTE MEDICATIONS

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Aim: To determine the involvement and changing role of pharmacists in the delivery of harm reduction equipment and the provision of substitute medications, and to describe their participation in recent public health strategies. Method: Using a standardised questionnaire, a longitudinal study was undertaken comprising 327 pharmacies from 28 districts in the southern suburbs of Paris. Results: From the 327 pharmacies, 95% of the lead pharmacists or their deputies responded in 1996 compared with 92% in 2000. The supply of condoms to intravenous drug users (IVDUs) fell from 99% in 1996 to 24% in 2000. The proportion of pharmacies supplying needles/syringes and Neo-Codion* (methylmorphine/codeine) remained static at 95% and 96%, respectively. However, these data reflect a reduction in the volume of supplies from 857 needles/syringes per day in 1996 to 566 needles/syringes per day in 2000; and 60 containers of Neo-Codion*/month/pharmacy in 1996 to 38 containers/month per pharmacy in 2000. During the same period the involvement of pharmacists in the supply of substitute medication rose from 51 to 66%. The number of patients on Subutex* or methadone increased by 105 and 43%, respectively. Pharmacists reported that they had supplied injecting equipment to one or more clients in receipt of substitute medication: 19% for Neo-Codion*, 35% for Subutex* and 14% for methadone. Participation of pharmacists in the wider addiction care networks fell during the period from 38 to 20%, but their understanding of the new public health policies increased so that the number of ‘problems’ encountered with IVDUs fell significantly (from 62 to 16%). Conclusion: Support of this development is important. It was rapid and accompanied by an improvement in relations between pharmacists and the target population. However, an increase in participation at pharmacy level was associated with a decrease of involvement in the wider ‘addiction network’ in favour of an increase in doctor-pharmacist relationships.

62 HIV-1 TAT PROTEIN AND NEURODEGENERATION: POTENTIAL INTERACTIONS WITH PSYCHOSTIMULANTS AND OXIDATIVE DAMAGE

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HIV infection is associated with dementia in a significant number of AIDS patients. The number experiencing HIV-associated dementia (HAD) is increased with concomitant intravenous drug abuse. Using in vitro models, our prior studies have determined that cocaine (but not BE) synergizes with HIV-1 Tat protein to produce significant cell death. We now report, using an in vivo animal model, that HIV-1 Tat injection results in significant neuropathology and oxidative damage. Sprague–Dawley rats were injected with saline, a mutant form of Tat (TatD31-61), or the intact Tat protein (50 mg) into the dorsal striatum. Following 2 or 24 h after injection, animals were sacrificed for neuropathological evaluation. The immunofluorescent marker, Fluoro-Jade-B, revealed significant striatal neuronal loss 24 h after microinjection in the Tat-injected animals, but not in the saline or mutant Tat-injected animals. Immunostaining of brain slides with monoclonal OX-42 (type 3 complement receptor, CD11b) antibody demonstrated that death of striatal neurons in Tat-injected animals was accompanied by microglial activation. Using immunochemical detection of protein carbonyls (biomarker of protein oxidation), we observed increased levels of protein carbonyls in the Tat-injected striatum as early as 2 h after microinjection, which suggests that an increase of protein oxidation precedes Tat-mediated neurodegeneration in the rat striatum. Given the capability of cocaine and methamphetamine to produce oxidative damage, these data suggest a mechanism whereby HIV and drugs of abuse may produce profound neuropathology and resultant HAD.

63 A MULTIDIMENSIONAL MEASUREMENT MODEL OF ADDICTION SEVERITY

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The assessment of drug and alcohol abuse severity by the Addiction Severity Index (ASI) may be improved by separating the subjective perception of drug and alcohol addiction severity from the frequency of use of four types of drugs (depressants, stimulants, narcotics, and hallucinogens). The items that form the ASI Composite Score (CS) measures of drug and alcohol abuse severity were factor analyzed in a broad sample of patients in substance abuse treatment (N = 4328). The six-factor model provided a good fit to the data in two sub-samples, N = 2221, RMSEA = 0.075, and N = 2107, RMSEA = 0.076. In a smaller, more specialized sample (N = 222), measures based on the factors were correlated with treatment outcomes. The six measures explained 6% of the variance in the proportion of positive urine tests F(6, 215) = 3.1, P < 0.01. Subjects reporting high levels of depressant use, and stimulant use each had a greater proportion of positive urine results, while those reporting distress resulting from alcohol abuse had a lower proportion of positive urine results. The Drug and Alcohol CSs only explained an additional 2% of the variance in positive urine tests. The use of hallucinogens explained 12% of the variance in criminal charges, F(6,215) = 6.1, P < 0.01. The Drug and Alcohol CSs only explained an additional 1% of the variance in criminal charges, F(8,213) = 4.9, P < 0.01. More sensitive assessments may result from the division of ASI measures of other problems domains into subscales, such as those examined here.

64 ANTAGONISM OF THE ANTINOCICEPTIVE AND DISCRIMINATIVE STIMULUS EFFECTS OF HEROIN AND MORPHINE BY 3-METHOXYNALTREXONE AND NALTREXONE IN MONKEYS

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It has been suggested that heroin and morphine may act on different opioid receptor populations. In support of this hypothesis, the opioid receptor antagonist 3-methoxynaltrexone (3-MeONTX) was reported to be more potent as an antagonist of the antinociceptive effects of heroin than of morphine in rodents. To assess the generality of this finding across species and experimental endpoints, the present study compared the potencies of naltrexone and 3-MeONTX as antagonists of heroin and morphine in two behavioral assays in rhesus monkeys. In an assay of thermal nociception, tail-withdrawal latencies were measured from water heated to 50 °C. In an assay of heroin discrimination, monkeys were trained to discriminate 0.1 mg/kg heroin (i.m.) from saline in a two-key, food-reinforced procedure, and percent heroin-appropriate responding and response rates were measured. Heroin and morphine produced dose-dependent antinociception, increases in percent heroin-appropriate responding and decreases in response rates. Heroin was approximately 20-fold more potent than morphine. Naltrexone (0.032–0.1 mg/kg) was equipotent in antagonizing all of the effects of heroin and morphine (pA2 values = 7.90–8.22). 3-MeONTX (0.1–3.2 mg/kg) also was equipotent in antagonizing the antinociceptive, discriminative stimulus and rate-suppressant effects of heroin and morphine; however, 3-MeONTX was approximately 100-fold less potent than naltrexone (pA2/pKB values = 5.96–6.36). These
results suggest that heroin and morphine act on pharmacologically similar populations of opioid receptors and indicate that 3-MeONTX does not differentially antagonize the effects of heroin and morphine in rhesus monkeys.

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66 Behavioral pharmacology of opioid antagonists with limited access across the blood–brain barrier

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Opioid antagonists such as naloxone and naltrexone have been investigated as antagonists of the peripheral effects of opioids, but these agents can enter the CNS and reverse analgesia or cause opioid withdrawal symptoms. These experiments evaluated the behavioral pharmacology of several opiate receptor antagonists that have limited access across the blood–brain barrier. Both direct and antagonist effects of CTAP, a potent and mu-selective opioid antagonist, were compared with those of naloxone methiodide (MNLX) and methyl-naltrexone (MNTX), quaternary derivatives of naloxone and naltrexone, in locomotor activity and operant behavior assays in rats. CTAP (0.1–10 mg per rat; i.c.v.) depressed locomotor activity, with the greatest decrease produced at 1.0 mg per rat. Whereas MNTX (0.1–10.0 mg per rat; i.c.v.) dose-dependently antagonized the locomotor effects of MS (sc) in a surmountable fashion, no dose of MS (1.0–560 mg/kg; sc) was able to surmount the dose-dependent antagonism produced by CTAP (0.1–10 mg per rat; i.c.v.). In operant studies, CTAP, MNLX, and MNTX were evaluated for effects on response rates in rats trained under a FR30 schedule for food reinforcement. Cumulative doses of MNLX (0.1–32 mg per rat; i.c.v.) and MNTX (0.1–17.8 mg per rat; i.c.v.) dose-dependently decreased response rates in rats pretreated (~4 h) with either saline or 5.6 mg/kg MS (sc). Acute MS pretreatment resulted in only a small increase in sensitivity to MNLX or MNTX (i.c.v.). Chronic administration of 10 mg/kg per day MS produced increased sensitivity to MNLX but not to MNTX or CTAP. Increasing the chronic dose of MS to 40 mg/kg per day produced increased sensitivity to MNTX and CTAP and further sensitization to MNLX (all i.c.v.). Whereas all three of these compounds with limited CNS access could function as opioid antagonists when administered centrally, they differed in their likelihood to produce abstinence effects during chronic MS treatment, with a rank order of CTAP < MNTX < MNLX.

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67 Patient reported drug use within correctional facilities from the drug evaluation network system (DENS)

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In theory, the Criminal Justice system should provide a correctional and detainment atmosphere free of illegal substances. ‘Contraband’ such as illegal drugs should not permeate the correctional population. However, data collected through the Addiction Severity Index has indicated that detainees reporting access to illegal drugs from within their confined environment. Data from the Drug Evaluation Network Study (DENS), a nationwide electronic system providing clinical information on substance abusers entering treatment in six cities and 65 programs, was used to identify reported drug use for those patients incarcerated for the 30 days prior to evaluation. Data are from a sample of 1550 patients presenting for inpatient or outpatient treatment programs from May 1996 through December 2001; all reported being in 'jail' for the 30 days prior to their evaluation. Patient data collected from the DENS project revealed illicit drug and alcohol use, during incarceration. About 69 patients (4.5%) reported alcohol use, while 29 (1.8%) reported alcohol use to intoxication. Reported use of illegal drugs included, 70 patients (4.5%) using heroin, 70 (4.5%) using cocaine, 64 (4.3%) using cannabis, three (0.19%) using opiates, and one (0.06%) using hallucinogens. One of the most striking findings was that 28% (N = 66) of those patients who used any drugs while in jail reported using more than one substance everyday for all 30 days. Data presented at CPDD will reflect treatment admissions collected up to 1 week prior to the conference.

67 Prevalence and persistence of withdrawal symptoms reported by a non-treatment sample of marijuana smokers

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Marijuana withdrawal symptoms have been reported in self-report and experimental studies, but we are unaware of published data on the timing and duration of symptoms following marijuana quitting. This study examines withdrawal symptoms reported by a convenience sample of 83 non-treatment-seeking marijuana smokers who had made at least one ‘serious’ quit attempt: 49 participating in a UCLA lung health study and 34 in non-treatment studies at the NIDA/IRP. Subjects were largely white (70%) males (87%), with an average age of 39.9 years (S.D. = 10.7), currently using marijuana (89%), using on average 2.5 joints per day (S.D. = 3.6). Subjects had used marijuana for 21.8 years (S.D. = 9.7) and had made an average of 4.4 ‘serious’ lifetime attempts to quit (S.D. = 12.6). The median quitting duration was 7.5 months (range 0–132). Subjects reported a mean of 4.0 (S.D. = 2.9) withdrawal symptoms; more than 2/3 of subjects reported three or more symptoms. Symptom onset occurred largely on the first day after quitting (median, mode = 1; range 1–3). Symptoms disappeared a median of 21 days after quitting (range 4–60). The most frequently reported symptoms were craving, irritability, and boredom, endorsed by 59, 41, and 37% of subjects respectively. Physical symptoms, including tremor, nausea, and diarrhea, were endorsed by less than 10% of subjects. The longest lasting symptom was ‘Improved Memory’ (median 60 days). The remaining symptoms lasted a median of one month (craving, increased appetite and sex drive, irritability, boredom, anxiety and trouble sleeping) or 3 weeks (decreased appetite, depression, and decreased sex drive). A factor analysis of withdrawal symptoms revealed four factors (eigenvalues 2.8, 1.4, 1.4, 1.4). Five of the seven symptoms lasting one month loaded on Factor 1 and the remaining two loaded on Factor 2. Grouping in time and statistical clustering of several withdrawal symptoms support the hypothesis that these symptom sets represent a true marijuana withdrawal syndrome.

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68 Stress response in comorbid alcoholism and PTSD

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The relationship between stress and substance use disorders has been an area of active investigation in recent times. In this study, the subjective, physiological and neuroendocrine response to both a physical and a social stressor delivered on 2 separate days to individual with PTSD (n = 11) alcoholism (n = 12). PTSD
alcoholism \((n = 9)\) and a control group \((n = 11)\) were compared. The physical stressor was the cold pressor test and the psychological stressor was a social speaking and mathematical calculation task. In general, there was a trend towards a greater ACTH response and a greater increase in heart rate after the social stressor as compared to the cold pressor response. These differences were particularly striking for the alcohol only and the PTSD only group. There were no overall differences in the response to the two stressors for other physiological (galvanic skin response, GSR) and subjective responses (craving, stress), however, for specific diagnostic groups, there appeared to be some potential differences in the response to different types of stressors. The alcohol/PTSD group experienced a four times larger increase in craving and two times larger increase in stress rating with the social stressor as compared to the physical stressor. There was no obvious difference in craving or subjective stress response between the two stressor types for other treatment groups. There were no differences between the response to these two types of stressors in GSR or pain rating. The social stressor task, as compared with a physical stressor task, may be a particularly important model in assessing the stress/relapse connection in individuals with comorbid disorders.

69 PSYCHIATRIC COMORBIDITY IN PRESCRIPTION OPIOID USERS IN A METHADONE PROGRAM

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There has been a steep increase in the number of prescription opioid-dependent individuals admitted to methadone maintenance treatment (MMT) as a result of the dramatic expansion of MMT services in the latter half of the 1990s in Ontario. The purpose of this study was to determine the prevalence of mental health symptoms in this population and to determine whether it differs from that reported for heroin users. A retrospective chart review of patients admitted to methadone treatment at the Centre for Addiction and Mental Health between 1997 and 1999 (after the expansion) was conducted \((n = 134)\).

Psychiatric information was obtained from the assessment interview which contains a brief psychiatric screening tool for the purpose of identifying patients that might benefit from a psychiatric consult or from the admission medical assessment. Four populations were compared: those who used prescription opioids only \((n = 31)\), those who reported prescription opioid use at admission but with a history of heroin use \((n = 24)\), those who used prescription opioids and heroin concurrently \((n = 58)\) and those who reported heroin use only \((n = 21)\). There was no significant difference with respect to gender distribution (overall 62.7% male) but the mean age varied \((37 + 1, 39 + 1, 35 + 1, 28 + 2\), respectively, \(P = 0.0001)\). At admission the frequency of at least one psychiatric symptom \((71, 75, 69, 43%)\); depressive symptoms \((58, 67, 60, 38%)\) and suicidal or self-harm ideation \((7, 13, 12, 14%)\) were not significantly different. Anxiety was less frequent in the heroin only group \((45, 54, 47, 10%, P < 0.02)\). More patients using prescription opioids only reported that they were already in treatment for psychological or emotional problems at the time of admission \((42, 17, 16, 14%, P = 0.02)\). In conclusion, prescription opioid users admitted to methadone maintenance treatment were more likely than heroin only users to report anxiety symptoms and those who only used prescription opioids were more likely to be engaged in treatment for psychiatric symptoms.

70 RELIGIOUS AFFILIATION, ALCOHOL AND DRUG USE AND AIDS RISK BEHAVIORS AMONG OPIATE DEPENDENT ADULTS SEEKING TREATMENT

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Whereas religion and spirituality have long been emphasized in drug and alcohol recovery treatment, recent research has suggested spiritual and religious factors should be included in all phases of comprehensive addiction research programs. Religious affiliation (RA) has been found to be a significant protective factor against alcohol and drug abuse, both in adolescent and adult populations. However, the results are mixed. Literature has reported that those with an identified RA were no less likely to have alcohol or drug problems than those with no identified RA. Conversely, others have found that RA is a significant protective factor against alcohol, drug, and tobacco initiation and later problems. Further research is clearly warranted. The present study sought to examine the role of RA in the severity of drug and alcohol problems and amount of AIDS risk behaviors among a population of opiate addicted adults seeking treatment. Participants \((n = 409)\) were assessed at intake to a clinical trial of burenorpine-naloxone and methadone using a demographic survey, the Addiction Severity Index (ASI), Michigan Alcohol Screening Test, Beck Depression Inventory and an AIDS risk behavior questionnaire. Results indicate that subjects reporting affiliation with any religion were equally likely to have severe problems with alcohol or drug use, family or social problems, employment problems, or depression than were those claiming no RA. However, RA did serve as a protective factor against engagement in AIDS Risk behaviors \((t (379) = 3.25, P < 0.001)\). Results suggest that among adults seeking treatment, RA alone does not serve as a protective factor against substance related problems, yet may reduce risk of contracting the HIV virus. Results of whether RA served as a predictor of recovery by examining concordance with 8 and 16 week follow up ASI data will also be presented.

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71 EFFECTIVENESS OF TREATMENT FOR METHAMPHETAMINE USERS: DRUG USE, CRIME, AND EMPLOYMENT OUTCOMES

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Evaluation research has supported the general effectiveness of treatment for substance use, but there is not yet a comprehensive literature on effectiveness of treatment for methamphetamine (MA) use. This paper assesses change in MA use, criminal activities, and employment across three periods: 24-months pre-treatment, during treatment, and 24-months post-treatment. The analysis considers the effect of ‘treatment as usual’ for MA in a large diverse publicly funded county treatment system. A sample of treatment admissions, mostly from 1996, were selected with a stratified random procedure (by gender, race/ethnicity, treatment modality). Data are from an intensive natural history interview for \(n = 349\) conducted in 1998 - 2000. Results from repeated measures analysis of variance show significant reduction in MA use and crime during and following treatment and increased employment following treatment over pre-treatment levels. For example, an average of 42% of months with criminal involvement before treatment reduced to 19% in the post-treatment period. The number of months with MA use dropped from an average 67% of the pre-treatment months to 34% of the post-treatment months. Patterns of change in MA use did not differ by gender or race/ethnicity. Reduction in criminal involvement was slightly more for women than for men. Both MA use and criminal involvement were reduced more during residential than during outpatient treatment. Supplemental regression analyses show lower levels of post-treatment MA use (percentage of months in the 24-month period) related to higher education, greater number of MA-related problems, lower percentage of months with MA use in the pre-treatment period, longer time in treatment, and residential (as compared to outpatient) treatment modality. Results provide a context within which to interpret results.
of other studies of treatment approaches specific to MA use and broadens the literature on treatment effectiveness.

72 CONSUMER PERSPECTIVES ON DUAL DIAGNOSIS TREATMENT

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A series of focus groups was conducted with clients with dual diagnosis to obtain their perspectives on treatment and how it might be improved. About 35 consumers participated in four focus groups. All participants had a dual diagnosis of substance abuse or dependence and serious mental illness. About 94% of the clients were currently receiving treatment for dual diagnosis. Males comprised 66% of the sample. The sample was predominantly Anglo (71%). The average length of services was 7.5 years for mental health and 5.6 years for substance abuse treatment. Their current treatment services included outpatient groups, medication management, methadone maintenance, case management and a day treatment program. Standard focus group methodology was used. Questions focused on three principal areas: their experiences living with mental health and substance abuse issues, positive treatment experiences, and negative treatment experiences. The primary themes that emerged across the four groups included: (1) the importance of client-centered services, (2) medication issues, (3) difficulties navigating complex systems, and (4) mental health/substance abuse treatment integration issues. Client-centered services were described as individualized, flexible, client driven, long-term, team based, and supportive. Medication issues focused on the difficulties encountered in trying to find the right medication and/or dosage and the notable benefits when this is accomplished. Accessibility problems, high staff turnover, poor coordination between systems, fragmentation, and insufficient funding were mentioned as system issues influencing their ability to obtain adequate treatment. A lack of staff cross-training in and integration of substance abuse and mental health treatment provision was discussed. Secondary themes included self-medication of psychiatric symptoms, poor resources, decriminalization of substance use, personal responsibility for managing their illness, and the need for someone with whom to discuss sensitive issues. Providers struggle with how best to treat this population. The current study provides many insights and suggestions for working with this population.

73 HIV AND HEPATITIS RISK ASSESSMENT IN METHADONE-MAIN- TAINED PATIENTS WITH ADULT ADHD: ARE THEY AT HIGHER RISK?

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Research indicates that individuals with poor impulse control are at greater risk of HIV/Hepatitis infection. The primary objective of this study is to investigate if methadone-maintained patients with adult ADHD are more likely to engage in intravenous drug use and sexual behaviors associated with HIV/Hepatitis infection than those without adult ADHD. All participants met DSM-IV criteria for opiate dependence and were on a stable dose of methadone for at least 3 weeks prior to study entry. Participants were interviewed using the DSM-IV SCID and the KSCID for adult ADHD. The presence of risk behavior was determined using the Risk Behavior Assessment (RBA), a structured clinical interview, and the Risk Assessment Battery (RAB), a 29 item self-report measure. At present, 67 participants have completed the study; 33 (49%) have been male, 26 (39%) Caucasian, 23 (34%) Hispanic, 18 (27%) African American; the average age was 42 + 7 years. About 16 (24%) individuals have been diagnosed with adult ADHD. Forty individuals (60%) have reported moderate to high-risk intravenous drug use and/or unsafe sexual practices. A trend of higher rates of risk behaviors has been reported by patients with adult ADHD compared to those without adult ADHD (69 vs. 57%). Individuals with current anxiety and/or affective disorders have had similar rates of risk behaviors compared to those without any current anxiety and/or affective disorders (54 vs. 61%). These preliminary data suggest that comorbid adult ADHD may in fact increase methadone-maintained patients’ chances of engaging in high-risk behavior associated with HIV/Hepatitis infection.

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74 LONGITUDINAL OUTCOME PATTERNS FOR METHADONE PATIENTS

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Treatment outcome patterns over time were examined for 387 methadone patients who completed 1- and 5-year follow-up interviews as part of the national Drug Abuse Treatment Outcome Studies (DATOS). Latent Class Analysis (LCA) identified four groups of patients with distinct patterns over time. These patterns were Immediate Improvement (low drug use and high treatment involvement at both time points), Delayed Improvement (high drug use at Year 1 and low use at Year 5), Substitution (high use of alcohol or drugs other than opiates and cocaine at both time points), and Continued Use (high use of opiates and cocaine at both time points). Immediate Improvement was the most common pattern, and described 59% of the sample. Delayed Improvement and Substitution each characterized 11%, and the remaining 19% showed Continued Use. Patients with Immediate Improvement tended to report fewer background problems at admission and were more satisfied with their DATOS treatment experience. Findings suggest a majority of methadone patients have positive outcomes over an extended period of time, and that treatment participation and satisfaction are central to their success.

75 RESEARCHING PRACTICE/PRACTICING RESEARCH: A QUALITATIVE STUDY OF THE METHAMPHETAMINE TREATMENT PROJECT

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In light of several recent federal initiatives that encourage the integration of research and practice in the field of substance abuse treatment, the need has emerged for a grounded understanding of how such integration takes place and what impact the process of integration has on those implementing changes. This study involved a qualitative investigation of the relationship between research and practice, as experienced by persons working on a clinically-based, multi-site study of methamphetamine treatment called the Methamphetamine Treatment Project (MTP), funded by CSAT. The study examined several components of the research-practice relationship, including the issue of technology transfer, which, in the MTP, was defined as the transfer of a research-generated technology (the Matrix Model) into clinical settings. A total of 85 persons (57 females, 28 males) were interviewed, 35 in one-on-one interviews and 50 in focus group interviews. Persons interviewed were either directly employed by the MTP (n = 77) or were involved administratively (n = 8) with the agencies in which the project was being conducted. The semi-structured interview covered both general perspectives on the relationship between research and practice and perspectives specific to the MTP. Interviews were analyzed utilizing qualitative data analysis software (i.e., ATLAS.ti). The data generated numerous findings. However, this paper will focus on
findings related to varying conceptualizations of ‘outcomes’ and treatment ‘success.’ It is at the intersection of research and practice that these concepts—central to the scientific study of drug treatment—acquire a nebulous quality, as research definitions and practice definitions of success can and do differ. MTP research assistants expressed particular concerns with accurately portraying the clients and their treatment efforts. Participants’ narratives about this issue will be presented within the context of current literature about measuring treatment outcomes. Suggestions will be made as to ways in which a rapprochement between different meaning systems might be achieved.

76 TIME SERIES ANALYSIS OF TREATMENT SYSTEM CHANGES FOLLOWING IMPLEMENTATION OF SAN FRANCISCO’S ‘TREATMENT ON DEMAND’ POLICY

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San Francisco’s substance abuse ‘Treatment on Demand’ initiative, launched in November 1996, provides an opportunity to investigate the effects of a treatment capacity expansion policy on a host treatment system. In this presentation, we use interrupted time series analysis to assess the effect of Treatment on Demand, independent of time, on number of treatment admissions, demographics, types of treatment provided, and proxy measures of treatment outcomes. Administrative data from San Francisco’s Department of Public Health were analyzed for admissions that occurred between FY 95–96 and FY 98–99 (n = 94,744). In these analyses, the number of admissions significantly increased as a function of Treatment on Demand. First-time treatment clients and persons with a primary heroin problem constituted greater proportions of admissions following Treatment on Demand implementation, and Native Americans, homeless persons, and those with a primary cocaine or primary marijuana problem constituted smaller proportions. Treatment on Demand was also associated with a redistribution of admissions among modalities, such that day treatment and methadone detoxification constituted greater proportions of admissions, and front-end treatments, particularly drop-in and central intake unit, constituted smaller proportions following implementation. Finally, Treatment on Demand was independently associated with successful treatment completion, with rates decreasing among day treatment admissions, but increasing among methadone detoxification admissions. Early treatment termination among methadone detoxification admissions also increased. Other changes in demographics, treatment types, and treatment outcomes were observed over the 48-month period, but these were functions of time and were not independently associated with Treatment on Demand.

77 CLONING OF A NOVEL VARIANT OF THE VESICULAR MONOAMINE TRANSPORTER-2 FROM PRIMATE BRAIN: RELEVANCE TO PSYCHOSTIMULANT EFFECTS

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Plasmalemmal membrane transporters, (i.e. dopamine, serotonin and norepinephrine transporters) sequester extracellular monoamines into neurons. Psychostimulant drugs of abuse (i.e. amphetamines and cocaine) modify the function of these transporters. The vesicular monoamine transporter-2 (VMAT-2), which sequesters monoamines into vesicles for storage and subsequent release, is also altered following psychostimulant (cocaine or amphetamines) treatment. The VMAT-2 gene is highly conserved between species but sequence variations within the coding and noncoding regions of the VMAT-2 gene exist. The relevance of these variants to VMAT-2 function and drug response or addiction is unknown. As non-human primates are widely used to investigate parameters of psychostimulant abuse, we explored whether variants in the VMAT-2 gene are expressed in non-human primates. Using RT-PCR, we isolated and sequenced a novel exon 2 splice variant of VMAT-2 from the substantia nigra of rhesus monkey (Macaca mulatta) brain. This clone shares a 96% homology to the human VMAT-2 coding region but lacks the start codon (within exon 2) used for the full-length VMAT-2 protein. Use of a potential alternative start codon in exon three would result in a predicted truncated VMAT-2 protein which lacks transmembrane region 1 and a portion of the large intravesicular loop. Current investigations focus on: (1) determining whether this alternative start codon is utilized, (2) determining if this variant exists in humans, and (3) the functional relevance of this variant. The discovery of a VMAT-2 splice variant may help to clarify VMAT-2 function and expands the possible mechanisms by which psychostimulants modify monoamine neurotransmission.

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78 THE USE OF NELFIVANIR AND TWO NUCLEOSIDES CONCOMITANTLY WITH METHADONE IS EFFECTIVE AND WELL-TOLERATED IN HEP C CO-INFECTED PATIENTS


Background: Many HIV-1 infected patients in our clinics are being treated with methadone (MTH) for drug addiction management. Many of these patients are also co-infected with HepC (co-HepC). The decision for ARV treatment regimens is difficult in these patients as most treatment options have side effects, including hepatic toxicity, and require MTH dosage adjustments. The use of NFV as part of a treatment regimen has been found to be very effective and tolerable in this population. Diarrhea is the most common side effect with NFV. MTH has been shown to have a constipating effect. We wanted to look at both the incidence of diarrhea and MTH dosage adjustments in patients treated with NFV and MTH, and safety of NFV in co-HepC. Methods: In this multi-site retrospective study we identified eligible patients through a systematic screening of medical records. We included patients treated with both NFV and MTH. We reviewed patient records for MTH dosage adjustments during treatment. We recorded viral load, CD4 changes and duration of therapy. Results: Data are available for 32 patients identified thus far from 2 of 7 of our community-based clinics. The cohort is 59% male, 63% African-American, 37% Latino and 84% co-HepC. Of 32 patients, 29 had been on a stable dose of MTH for 30 days or longer. Only 2 patients of 29 (7%) reported NFV-related diarrhea, both were moderate cases. The mean length of treatment with NFV was 22 months. 29 (7%) reported NFV-related diarrhea, both were moderate cases. None of these patients required MTH dosage adjustments.

79 LOCOMOTOR SENSITIZATION AND 5HT2C RECEPTOR HYPOSENSITIVITY FOLLOWING REPEATED ADMINISTRATION OF 3,4 METHYLENEDIOXYMETHAMPHETAMINE (+/-MDMA)

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Serotonin (5-HT) released by (+)-MDMA stimulates 5-HT2C receptors (5-HT2CR) to exert a strong inhibitory influence on acute (+)-MDMA-evoked hyperactivity as evidenced by the fact that 5-HT2CR antagonists greatly enhance this behavior. In the present experiment, we analyzed whether a repeated, intermittent regimen of (+)-MDMA (4 mg/kg per day, SC, 7 days) would result in behavioral sensitization to (+)-MDMA simultaneously with a functional down-regulation of the 5-HT2CR. Male Sprague–Dawley rats (N = 94) were pretreated with saline (1 ml/kg per day, SC, 7 days) or (+)-MDMA (4 mg/kg per day, SC, 7 days). At 24 or 72 h following the last injection, locomotor activity was measured upon challenge with either saline (1 ml/kg, SC), (+)-MDMA (4 mg/kg, SC), or the 5-HT2CR agonist MK 212 (2 mg/kg, SC). At both 24 and 72 h withdrawal, (+)-MDMA elicited hyperactivity, while MK 212 suppressed locomotion in saline-treated rats (P < 0.05). At 24 h withdrawal, rats exposed to the (+)-MDMA regimen expressed greater (+)-MDMA-evoked hyperactivity relative to saline-treated controls (P < 0.05). This sensitization was associated with a loss of 5-HT2CR responsivity as (+)-MDMA-treated rats displayed tolerance to MK 212-induced locomotor suppression (P < 0.05). At 72 h withdrawal, sensitization to MDMA-evoked activity was also expressed (P < 0.05), albeit diminished compared to the 24 h withdrawal time point. A functional recovery of 5-HT2CR sensitivity 72 h after treatment cessation is suggested by the observation that MK 212-induced locomotor suppression did not differ between saline- and (+)-MDMA-treated rats at this time point. The present results suggest that down regulation of 5-HT2CR may trigger or contribute to the cascade of mechanisms that account for behavioral sensitization to (+)-MDMA.

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80 Social influences and risk-taking behavior among adolescent cannabis users


Risk factors for adolescent substance abusers are many and varied and often interact in a circular manner to escalate drug use and the problems associated with drug use. Social influences as risk factors may include frequency of drug use, influence of friends, and poor school performance. The interrelationship between cannabis use, deviance, and risk-taking behavior is examined in this paper. Adolescents of the Cannabis Youth Treatment Study (N = 600) were asked which of 18 behaviors (other than drug use) they participated in during the past year that may have gotten them into trouble or been against the law. These behaviors ranged from being a member of a gang, taking something from a store without paying for it, to intentionally setting a building, car or other property on fire, or being involved in the death or murder of another person. The baseline responses were dichotomized into two groups of crime (54% committed two or more behaviors) and non-crime (44% committed none or 1 behavior; 2% invalid). Compared to the non-crime group, the crime group had a higher percentage of males (P = 0.012), a higher substance use frequency (P < 0.005), were more influenced by friends (P < 0.0001), and had lower grades in school (P < 0.017). These findings point to the complex challenge of treating adolescents for social influences and risk-taking behaviors in addition to ‘just drug use’.

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81 Symptoms and signs of nicotine withdrawal in smokers: a placebo control study

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Cigarette-abstinent smokers often describe aversive withdrawal symptoms associated with the abstinence period; these symptoms are often accompanied by physiological signs (e.g., HR decrease). These symptoms and signs are attributed to nicotine withdrawal, though most studies examining them have not used a placebo control design (i.e., a denicotinized cig condition). A lack of a placebo design means that some symptoms and/or signs associated with tobacco abstinence may be mislabeled as nicotine withdrawal. This potential mislabeling may mean that some symptoms are treated ineffectively with nicotine replacement therapy. This study’s goal was to evaluate the symptoms and signs of nicotine withdrawal in smokers under placebo-control conditions so that nicotine withdrawal might be identified accurately. About 30 smokers (18 men, >15 cig/day for the past 2 yr), participated in this three condition, within-subject, outpatient, placebo control study. About 5-day conditions (denicotinized, nicotinized, or no cigs) lasted Mon–Fri, were Latin-square ordered, and were separated by a minimum 72 h washout period. Payment ($400) was contingent on compliance, monitored daily with CO and cig butt counts and thrice-weekly with urine cotinine. Subjective withdrawal ratings and resting HR were recorded daily. Preliminary analyses indicate that difficulty concentrating, restlessness, and impatience are more likely symptoms of tobacco abstinence (i.e., suppressed in the denicotinized cig condition), while other symptoms (urge to smoke, hunger, desire for sweets, irritability/frustration/anger) are more likely symptoms of tobacco abstinence (i.e., suppressed in the denicotinized cig condition). HR decreased in the denicotinized cigarette and no smoking conditions, and thus is likely a sign of nicotine withdrawal. These results indicate that nicotine withdrawal may underlie some but not all symptoms reported during tobacco abstinence. Development of non-nicotine interventions for tobacco cessation should focus on those symptoms not attributable to nicotine withdrawal.

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82 Onset, magnitude, and duration of abstinence effects following heavy marijuana use

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Abstinence effects following marijuana smoking or oral THC administration have been well documented. This paper provides information on the reliability of specific effects, as well as time of onset, magnitude, and duration of such effects. A 50-day study assessed daily marijuana users (N = 21) during a 5-day baseline (smoking as usual) period and a 45-day marijuana abstinence period. Data were collected daily via use of an Interactive Voice Response telephone system and twice weekly during laboratory visits. A control group of 11 ex-marijuana smokers provided the same assessment data during the study period. Planned contrasts were performed comparing mean withdrawal effect scores during the baseline period with 15, 3-day abstinence period segments. During the abstinence period, the effects and symptoms that changed significantly from baseline included: irritability, restlessness, nervousness, shakiness, anger and aggression, sleep difficulty, strange dreams, sweating, decreased appetite, weight loss, and stomach pain. The onset of most effects occurred 2–4 days after the initiation of abstinence. Time of peak severity was observed between days 2 and 4, with most symptoms peaking around day 4. The mean increase of symptom peak effects ranged from 1.2 to 2.5 points on a 0–3 point scale (none, mild, moderate, severe). Most effects returned to baseline levels by the end of the second week of abstinence, although some effects such as strange dreams remained elevated throughout the study. 67% of marijuana users experienced four or more symptoms (symptom defined as an increase of >1 point on the 0–3 point scale). These data replicate and extend prior findings showing that a clinically significant withdrawal syndrome occurs in a subset of regular marijuana users. The study also
provides initial information on the parameters of the timecourse and severity of this syndrome. Studies with a wider range of marijuana users and larger sample sizes are needed to better determine the incidence of the syndrome and its specific effects.

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83 Predictors of 12-month return-to-custody among male and female parolees from prison-based therapeutic community substance abuse programs

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The purpose of this study is to determine differential predictors of recidivism among male and female parolees from prison-based therapeutic community (TC) substance abuse programs (SAPs). The current initiative in California to provide TC treatment to prison inmates is the largest of its kind in the nation, if not the world. It also represents the largest effort to date to provide TC treatment to females inmates. Previously, most prison-based TC treatment programs treated only male inmates, and thus have yielded findings that might be considered male-specific. This study seeks to separately identify and then compare factors that predict 12-month return-to-custody (RTC) rates for male and female parolees from prison-based TC SAPs. Intake assessment data was collected on selected demographic, psychosocial, substance use, and criminal history variables from male and female inmates entering 15 prison-based TC SAPs in California as part of a 5-year process evaluation of these programs. RTC data on parolees was obtained from the Offender Based Information System (OBIS) maintained by the California Department of Corrections. Preliminary analyses on 3600 parolees (1400 males, 2200 females) indicated that female parolees were returned to custody at a significantly lower rate than males (16 and 27%, respectively). However, this was due primarily to a significant difference between all female parolees and male parolees from higher-security male prisons (16 and 43%, respectively). Separate logistic regression analyses will be performed to determine if predictors of 12-month RTC among male parolees (and specifically among high-security male parolees) differ from predictors of 12-month RTC among female parolees from prison-based TC SAPs. The results of this study may provide valuable information to treatment providers with respect to developing curricula that more directly address the unique needs of both male and female inmates in these programs.

84 The modulating effects of alcohol on cocaine-induced place preferences

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Cocaine and alcohol continue to be one of the most highly abused polydrug combinations. Behavioral and physiological evidence suggests that combining alcohol with cocaine may modulate the effects produced by cocaine alone. To assess whether such modulation is evident in a measure of cocaine’s affective properties, the present study examined the effects of a low and high dose of alcohol on cocaine-induced conditioned place preferences (CPP). In the low-dose alcohol analysis, three groups of male Sprague–Dawley (SD) rats (n = 16/group) were injected IP either with 20 mg/kg cocaine, 0.5 g/kg alcohol or the cocaine/alcohol combination. In the high-dose alcohol analysis, three groups of male SD rats (n = 16/group) were injected IP either with 20 mg/kg cocaine, 1.5 g/kg alcohol or the cocaine/alcohol combination. Immediately after injection, animals were restricted for 30 min to a distinctive compartment (CS+) of a place preference chamber. On the following day, subjects were injected with the vehicle and restricted to the other side (CS−) of the chamber. This procedure was repeated for a total of four conditioning cycles. Following conditioning, subjects were given 15-min free access to the entire chamber in order to assess their compartment preference. Both groups of animals injected with cocaine displayed a significant preference for the CS+ compartment. Both groups of animals injected with alcohol failed to show a conditioned effect. However, when a low dose of alcohol was combined with cocaine, animals injected with the combination failed to display a significant CPP and spent an amount of time in each compartment that was the exact numerical average of the cocaine and alcohol alone effect. When a high dose of alcohol was combined with cocaine, the cocaine-induced CPP was further attenuated, with the combination producing an effect that was indistinguishable from the effect produced by alcohol alone. Taken together, this evidence suggests that alcohol can modulate the affective properties of cocaine and that this effect is dose dependent.

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85 Peripheral selectivity and apparent efficacy of dynorphins and non-peptidic κ-opioid agonists in rhesus monkeys

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The present studies tested the hypothesis that the dynorphins act as high efficacy, peripherally selective agonists at the proposed ‘κ1’ subtype opioid receptor in non-human primates. This hypothesis was tested in rhesus monkeys trained to discriminate the proposed ‘κ1’ agonist U69593 from vehicle (n = 3) in a food reinforced operant procedure (a presumed centrally-mediated effect). The same hypothesis was tested in a neuroendocrine biomarker assay in intact female rhesus monkeys (prolactin release; n = 4). This neuroendocrine effect may be mediated by opioid receptors in the hypothalamus, and these receptors may lie functionally outside the blood-brain barrier. All testing was completed using a single-dose (time course) design, in order to enhance the comparability of findings across assays and across compounds. Non-peptidic κappa-agonists (U69 593 and bremazocine; 0.001–0.01 mg/kg, s.c.) were generalized in all subjects trained to discriminate U69 593. In contrast, dynorphin A (1–17) and the stable dynorphin A (1–8) analog, E2078 (0.1–1 mg/kg, i.v.) were not fully generalized. In contrast, all the above peptidic and non-peptidic opioids produced potent (e.g., 0.001–0.01 mg/kg) and dose-dependent prolactin release, with sigmoidal dose-effect curves. These dose-effect curves were surmountably antagonized by naltrexone (0.1 or 0.32 mg/kg, s.c.), consistent with mediation by kappa opioid receptors. Furthermore, the neuroendocrine effect of E2078 (0.0032 mg/kg) was partially blocked by the ‘peripherally selective’ opioid antagonist quaternary naltrexone (0.32 mg/kg, s.c.). Overall, the present studies are consistent with the hypothesis that the dynorphins are high efficacy kappa opioid agonists in primates in vivo, although they may act as peripherally selective compounds following parenteral administration.

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86 Polysaturated fatty acids and relapse vulnerability in cocaine addicts


Introduction: There is mounting evidence that low plasma levels of some polysaturated fatty acids (PUFAs) are associated with several
psychiatric disorders, including affective and aggression disorders. PUFAs status could also influence the risk of relapse to the abuse of substances through actions on central serotonergic and dopaminergic systems, known to play a role in reward mechanisms. Methods: PUFAs status was assessed among 38 cocaine dependent subjects only at baseline, 2 weeks after admission to an inpatient unit. Resumption of substance use was assessed 3, 6 and 12 months following discharge. Results: Of the 32 patients who remained available for follow-up after 12 months, 12 had relapsed. Subjects relapsing at 3 months had significantly lower baseline levels of total n-6 PUFAs, total n-3 PUFAs and arachidonic acid (AA, 20: 4n6) when compared to non-relapsers by ANCOVAs with age and weight as covariates. Lower baseline total n-6 PUFAs and AA were still predictive of relapse 6 and 12 months following discharge. Baseline PUFAs levels were better predictors of relapse than patients’ age, marital status, educational level, cocaine use parameters or psychopathology that were not significantly different when patient groups were compared. Conclusions: Low levels of n-6 and n-3 PUFAs as measured in cocaine addicts during inpatient admission predicted relapse after their discharge. These data suggest, but do not prove, a causal relationship between n-6 and n-3 status and relapse vulnerability but provide a rationale to explore relationships between addictive disorders and PUFAs status in observational and interventional trials.

87 CEREBRAL BLOOD FLOW OF COCAINE ABUSERS DURING CONFINEMENT AND AFTER RELAPSE

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This study examined the direct effects of repeated cocaine exposure and withdrawal on cerebrovascular function. A double-blind, multi-day, repeated dose, within-subject design was used. Cocaine dependent volunteers (n = 9) resided as inpatients for 6 weeks and were studied during 4-day bouts of cocaine exposure (175 mg, p.o. given five times at 1-h intervals) and during 28 days of withdrawal. Blood flow velocity was recorded from the anterior and middle cerebral arteries using transcranial Doppler sonography as follows: after 4 days of abstinence, on Days 1 and 4 of dosing, and on Days 1, 10 and 28 of withdrawal. Arterial systolic and diastolic velocities were elevated (P < 0.05) on the fourth, but not first, day of cocaine administration and on the first day of abstinence only. Pulsatility index for each artery was not affected during cocaine administration, but increased (P < 0.05) during early abstinence. These data suggest that cocaine constriction of the large cerebral arteries may increase with repeated dosing. Cocaine withdrawal leads to increased resistance (i.e., increased pulsatility) in distal vessels; this is most profound during early abstinence. These results help to explain the increased risk of stroke in cocaine abusers.

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88 DECREASED COCAINE SELF-ADMINISTRATION IN DOPAMINE D-1 RECEPTOR KNOCKOUT MICE

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We tested the hypothesis that mutant mice that lack the dopamine D1 receptor are abnormal in their cocaine self-administration behavior. We studied responding maintained by various concentrations of liquid food as well as various doses of i.v. cocaine to evaluate both general operant performance and the reinforcing effects of cocaine. Adult mice (C57BL/6 × 129Sv) were mildly food-restricted to maintain stable body weight but had water freely available. Behavior in one of two nose-poke holes was maintained by liquid food under a FR 1 schedule of reinforcement. Nose pokes in the active hole selectively increased over the first five sessions and food maintained significantly higher rates of responding than water in both groups of mice (P = 0.16–0.19). However, compared with wild types, levels of nose poke behavior maintained by all concentrations of food were lower in D-1 mutants.

When i.v. cocaine injections were available (1.0 mg/kg per injection), all 19 wild type mice self-administered a minimum of 20 mg/kg per session and levels of drug intake stabilized across sessions, whereas only two of 16 D-1 mutant mice met these criteria for drug self-administration. Varying the cocaine dose produced an inverted U-shaped dose-effect function in wild type mice. In contrast, cocaine dose-effect functions in D1 mutants were flat, even in the two mutants that initially met criteria for cocaine self-administration. When food and cocaine (0.32–3.2 mg/kg per injection) were available in alternate test sessions in D-1 mutant mice, food consistently maintained behavior greater than water but cocaine did not maintain behavior greater than saline injections. These results suggest that D1 mutant mice have deficits in operant performance and also that the reinforcing effects of cocaine are diminished in these mice.

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89 THE SF-36V AND THE ADDICTION SEVERITY INDEX TAP SIMILAR CONSTRUCTS


Objectives: The Veterans SF-36 (SF-36V) is the VA’s most widely used measure of health-related quality of life, whereas the Addiction Severity Index (ASI) is the VA’s mandated measure of functional status for patients in substance dependence treatment. This study examines the concurrent validity of selected composite scores of the ASI and the SF-36V. We hypothesized the ASI medical and psychiatric composite scores would correlate reliably with the corresponding SF-36V subscales and summary components. Methods: As part of a clinical trial comparing integrated versus referral models of primary care for veterans in substance dependent treatment, 269 veterans were assessed at treatment admission. Inclusion criteria were self-report of a chronic medical condition or screening positive for an asymptomatic medical condition. Correlations were performed between ASI composite scores (higher scores indicate worse functional status) and SF-36V scales and summary components (lower scores indicate worse functional status). Results: Of the 269 participants recruited, 236 (88%) completed data for all SF-36V and ASI scales. The ASI Medical Composite Score (mean = 0.52; S.D. 0.38) demonstrated robust inverse correlations with SF-36V scales that related to physical health including Physical Functioning (r = −0.57), Role Physical (r = −0.65), Bodily Pain (r = −0.67), General Health (r = −0.59), and the Physical Component Summary (r = −0.66; all P’s < 0.001). It correlated less strongly with other SF-36V scales. The ASI Psychiatric Composite Score (mean = 0.44; S.D. 0.24) had robust inverse correlations with SF-36V scales related to mental health including Vitality (r = −0.64), Role Emotional (r = −0.69), Mental Health (r = −0.76), and the Mental Component Summary (r = −0.76; all P’s < 0.001). It correlated less strongly with other SF-36V scales. Conclusions: The ASI Medical Composite Score accounted for 32–44% of the variance in SF-36V physical functioning scales, and the ASI Psychiatric Composite Score accounted for 41–58% of the variance in SF-36V mental health scales.
90 COMORBIDITY AND CRAVING FOR CRACK

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Numerous investigators have reported comorbidity of psychiatric diagnoses with cocaine dependence, and cocaine withdrawal is commonly accompanied by symptoms of affective disorders which may persist for weeks. There is little consensus about the clinical significance and management of these symptoms. Craving for cocaine also may be associated with symptoms suggestive of affective and anxiety disorders; recurrence of anhedonic and dysphoric emotional states has been described as predictor of relapse. We examined the relationship of craving as reflected on the Halikas Drug Impairment Rating Scale (HAL-DIRS) with presence of DSM-IV diagnoses and symptoms of affective disorders. The sample consisted of subjects participating in a pharmacotherapy trial in a community treatment program \((N = 144)\). Structured Psychiatric Diagnostic Interview, Addiction Severity Index, HAL-DIRS and Beck Depression scales were given at baseline; HAL-DIRS and Beck scales were repeated weekly for 8 weeks. Because significant difference was not demonstrated among the medication groups, subjects were combined for this analysis. Comparisons of subjects without comorbidity \((N = 20)\); with antisocial personality disorder only \((N = 23)\); affective disorder only \((N = 36)\) and both ASP and depression \((N = 64)\) suggest that lifetime comorbidity does not predict craving severity. Results of interval comparisons of craving items, current affective symptoms, and comorbid diagnosis will be presented.

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91 IMPROVEMENT IN LIVER FUNCTION TESTS DURING TREATMENT FOR METHAMPHETAMINE ABUSE

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Many patients entering treatment for methamphetamine dependence have evidence of mild to moderate liver damage as indicated by elevated serum enzyme levels (alkaline phosphatase, SGOT, SGPT, and GGT). This report presents data on change in liver function tests observed over the course of treatment for methamphetamine dependence. Data were collected in several clinical trials utilizing one or more of the following treatment strategies; relapse prevention, contingency management, and placebo controlled medication trials. The results from these studies were pooled for analyses. Data were grouped by treatment outcome, which was defined as being successful (i.e., provided a urine sample which was methamphetamine negative at the first follow up interview) or unsuccessful (i.e., provided a urine sample which was methamphetamine positive at the first follow up interview). Our findings suggest that participants with mild to moderate liver damage at intake who successfully completed the treatment program evidence some recovery of liver function. Conversely, participants who had an unsuccessful treatment episode showed essentially no improvement in liver function tests. These results suggest that successful treatment for methamphetamine dependence may improve liver function.

92 TOBACCO AND DEPRESSION, EVIDENCE FROM CHILE

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AIM: Martini et al. (in press) describe a tobacco-depression gradient based on recent US surveys of adolescents, with highest, lower, and lowest depression among current, former, and never smokers, respectively. They also speculate that this relationship might be due to smoking-associated stigma and self-esteem problems associated with failed efforts to quit. We use the Martini et al. method to re-examine the tobacco-depression association in Chile, where youth smoking rates are very high and there is little social stigma attached to teen smoking. DATA: The data are from a nationally representative sample survey of school-attending youths in Chile, conducted in 1999, with multi-item sets used to assess current (past 30 days), former, and never smoking status, as well as depressed mood \((x = 0.7)\), and other characteristics. RESULTS: Among 46,908 students in the sample, an estimated 43% were current smokers, 17% former smokers, and 40% never smoked. Multiple logistic regression with variances corrected for design effects showed a tobacco-depression gradient like the one recently reported, with current smokers most likely to have recent depressive symptoms (estimated odds ratio, \(OR = 1.5\); \(P < 0.01\)), and former smokers intermediate \((OR = 1.2; P < 0.01)\), as compared to never smokers. Statistical adjustment for male-female differences, and use of alcohol and/or marijuana, did not change these estimates appreciably. DISCUSSION: The observed tobacco-depression gradient is reproduced in these epidemiological survey data from Chile, where teen smoking is more prevalent and less of a social stigma than in the US. Future prospectively gathered study data can clarify the causal ordering of tobacco smoking and depression, with direct measurements of social stigma and self-worth associated with failed efforts to quit.

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93 CHANGES IN CHARACTERISTICS OF INDIVIDUALS SEEKING SUBSTANCE ABUSE TREATMENT AFTER THE SEPTEMBER 11TH TERRORIST ATTACKS

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There has been high profile speculation that the September 11th terrorist attacks produced substance abuse and psychiatric problems among individuals who did not previously have such disorders. The Drug Evaluation Network System (DENS) is an ongoing electronic system providing Addiction Severity Index information on patients entering substance abuse treatment programs \((N = 48)\) in seven cities. Thus, DENS provided a unique opportunity to compare the nature and severity of substance use and other problems of patients admitted in the 3 months before 9/11 \((n = 1552)\) and after 9/11 \((n = 1544)\). We did not see an increase in the volume of admissions. There was a significant difference between the two groups \((MANOVA, P < 0.001)\) using ASI composite scores, although the magnitude of these differences was small. There were significantly lower scores \((P < 0.05)\) and less in medical and employment domains, and marginally significantly lower scores \((P < 0.08\) or less) in drug and psychological domains for the post-9/11 group. There were no differences in the alcohol, legal, and family domains. To this point there is no indication of extreme differences in the substance use or personal health problems of patients in this sample. By June, analyses will be available for 6-month pre-post comparisons as well as a separate analysis of NY area admissions.
94 DOES REINFORCEMENT DENSITY MODERATE THE EFFECTS OF PHARMACOTHERAPY FOR DEPRESSION IN METHADONE-MAINTAINED OPIATE-DEPENDENT PATIENTS!

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The pharmacological treatment of depressive disorders has shown considerable efficacy among substance abusers. However, treatment mediated changes in depression have not been consistently related to reductions in illicit substance use. Behavioral theories of choice stipulate that the presence of alternative competing reinforcers and the environmental constraints on their accessibility are important factors in determining illicit substance use. Similarly, behavioral treatments of depression highlight the importance of contacting natural reinforcers in the environment to promote change. Thus, environments with a high density of alternative reinforcers to drug use should facilitate improvement in substance use and depressive disorders. This study tested the moderating effect of reinforcement density on the pharmacological treatment of depressive disorders among methadone-maintained opiate dependent patients. About 95 methadone-maintained opiate dependent patients (59 males; 47 females) were randomized in a 12-week, double blind, placebo controlled trial of Sertraline (Placebo n = 47; Sertraline n = 48). All patients met DSM-III-R criteria for a depressive disorder, demonstrated a clinically significant level of depression at baseline (HAM-D: M = 20.9; S.D. = 4.8), and were assessed weekly for depression severity and substance use. Sertraline, or identical appearing placebo, was advanced in a fixed-flexible schedule to four pills (200 mg/day) or maximum tolerated dose. Of the 95 patients randomized, 74% (Placebo = 81%; Sertraline = 67%) completed the 12-week study. It was predicted that the combined effect of a high density of reinforcers at baseline and active antidepressant medication will yield the greatest rate of change in depression and substance use. These findings may highlight the conditions in which pharmacological interventions are most efficacious for treating this comorbid population.

95 COCAINE AND HEROIN SELF-ADMINISTRATION IN RATS BRED FOR SACCHARIN PREFERENCE: SEX DIFFERENCES

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Rats selectively bred for high (HiS) and low (LoS) intake of a saccharin solution were compared on their rate and success of acquisition of i.v. cocaine and heroin self-administration. It was hypothesized that saccharin preference may be a predictor of drug self-administration. Rats were trained to self-administer i.v. cocaine and heroin under a fixed-ratio 1 (FR 1) schedule, and cocaine-reinforced behavior was examined under a progressive-ratio (PR) schedule. There were 4 cocaine (0.2 mg/kg) groups (HiS males and females and LoS males and females) and another set of 4 heroin (0.015 mg/kg) groups. Rats were allowed 30 days to reach a criterion of 100 (cocaine) or 20 (heroin) infusions/day during 6-h sessions for 5 days. The HiS females acquired cocaine self-administration more rapidly than the LoS females, and females of both phenotypes met the acquisition criteria more rapidly than males. In both HiS and LoS cocaine groups a greater percentage of females (vs. males) met the acquisition criteria within 30 days. The female (vs. male) heroin groups showed a more rapid rate of acquisition, but there was no difference due to saccharin phenotype. All of the heroin groups met the criteria within 30 days. There were higher break points on the PR schedule in HiS females versus males, but no differences in females due to phenotype. In conclusion, HiS female rats show more rapid and successful acquisition of i.v. self-administration of a low dose of cocaine than LoS rats. Female rats (vs. males) consistently showed accelerated rates of acquisition and maintenance (PK) of cocaine self-administration and acquisition of heroin self-administration.

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96 CROSS-SECTIONAL COMPARISON OF OPIOID- AND COCAINE-DEPENDENT INDIVIDUALS WITH AND WITHOUT PHYSIOLOGICAL DEPENDENCE TO COCAINE

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The present study examined the relevance of physiological dependence to cocaine for 719 individuals diagnosed with current opioid and cocaine dependence upon admission to a treatment research program. Individuals completed the Structured Clinical Inventory for the DSM-IV and the Addiction Severity Index (ASI). Participants were classified for separate analyses using a two group design (Physiological Dependence (n = 551) and No Physiological Dependence (n = 168)) and a three group design (Withdrawal (physiological dependence with withdrawal; n = 336), Tolerance Only (physiological dependence without withdrawal; n = 215), and No Physiological Dependence (n = 168)). Study groups were compared for differences in rates of substance use disorders, nonsubstance use psychiatric disorders, and ASI scores. The results showed that the Physiological Dependence group exhibited more frequent cocaine use in the past 30 days, higher ASI Medical and Drug Use composite scores, and higher lifetime rates of alcohol, cannabis, sedative, stimulant, and hallucinogen dependence, than the No Physiological Dependence group. The Withdrawal group also had higher ASI Psychiatric composite scores, and higher current and lifetime rates of both major depressive disorder and posttraumatic stress disorder than the Tolerance and No Physiological Dependence groups. These findings indicate that physiological dependence to cocaine was associated with more severe problems, and that those who reported cocaine-related withdrawal exhibited the highest rates of substance use and psychiatric impairment.

97 IDENTIFICATION OF NEW POTENTIAL LIGANDS FOR GHB RECEPTOR SITES USING [3H]NCS-382 AS A RADIOLIGAND

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Gamma-hydroxybutyrate (GHB), an endogenous metabolite of gamma-aminobutyric acid (GABA), acts as an inhibitory neurotransmitter or neuromodulator in the brain. Often classified as a ‘club drug,’ GHB is commonly abused in combination with alcohol, and is also used as a ‘date-rape’ drug due to its potent amnesic effects. The exact molecular mechanisms of GHB are unclear, however GHB binds to low-affinity and high-affinity sites in cerebral cortex and hippocampus. An analog of GHB, NCS-382 (a GHB antagonist) exhibits specific binding to GHB receptors in rat brain and displaces [3H]GHB with an affinity approximately ten times greater than GHB in hippocampus and cerebral cortex (Mehta et. al., JPET 2001, 299:1148-53). Recently we have also demonstrated that baclofen and GABA inhibit approximately 25% of specific [3H]NCS-382 binding in rat brain. In this study we examined potential selective ligands for the GHB receptor using [3H]NCS-382 as a radioligand. GHB and 4-phenyl-GHB displaced [3H]NCS-382 binding in a concentration-dependent manner. In contrast, 4-methyl-GHB, 5-hydroxypentanoic acid, and 4-dimethyl-GHB partially inhibited [3H]NCS-382 binding (~ 80%). GHB metabolites 1,4 butanediol, 1,5 pentanediol, and gamma-butyrolactone did
accompanied by arousal as measured by subjecti
groups increase their preference for alcohol in response to the alcohol
experimental e
98 EMOTIONAL CONTROL OF ALCOHOL AND ALPRAZOLAM PREFER-
ence in PTSD
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Many patients with posttraumatic stress disorder (PTSD) use alcohol
and benzodiazepines and express self-medication motives for their use.
This laboratory study experimentally examines the effects of emotional
states on preference for alcohol and alprazolam in alcohol users who
have experienced trauma. PTSD and control subjects who experienced
trauma without developing PTSD are initially exposed to letter-coded
doses of alcohol, alprazolam and placebo under double-blind, double-
dummy conditions. On four subsequent days, emotions are induced
using the following procedures: (1) a trauma script induces anxiety; (2)
the Point Subtraction Aggression Paradigm (PSAP) elicits aggressive
behavior and anger; (3) a neutral script based on a nonalcohol-
associated relaxing event reduces arousal and negative affect; and (4)
exposure to an alcohol cue consisting of preparing, smelling, and
tasting the subject’s favorite alcohol beverage induces cue-craving.
After performing each emotion-inducing procedure, subjects express
their preference for letter-coded alcohol, alprazolam and placebo using
the Multiple Choice Questionnaire (MCQ), which allows subjects to
assign a monetary value to each drug by indicating a preference
between each letter-coded drug and varying amounts of money. Each
administration of the MCQ is reinforced by immediately delivering the
preferred letter-coded drug or amount of money chosen in a randomly
selected response to the MCQ. Preliminary results indicate that PTSD
subjects show an increased preference for sedatives following exposure
to the trauma script and the PSAP relative to control subjects. Both
groups increase their preference for alcohol in response to the alcohol
cue. The anxiety and angry emotional states induced in this study are
accompanied by arousal as measured by subjective reports and
increases in heart rate and skin conductance. These findings provide
experimental evidence that distressing and angry emotions affect
preference for sedative medications in PTSD and support the self-
medication hypothesis of drug use.

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99 IMPACT OF THE FDA LAAM LABELING WARNING OF A VA
NARCOTIC TREATMENT PROGRAM IN NEW YORK CITY
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LAAM has been extensively studied since the 1970’s and in July 1994
was approved by the Food and Drug Administration (FDA) for
maintenance treatment of opiate dependence. The New York VA Clinic has been using LAAM as an alternative to methadone since
October 1994 and it has proven as safe and effective as methadone and
been readily accepted by patients. We have treated over 1000 patients
with no significant adverse effects. We have also used LAAM as a
heroin detoxification agent and we have recently initiated take-out
doses of LAAM for highly functional rehabilitated patients who
require maintenance treatment. Because it is given only in the Clinic to
all but a few, the diversion and stigma associated with methadone has
been eliminated. In November 2000, the American Methadone
Treatment Association (AMTA) issued guidelines on the use of
LAAM based on reports of death from torsade de pointes, associated
with prolonged QTc interval. We reviewed our patients’ clinical status
and found no adverse events were occurring with LAAM use, but we
moved to implement these guidelines to the extent possible. In April
2001 Roxane Pharmaceuticals and the FDA issued a black box
warning that advised using LAAM as a second line treatment for
patients who did not respond to methadone. We informed our patient
population of this warning and indicted that we would be evaluating
their cardiograms. There was no panic or rush to transfer to
methadone. We have reviewed these EKGs and over the past several
months we have transferred patients with a QTc interval over 450 to
methadone. This process is ongoing. Some patients have requested
to remain on LAAM, have signed consent to remain on LAAM, as they
believe that increasing their clinic visits, or using methadone will lead
hardship or to relapse. This presentation will overview our current
experience, patient satisfaction after transfer to methadone, requests to
return to LAAM, stabilization on methadone and staff issues related
to this transfer.

100 PAIN TOLERANCE IN ADOLESCENTS: EFFECTS OF TOBACCO USE
AND GENDER
D. Cavallo, C. Pearson, T. Dahl, E. Lavelle, R. Wu, S. McKee, T.P.
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Understanding factors that mediate maintenance of smoking in
adolescents is the key to developing better smoking cessation programs
for this population. In adult smokers, it has been suggested that the
avoidance of negative states like pain and anxiety may play a
significant role in maintaining smoking behavior. Previous studies
with adult smokers have demonstrated the ability of nicotine to
decrease sensitivity to pain in males, but the effect has been less
evident in females. This study will present a preliminary evaluation of
pain tolerance in male and female adolescent smokers and nonsmok-
ers. About 62 subjects, 34 nonsmokers and 28 smokers, participated
in two separate sessions at the Children’s Clinical Research Center
(CCRC) of Yale-New Haven Hospital. Smokers continued to smoke
prior to the first outpatient nonabstinent session, but were abstinent
from cigarettes for 42 h prior to the second inpatient abstinence
session. Pain tolerance was evaluated in both sessions using the cold-
pressor task, in which subjects were asked to place their dominant
hand in a bucket of cold water (0-3°C) for a period of 90 s. They
were told that they could remove their hand from the water if and
when they could no longer endure the pain (pain tolerance). A
preliminary analysis of the pain tolerance data indicates a significant
main effect of smoking status [F(1,58) = 11.06, P < 0.01], a significant
smoking* sex interaction [F(1,58) = 9.41, P < 0.01], and a significant
main effect of time [F(1,58) = 5.52, P < 0.05]. Post hoc analyses
indicate that female smokers had significantly lower levels of pain
tolerance during both the nonabstinent and abstinent sessions when
compared with female nonsmokers (P < 0.001), male smokers (P <
0.01), and male nonsmokers (P < 0.01). These findings suggest that
cigarette smoking and gender mediate changes in pain tolerance in
adolescents.

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101 ELECTROCARDIOGRAPHIC FINDINGS IN LONG-TERM COCAINE
USERS
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The acute effects of cocaine on the ECG are well known. Long-term effects caused by cocaine are less studied. We evaluated resting ECGs in 466 males and females at baseline in a pharmacologic trial for the treatment of cocaine dependence. The subjects had a mean age of 33 and a median age of 35 with a range of 19–52 years of age. There were 200 Caucasians, and 266 African–Americans, 365 males and 101 females. Patients had used cocaine on an average of 9 years and were spending approximately $900.00 a month on cocaine in the 30 days prior to enrolling in the study. About 47 patients had a non-specific T-wave and ST segment changes, (NSTTWW) five had T-wave inversions, and two had Wolf Parkinsson White syndrome. Five African–American subjects had evidence of past myocardial infarctions. African–Americans were seven times more likely to have abnormal NSTTWW than Caucasians ($x^2 = 22.10, df = 1, P < 0.001$). African–American males were ten times more likely to have NSTTWW changes than Caucasian males ($x^2 = 22.49, df = 1, P < 0.001$). ECG abnormalities occurred at similar rates in males and females but African–American males, despite similar use patterns to Caucasians, had higher rates of abnormal electrocardiograms. African–American males using cocaine may have additional risk factors that contribute to abnormal electrocardiograms.

**102 PREVENTING ALCOHOL-EXPOSED PREGNANCIES IN COLLEGE WOMEN**

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Many young women place themselves at risk for alcohol-exposed pregnancy (AEP) through drinking and inadequate contraception. Although most non-dependent drinkers reduce drinking upon awareness of pregnancy, teratogenic effects (especially during weeks 3–10 of gestation) may have already occurred during critical early phases of embryonic development. Project BALANCE is a randomized clinical trial of a motivational intervention targeting the dual behaviors of risky drinking and ineffective contraception in college women. The study includes an epidemiologic survey of the female college population and an intervention for women who who screen eligible. The 200 participants are moderate to heavy drinkers who drink frequently and/or binge drink who are sexually active, fertile, not currently pregnant, and not using contraception adequately. They will complete an assessment battery and are randomized to either an information-only condition or a one session, 2 h motivational interviewing (MI) session. Measures include the TimeLine Follow Back for drinking and contraception, a risk questionnaire, the AUDIT, the OQ-45, and the NEO-Five Factor Inventory. The MI session is conducted in a counseling style designed to express empathy, develop discrepancy, roll with resistance, and support self-efficacy. Discrepancy is fostered through the provision of personalized feedback about risk behaviors, including drinking, contraception, and other behavioral patterns. Data collection is underway. Results from the first 6 months of the epidemiologic survey (approximately 200 women), and the baseline assessment and 1-month outcome for approximately 40 women will be presented. We will also discuss the feasibility and technical challenges of providing and processing personalized feedback in a single session and of conducting follow-up using multiple means (telephone, mail, and internet-based). If the MI intervention is superior to the information only condition, it will be a portable, low-cost method of motivating young women to reduce their risk of alcohol-exposed pregnancy.

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**103 SUBSTANCE USE, AFFECTIVE PROBLEMS AND PERSONALITY TRAITS IN WOMEN: A TEST OF TWO MODELS OF COMORBIDITY**

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Although the association between personality traits, affective disorders and substances use is well-documented, the majority of these studies has been conducted on clinical samples which limit conclusions about the direction of causality. The objective of this investigation is to examine in non clinical subjects if specific personality traits or affective problems are associated with substance use. Two explanations of comorbidity were examined: (1) the self-medication model which posits that a particular substance is chosen due to its psychopharmacologic effects on pre-existing psychiatric conditions or affective states, and (2) the social deviance model which postulates that maladaptive traits are associated with the deviance or diversity of substances used. Based on a sample of 612 individuals, 82 normal subjects were selected to form four groups of consumers: non-consumers, alcohol users, cannabis users, and those who use other illicit substances (such as cocaine or heroin). Only consumers of ‘other’ illicit substances differed significantly non-consumers, and only for the trait of novelty seeking. Furthermore, a comparison of the four groups of consumers demonstrated that scores for novelty seeking increased linearly from the non-consumers to the group who consumed substances that were most socially deviant. The findings support the conclusion that the social deviance model may be globally more relevant than self-medication to explaining certain forms of substances use comorbidity in women.

**104 RETENTION OF COURT-REFERRED YOUTHS IN RESIDENTIAL TREATMENT PROGRAMS: CLIENT CHARACTERISTICS AND TREATMENT PROCESS EFFECTS**

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The juvenile justice system relies heavily on residential treatment services for adolescents. Treatment drop-out limits the likely effectiveness of these services. In this report we examine the client and program characteristics associated with program retention among a sample of adolescent probationers referred to residential rehabilitation by the Juvenile Court in Los Angeles. As part of the 3-month interview, participants in the present study ($N = 291$) were asked about their perceptions of counselors, other residents, and their feelings of safety in the program. In addition, they were asked whether they needed and had received various services (e.g., job training, legal advice, and family counseling). Results of a multivariate survival analysis reveal that pre-treatment characteristics including treatment motivation, substance use severity, and environmental risk factors contribute significantly to the prediction of treatment retention. Importantly, however, treatment program factors that may be under the control of providers independently predicted retention. These factors include safety, counselor support, resident support, and over- and under-provision of services. Post-hoc analyses suggest that underprovision of vocational/job training services was strongly associated with early treatment termination. These results suggest that treatment retention in residential programs for adolescent drug users might be improved by increasing the availability of various treatment services.

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**105 NON-CONTINGENT NICOTINE ENHANCES RESPONDING MAINTAINED BY BEHAVIORALLY CONTINGENT ENVIRONMENTAL CUES**

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We have demonstrated previously that environmental cues can act synergistically with intravenous infusions of nicotine (NIC) to promote the rapid acquisition of self-administration (SA) in rats. The effectiveness of these cues (a 1-s cue light signaling NIC delivery, followed by a 1-min period during which the chamber light was turned off) and responding was not reinforced) in maintaining high levels of NIC-SA was found to be dependent on their contingent relationship with bar pressing that delivers NIC infusions, since yoked animals that bar pressed for NIC while exposed to non-contingent lighting events acquired SA at rates that were not different from those produced by responding for NIC alone. In the present experiments we asked whether the enhancement of operant behavior can occur when cue presentations are contingent on the animal’s behavior but NIC infusions are non-contingent (i.e. controlled by another rat in a yoked design). We also investigated the effectiveness of non-contingent nicotine in reinstating bar pressing after a period of nicotine withdrawal. Non-contingent NIC (0.03 mg/kg, free base) significantly enhanced bar pressing for contingent cues, compared to contingent cues without NIC, and to contingent or non-contingent NIC without cues. Furthermore, infusions of non-contingent NIC during extinction reinstated bar pressing to levels comparable to those obtained by rats that received contingent cues and NIC, and that did not differ from pre-extinction levels of responding. These data suggest the novel hypothesis that NIC can enhance the reinforcing properties of other stimuli by a mechanism that is not dependent on a predictable temporal association with either the stimulus or the behavior. These results may have implications regarding the pattern of NIC delivery that is sufficient to promote and sustain smoking behavior.

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106 ATTEMPTING TO DISENTANGLE THE MU AND KAPPA OPIOID ACTIONS OF BUTORPHANOL WITH NALTREXONE BLOCKADE IN HUMANS

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Butorphanol is an opioid partial agonist at mu and kappa receptors. Research suggests that butorphanol produces predominantly mu agonist activity at typical doses in humans. Kappa agonist agents are of potential therapeutic interest for the treatment of stimulant physical dependence on opioids, residing for 9 weeks on our closed residential unit. After a safety session, fifteen experimental sessions were conducted at least 2 h apart. Using a randomized, placebo-controlled, crossover design, subjects received naltrexone (0, 1, 3, 10 or 30 mg, p.o.) 60 min before administration of butorphanol (0, 6 or 12 mg/70 kg, i.m.) under double-blind conditions. An array of subjective measures (e.g., mood assessment, adjective checklist, ARCI scale) and physiological measures (e.g., pupil diameter, cardiovascular outcomes, galvanic skin response and urine output and osmolality) were collected before and after drug administration. Naltrexone produced dose-dependent decreases in the mu-like effects of butorphanol (e.g., ratings of good effects and miosis), while dysphoric subjective effects (e.g., bad effects) of butorphanol were increased by partial blockade with naltrexone at 10 mg. Blockade was not complete even at the highest dose of naltrexone (30 mg). Urine output tended to increase when naltrexone (10 and 30 mg) was given before active butorphanol. Although these data suggest that partial blockade by naltrexone can modify the qualitative dynamic profile of butorphanol, the kappa-like effects appear modest in humans.

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107 KAPPA OPIOID RECEPTOR (KOR) PHOSPHORYLATION BY G-PROTEIN RECEPTOR KINASE 3 (GRK3) RESULTS IN PROLONGED BEHAVIORAL TOLERANCE

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The mechanisms underlying behavioral tolerance to opiate drugs are complex, and the contribution of receptor desensitization is not clear. To test the hypothesis that agonist-induced desensitization of KOR contributes to a behavioral tolerance to opiates, we generated an affinity purified, rabbit polyclonal antibody (anti-KOR-P) able to detect the receptor phosphorylation event previously shown to be required for homologous desensitization of KOR in an in vitro gene expression system (Appleyard, 1999). Antibody specificity was established by elisa, western, and confocal analysis. Using the antibody, brain KOR isolated from mice treated with U50,488 showed a strong increase in anti-KOR-P labeling by western blot analysis. Labeling increased 59±22% after a single dose of U50,488 (30 mg/kg, i.p.) and 110±29% in mice made behaviorally tolerant following 5 days of U50,488 (escalating dose). Administration of U50,488 to mice lacking GRK3 failed to increase anti-KOR-P labeling, despite evidence of normal analgesia. Analgesic tolerance to U50,488 was also significantly reduced in onset and magnitude in GRK3 knockout mice. Surprisingly, the phosphorylation of KOR remained elevated for over one week following cessation of drug, and the return of normal analgesic sensitivity corresponded to the return to basal phosphorylation of KOR. Thus, the anti-KOR-P demonstrated that agonist-induced phosphorylation of KOR mediated by GRK3 underlies behavioral tolerance to a kappa opioid.

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108 DOES RELIGION IN THE BEHAVIOR REPERTOIRE PROTECT AGAINST INITIAL OPPORTUNITIES TO TRY MARIJUANA? EVIDENCE FROM THE PACARDO STUDY OF ADOLESCENTS IN LATIN AMERICA

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Building from behavior repertoire research initiated by Johanson et al. (1996), we estimate the degree to which religion in the adolescent behavior repertoire might provide protection against initial opportunities to try marijuana. Data are from the NIDA-sponsored PACARDO nationally representative sample surveys of school-attending adolescents in Panama, Central America, and the Dominican Republic, gathered in 1999–2000. Among 10,429 adolescents with no prior opportunity, 495 reported recent opportunity to try marijuana. We assessed religion via a multi-item scale from Johanson’s Behavior Repertoire Self-Rating (BRSR) questionnaire (daily prayer, frequency of church attendance, etc.). Multiple logistic regression and structural equations models (SEM) were used to estimate the hypothesized protective relationship between prominence of religion in the adolescent behavior repertoire and occurrence of marijuana exposure opportunity, with statistical adjustment for separately measured covariates such as religiosity (e.g., level of devotion). As hypothesized, there was an inverse association (estimated odds ratio, OR = 0.45; P < 0.05): greater prominence of religion in the behavior repertoire...
was associated with less marijuana exposure opportunity, even with statistical adjustment for age, father’s education, private school attendance, and male-female differences in marijuana exposure opportunity. Evidence from the SEM also indicates an inverse relationship, even when religiosity is controlled. Subgroup analyses (e.g., Catholic, Protestant) add strength to the base of evidence, consistent with an inference that the protection against marijuana exposure opportunity is linked with religious behavior, independent of religious devotion. New research will help clarify underlying mechanisms to guide preventive interventions, such as possible protection via social networks of similarly behaving peers or family members.

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109 Unlimited access to heroin self-administration, precipitated withdrawal, and the effects of Buprenorphine
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To date little work has focused on extended access to heroin in rodents using the intravenous self-administration (SA) model. The present study characterized heroin intake using 23-h sessions of heroin SA. Male Wistar rats were trained to nose-poke for food and water administration in 23-h sessions for 5 days prior to and following recovery from surgical implantation of jugular catheters. A lever was then introduced and rats were allowed to self-administer heroin (0.06 mg/kg/0.1 ml infusion/s; FR1; 20-sec time out) for 5–6 weeks. Somatic signs of heroin withdrawal were also examined by precipitated withdrawal using naloxone administration (0 and 1 mg/kg, s.c.) immediately following the active phase (18:00–06:00 h) of the last heroin session. Following a re-establishment of heroin SA, the influence of buprenorphine on this behavior was examined using an injection of buprenorphine (0, 0.01, 0.04, 0.2 mg/kg, s.c.) 15 mins prior to the active phase. Total heroin intake increased markedly by week 3, peaked by week 5, and thereafter, remained at a stable level. Immediately following the last session, naloxone produced a robust precipitation of withdrawal signs, and there was a direct correlation between the amount of heroin that had been self-administered with the amount of withdrawals signs observed. Exposure to buprenorphine produced a dose-dependent reduction in heroin intake, with the largest reduction by the 0.2 mg/kg dose. There were no major changes in food and water intake patterns over the course of heroin self-administration. These results suggest that rats will self-administer heroin to the point of producing dependence, and that heroin SA in dependent animals may be attenuated in this model by a partial opiate agonist.

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110 Facile rearrangement of 5-silylthebaine
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In an attempt to improve the selectivity of the 3-O-demethylation of thebaine to oripavine with L-Selectride, a 5-trimethylsilyl (TMS) protecting group was introduced into thebaine with the aim of adding steric bulk around the competing 6-methoxyl group. Treatment of 5-TMS-thebaine with L-Selectride produced only 5-TMS-neohydrothebaine other than the expected oripavine. Neohydrothebaine is a known rearrangement product of thebaine with strong Lewis acids, but does not occur with mild Lewis acids such as lithium. 5-TMS-neohydrothebane could be obtained alternatively by reacting 5-TMS-thebaine with MgI2 to form the iminium salt and reducing it with LiAlH4. Thus, L-Selectride must act as both Lewis acid and reducing agent. Treatment of 5-trimethylsilylthebaine with K-Selectride led to no rearrangement, showing that the lithium ion of L-Selectride acts as a Lewis acid. We propose that the facile rearrangement is due to the beta-silicon effect: the ability of silyl group to stabilize cations ions at the beta position.

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111 Cross-desensitization between opioid agonists and chemokines in rats
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Previous studies have shown that pretreatment with RANTES/CCL5 (100 ng) or SDF-1 alpha/CXCL12 (100 ng), 30 min before DAMGO (400 ng), totally blocked the antinociception induced by the mu opioid agonist DAMGO. In the present experiments, canulas were placed into the periaduquectal grey (PAG) of rats. The cold water tail-flick test was used to measure antinociception. The chemokine SDF-1 alpha/CXCL12 or RANTES/CCL5 was administered over a range of 1–4 h before injection of 400 ng DAMGO to detect possible cross-desensitization between chemokine and opioid receptors. The results showed that: (1) Pretreatment with RANTES/CCL5 (100 ng) up to 1 h before 400 ng DAMGO administration significantly reduced the antinociceptive effect induced by DAMGO, but pretreatment of RANTES/CCL5 2 h before 400 ng DAMGO had no effect on the antinociception; 2) SDF-1 alpha/CXCL12 (100 ng), up to 2 h before 400 ng DAMGO administration, significantly reduced the antinociceptive effect induced by DAMGO, but pretreatment with SDF-1 alpha/CXCL12, 4 h before 400 ng DAMGO administration, had no effect on the antinociception. These results suggested that cross-desensitization between the mu-opioid receptor and CCL5 receptor(s) or CXCL12 receptor is dependent on the timing of the injection.

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112 Contrasting effects of gabapentin release on aggression in adults with and without a history of child- hood conduct disorder
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Twenty male and female research subjects participated after giving their informed consent. Subjects were divided into a conduct disorder (CD) group and a matched control group with N = 10 in each group. Subjects were excluded if screening indicated any history of medical or psychiatric illness, or recent drug use detected by urine drug screen analysis. Subjects received doses of 200, 400 and 800 mg of Gabapentin in an ascending sequence with intervening placebos. Each drug dose was separated by 1 week. Each experimental day consisted of 6 sessions in which aggression was measured using a 3 option version of the Point Subtraction Aggression Paradigm (PSAP) software. Subjects participated 2 or 3 days per week. Twelve subjects have completed or are currently participating. Monetary reinforced responding, a measure of motor activity, was unaffected in both groups. Preliminary data suggest different effects of Gabapentin in these two groups.

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113 Ecstasy and the use of other illicit drugs: A new epidemic?

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In recent years, there has been a growing concern about the use of ecstasy, fueled by survey results showing increasing prevalence among youth, increases in emergency room visits, and numerous anecdotal and media reports. Despite this concern, major gaps exist in our understanding of risk factors for ecstasy use in the United States, and the extent to which ecstasy users emerge from a pool of relatively drug-naive individuals versus experienced drug users. To fill this gap, we used data from the 1998 National Household Survey on Drug Abuse (NHSDA), a nationally representative sample of the US household population. There were differences by race/ethnicity, with whites more than three times more likely to have ever used ecstasy than African-American (1.75 vs. 0.50%) and Hispanics at intermediate levels (1.21%). Prevalence of use was slightly higher for males compared to females. Most striking are patterns of use of other drugs among ecstasy users versus non-users. Across all age groups, nearly all ecstasy users had used marijuana (99%), most had used cocaine, and at least 10% had used heroin. Differences were most pronounced in the youngest age group (age 12–17) where extremely large differences were found for the prevalence of marijuana use (97.1 vs. 15.6% for ecstasy users and non-users, respectively), cocaine (52.6 vs. 1.4%) and heroin (13.5 vs. 0.04%). The magnitudes of the differences in prevalence of cocaine and heroin use for ecstasy users versus non-users was much larger than those found for marijuana users versus non-users. For all age groups, onset of ecstasy followed or was concurrent with (same year) onset of marijuana, cocaine, or heroin use. These findings counter the notion that ecstasy users are relatively naive users and indicate that ecstasy use is part of a constellation of multdrug use, particularly among younger users. These findings from the United States are consistent with emerging results from Europe, which indicate that ecstasy use is strongly associated with dependence on other drugs and psychiatric morbidity, and have important implications for the design of prevention strategies targeting ecstasy use.

114 What happens in the brain when patients attempt to inhibit ("STOP") cue-induced drug craving?

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Neuroimaging studies have now begun to characterize the brain substrates of cue-induced drug craving (“GO!”) states, as these may contribute to relapse vulnerability. In cocaine users, drug cues commonly activate limbic attentional (anterior cingulate) and affective (e.g., amygdala) circuitry. Other recent findings in our cocaine population—hypoactivity and gray matter hypodensity in the ventromedial orbitofrontal cortex, VMOFC; neuropsychological dysfunction—point to a complementary source of relapse vulnerability: frontal defects. Defects in our cocaine patients’ frontal inhibitory (“STOP”) circuitry may help explain their struggle to inhibit cue-related craving and to resist drug use. We have thus modified our usual imaging paradigm to capture brain activity during attempted inhibition of cue-induced cocaine craving to our drug videos. This inhibition condition (in which patients apply a previously-taught inhibition tool) is contrasted both with attempted increases in craving (as a control for effort), and with our standard craving induction (cocaine and nondrug videos; current n = 9). All conditions are imaged within a single 35 min session, using Arterial Spin Labeled perfusion (fMRI and previously-validated 5 min video segments from our earlier cue-induced craving studies in the Positron Emission Tomography (PET) setting. Our prediction is that (1) cocaine video cues will trigger differential limbic activation (e.g. amygdala, as in our PET O-15 studies), and that (2) successful inhibition of craving will be associated with increased activity in the frontal “STOP!” circuitry—blunting downstream limbic (amygdalar) activation. Preliminary results are consistent with both these predictions, and highlight the potential of the new paradigm in predicting treatment outcomes, and in screening interventions (behavioral or medication) which might boost the patients’ ability to inhibit craving; to “STOP” their drug use. NIDAI01DA10241.

115 A comparison of prevention programs for combating alcohol misuse on college campuses

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College students’ drinking constitutes a major challenge to educators and health professionals to develop a way to reduce this problem. The current study surveyed 159 college freshmen at the beginning of the semester about their attitudes and knowledge about alcohol and also about their current drinking behavior. Students were then semi-randomly assigned to participate in one of three prevention programs (Moderation group, Alcohol Skills group, and the Social Norms group), which served as the drug and alcohol education portion of a required freshmen class. After the prevention programs, the students were reassessed in the middle of the semester and again at the end of the semester. Analyses revealed that all groups reported an increase in problems from baseline to the end of the semester. There was also a significant difference between the three groups in the number of alcohol-related problems they encountered between baseline and mid-semester.

116 A combination of D9-tetrahydrocannabinol and opioids with circumvention of morphine tolerance

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Recent reports indicate that a low dose of delta-9-tetrahydrocannabinol (D9-THC) enhances the potency of oral opioids; these drug combinations have not yet been tested in tolerant animals. We first evaluated the efficacy of a combination of D9-THC and morphine or codeine via the tail flick test for antinociception in ICR mice tolerant to D9-THC, morphine or codeine. The combination of low doses (20 mg/kg p.o.) of D9-THC and morphine was equally effective in non-tolerant and morphone-tolerant mice; however, the efficacy of the combination of low doses of D9-THC and codeine (25 mg/kg p.o.) was significantly decreased in codeine-tolerant mice. D9-THC-tolerant mice also showed a decrease in the antinociceptive effect of both combinations, implying that the cannabinoid component of the combination is a critical component of opioid enhancement by D9-THC. Second, we evaluated the efficacy and potential for tolerance development after a 7-day treatment of D9-THC in combination with morphine or codeine. These mice developed significant tolerance to D9-THC, but not to morphine or codeine. The results show that a combination of low oral doses of D9-THC and opioids such as morphine or codeine may be used to maintain high antinociceptive effect while circumventing opioid tolerance, as well as provide relief in animals already tolerant to opioids.

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A randomized trial of once-daily slow-release oral morphine versus methadone for heroin dependence

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Recent formulations of morphine sulphate in polymer coated granules such as Kapanol™ (also known as Kadian™ or MorcapSR™) allow for once daily dosing, although no controlled evaluations of once daily morphine treatment of heroin dependence have been published. An outpatient, open label comparison of once daily morphine (Kapanol™) with methadone was conducted using a randomised crossover design. Eleven stable methadone maintained patients using heroin on average once per week commenced the study which consisted of 6 weeks methadone and 6 week morphine in random order. Morphine and methadone doses were once daily and were supervised. Heroin use was measured in the last week of each treatment period by self report, and by detection of 6-monoacetymorphine (6-mam) in hair and urine. The severity of opiate withdrawal symptoms immediately prior to each daily dose, the severity of dependence on heroin, and mental health/social functioning were also measured. Nine subjects completed the study. Of those who completed, there were no clinically or statistically significant differences in heroin or other drug use, severity of dependence, or mental health/social functioning. There was good agreement between self report, urine and hair measures of heroin use. Four subjects used no heroin in the last week of morphine treatment and had no 6-mam detected in hair or urine. There was a trend for the severity of opiate withdrawal symptoms immediately prior to each daily dose, the severity of dependence on heroin, and mental health/social functioning were also measured. Nine subjects completed the study. Of those who completed, there were no clinically or statistically significant differences in heroin or other drug use, severity of dependence, or mental health/social functioning. There was good agreement between self report, urine and hair measures of heroin use. Four subjects used no heroin in the last week of morphine treatment and had no 6-mam detected in hair or urine. There was a trend for the severity of opiate withdrawal symptoms between doses to be less with morphine than with methadone (withdrawal score 2.2 and 4.8, P = 0.06). The transfer to morphine from methadone was conducted incrementally, based on an estimated dose equivalence of 4:1. Once stabilised, the mean morphine dose was 6.26 times the starting methadone dose. Morphine was generally well tolerated and was preferred by seven out of nine subjects. No subjects complained that morphine did not “hold” for the 24 h dosing interval. New formulations of morphine such as Kapanol™ are promising once daily alternatives to methadone for the treatment of heroin dependence.

Demographics, drug use patterns, and treatment outcomes among adolescent heroin users

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The purpose of this study was to examine demographic factors, drug use patterns, and treatment outcomes among adolescent heroin users. The present data are derived from a larger national research effort examining adolescent treatment outcomes. Adolescent heroin users (n = 45) and non-heroin users (n = 108) in residential substance abuse treatment were compared on key baseline and treatment outcome variables. Demographically, the heroin group was comprised of more females (31.1% vs. 17.6%, P < 0.05), older adolescents (M = 17.1 vs. 16.3, P < 0.05), and more Caucasian youth (84.4% vs. 57.4%, P < 0.05) relative to the non-heroin group. On admission, heroin users reported more days of drug use in the prior 90 days (M = 71.4 vs. 54.9, P < 0.001), more days of being high (M = 58.9 vs. 40.1, P < 0.001), and more days of impairment (M = 53.1 vs. 21.5, P < 0.001). Relative to the non-heroin group, heroin users also exhibited greater mental distress, greater behavioral disturbance, and higher rates of needle risk and sexual risk behaviors. At 12 months, the abstinence rate among heroin users was significantly lower (27%) than among the non-heroin users (44%, P < 0.001). Overall, these findings indicate that adolescent heroin users differ from non-heroin users on several key demographic, drug use, and treatment outcome variables. The unique needs of adolescent heroin users should be considered in the design, implementation, and evaluation of adolescent substance abuse treatment interventions.

Clinical effects of smoked marijuana on cognitive performance

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Concern about adverse effects on cognitive functioning from regular marijuana use has been raised in the literature (Block and Ghoneim, 1993; Pope and Yurgelun-Todd, 1996). Budney et al. (1997) assert that cognitive deficits occur in regular marijuana smokers; however, such deficits tend to remit with abstinence from marijuana smoking. This outpatient investigation evaluated the effects of regular marijuana smoking on cognitive performance in human subjects, and assessed if performance changed over time. Evaluation, using a cognitive assessment package (CalCAP) that measures reaction time and speed of information processing, occurred at baseline, mid-study, and at study’s end. CalCAP tasks include the assessment of cognitive functioning in the form of timed psychomotor skills requiring sustained attention, serial pattern matching, largely a measure of divided attention, and lexical discrimination. Tasks increase in difficulty as the test progresses. Research participants included males and females, ages 18 – 60, from the New York City metro area. Participants smoked at least five marijuana cigarettes per week prior to study entry, and were treatment seeking. Thus far, baseline data have been collected for 7 marijuana-dependent individuals. Preliminary analyses suggest there are no differences between heavy and light users on the 10 CalCAP subtests at baseline. However, all mean subtest scores are lower than the normative mean subtest scores, suggesting overall impairment in this sample.

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Immunolesioning of cholinergic neurons in the nucleus accumbens: effects on cocaine self-administration in rats

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Cholinergic and dopaminergic systems are known to negatively influence the activity of each other in the basal and limbic forebrain. This study was undertaken to determine if cholinergic systems are involved in the reinforcing effects of cocaine. Rats were trained to self-administer cocaine on an FR2 schedule of reinforcement and were administered 0.25 μg of the cholinergic neurotoxin IgG192-saporin into each side of the nucleus accumbens (NAcc). Nearly complete destruction of cholinergic neurons following IgG192-saporin administration was confirmed by immunostaining coronal sections taken from treated animals for choline acetyltransferase. IgG192-saporin administration resulted in a gradual shift in the cocaine dose-effect curve over the first 4 days that could be classified as either a downward or leftward shift, as the number of infusions administered for all doses of cocaine was significantly decreased by approximately 50%. Analysis of interinfusion intervals was consistent with a leftward shift, in that behavior maintained by 0.083 mg/infusion of cocaine was irregular prior to lesioning but after IgG192-saporin administration became orderly and similar to the pattern maintained by 0.17 mg per infusion. Similarly, the infusion pattern maintained by 0.17 mg per infusion of cocaine after lesioning was similar to that maintained by 0.33 mg per
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121 Initial pilot testing of an integrated treatment manual for stimulant dependence and an eating disorder in women

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Most treatment outcome studies of eating disorders do not include substance abusers as study subjects. Currently, the treatment of the two disorders is usually separate and sequential. Treating the two disorders separately ignores the possible weight-related motivation that has been reported to exist for women. Presented here are the results of the initial pilot study used to test the integrated manual for women with stimulant dependence and an eating disorder involving binge eating. To date, 7 women have finished the 11 week integrated treatment and 4 of these women have completed the 3 month follow-up. Three more women are at week 8 of the integrated treatment. The eating disorder and substance abuse outcomes for the 4 women who have completed the 3 month follow-up are as follows: 4 subjects (2 ephedrine abusers, 1 prescription thyroid abuser and 1 crack cocaine abuser) maintained the binge free status that they achieved at the end of the 11 week treatment program and only 1 was still using any stimulants (cocaine abuser). Improvement in eating disorder pathology as measured by the Eating Disorder Examination at 11 weeks and 23 weeks were stable and averaged a 50% improvement in change scores over the four subjects. The 3 women (1 adderall abuser, 2 ephedrine abusers) who have completed the 11 weeks trial have had good results as well. Two are binge free at the end of treatment and substance free since at least week 3 of the trial. The other subject has had a 28% change in her binging and has been substance free since week 6. The 23 week follow up of these 3 subjects and the 3 subjects now at week 8 will be presented as well data from other variables such as SCID I and II, BDI, BAI and Self-Harm Inventory. The next phase of the study testing the integrated treatment approach (15 subjects) versus sequential treatment (15 subjects) for women with stimulant dependence and an eating disorder can now move forward. Implications for future treatment and research directions will be discussed.

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122 Impulsivity and rapid discounting of delayed hypotheti-cal rewards in cocaine-dependent individuals

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In an effort to measure impulsivity in humans, investigators have studied the value of delayed rewards by presenting hypothetical choices to Ss: a large reward received after some delay vs. smaller rewards available immediately (e.g., Madden et al., 1999; Petry and Casarella, 1999). For any specified delay, the point at which the smaller immediate reward is equivalent to the larger delayed reward is the point of indifference. If a variety of time delays are presented, the points may be plotted as an indifference curve to gain information about the rate at which the subjective value of a reward decreases with increasing delays to reward delivery. This approach to understanding impulsivity has been termed delay discounting (see Green et al., 1994). The current study examined delay discounting in 12 crack cocaine dependent (CD) and 13 non-drug using control (CON) Ss. The CON group was matched to the CD group on age, gender, income, and estimated IQ. All Ss were presented with hypothetical immediate and delayed rewards with the 16 delay conditions ranging from 5 min to 25 years. Delays were set to 5 min because pilot work suggested that CD participants were intolerant of minimum delays used in some previous research (e.g., 1 week). All Ss were presented with hypothetical monetary rewards while the CD group was also presented with hypothetical crack cocaine rewards. The objective value of the rewards ranged from S1 to $1000. Consistent with previous research studying substance abusing Ss, hyperbolic discounting functions provided a good fit of the data. The CD group discounted monetary rewards at a higher rate than the CON group and the CD group discounted crack cocaine rewards at a higher rate than monetary rewards. Moreover, scores on self-report measures indicated greater impulsivity in the CD group when compared to the CON group, although scores on the self-report measure were not associated with discounting of delayed rewards.

123 Conditional control of lithium chloride-induced taste aversion by naltrexone in rats treated with acute doses of morphine

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To assess subjective effects associated with acute opioid dependence, the conditional control of lithium chloride (LiCl)-induced taste aversion by naltrexone (NTX) was characterized in rats treated with acute doses of morphine (MS). Two groups of adult male Sprague-Dawley rats were trained to discriminate MS (5.6 mg/kg, −4 h) + NTX (0.3 mg/kg, −0.25 h) from SAL (1 ml/kg, −4 h) + NTX (0.3 mg/kg, −0.25 h) under a discriminated taste aversion assay. For rats in experimental group EMN, MS + NTX were given prior to a pairing of saccharin (SAC; 0.25% w/v) with LiCl (75 mg/kg), while SAL + NTX were given prior to a pairing of SAC with SAL. Training conditions were reversed for subjects in experimental group ESN such that MS + NTX were given prior to SAC-SAL pairings, while SAL + NTX were given prior to SAC-LiCl pairings. Two matched control groups received the same drug treatments prior to SAC access but always received postsession injections of SAL. Control conditions, defined as the statistically significant difference in drinking between experimental and control rats, was established in EMN rats in an average (±S.E.M.) of 33 (±2) sessions and in ESN rats in 46 (±4) sessions. In tests of conditional control in EMN subjects and their matched controls, 0.3 mg/kg NTX produced conditional control after pretreatment with 3.2, 5.6 or 10 mg/kg MS (−4 h). Similarly, NTX doses of 0.3–3 mg/kg produced conditional control when administered 4 h after pretreatment with 5.6 mg/kg MS. In contrast, conditional control by NTX (3–100 mg/kg) did not occur after 4 h SAL pretreatment. Conditional control was dependent on the time of NTX administration (5–30 min prior to SAC) and duration of MS pretreatment (−2−5 h before NTX). Conditional control by NTX in MS-pretreated rats was not dependent on the concentration of SAC, as conditional control occurred at all SAC concentrations (0.06−0.25%), but not H2O. These data characterize the relationship of dose and time of administration to the subjective effects of acute MS dependence, and demonstrate the applicability of this assay to research on acute dependence.

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124 RANDOMIZED COMPARISON OF BUPRENORPHINE-, CLONIDINE- AND ANESTHESIA-ASSISTED HEROIN DETOXICATION AND NALTREXONE INDUCTION

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Controversy continues over the role for general anesthesia in opiate detoxification and naltrexone induction. No controlled studies of this procedure have yet been published. We report updated results from a randomized, controlled trial of three detoxification/naltrexone induction methods: anesthesia/propofol-assisted (A), buprenorphine-assisted (B), and clonidine-assisted (C). Patients were admitted to the hospital (day 0) for 72 h, followed by twelve weeks of naltrexone maintenance and twice weekly relapse prevention psychotherapy. All patients received clonidine and other comfort medications during detoxification. Naltrexone (NTX) was initially administered at different times in each study arm: in group A on day 1, in B on day 2, and in C on day 7. Fifty-three heroin-dependent patients (33 male and 20 female) were randomized and began this study. Among these 53 patients, completers (received first NTX dose) comprised 19/19 in A, 17/18 in B, and 4/16 in C. Withdrawal scores during the inpatient hospitalization appear to be highest in the A group and lowest in the B group. There were several serious adverse events, including pulmonary edema and a psychiatric hospitalization in group A, with no serious adverse events in the other groups. Nearly complete abstinence from heroin (at most 2 opiate-positive urines) was maintained during 12 weeks of aftercare among 3/18 (one patient currently running with 8 weeks of abstinence in group A, 3/18 per week) suggested less heroin use in groups A and B during aftercare. Data collection is continuing.

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125 REINFORCING EFFECTS OF INTRAVENOUS BUPRENORPHINE COMPARED TO THE BUPRENORPHINE/NALOXONE COMBINATION IN NON-DEPENDENT HUMANS

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Buprenorphine (BUP) is currently under investigation as a treatment medication for opioid dependence. In an effort to reduce illicit diversion of BUP, a combination tablet containing buprenorphine and naloxone (BUP/NX) has been developed. The present double-blind, placebo-controlled, inpatient study compared the reinforcing effects of intravenously administered BUP (2 and 8 mg) and BUP/NX (2 mg BUP:0.5 mg NX and 8 mg BUP:2 mg NX). Participants (N = 6) were detoxified from heroin during the first week after admission. During subsequent weeks, participants received a sample drug dose and $20 on Mon, and they could self-administer either the sampled dose or $20 during choice sessions on Thurs and Fri. By responding under a modified progressive-ratio schedule during a 10-trial self-administration task, participants could choose 1/10th of the sampled dose or 1/10th of the sampled money amount during each trial. The PR value increased independently for each option. The total amount of drug and/or money chosen during the self-administration task was given as a bolus dose at the end of the task. All active doses maintained higher break points (largest completed ratio) than placebo. There were no significant differences in break points between BUP and BUP/NX or between the different doses of drug. However, subjective ratings, including “Good Drug Effect,” were dose-dependently increased for both BUP and BUP/NX, and were greater for BUP alone, compared to BUP/NX. These results demonstrate that both BUP alone and the BUP/NX combination served as reinforcers in non-opioid-dependent individuals. These findings also underscore the importance of evaluating both subjective and reinforcing effects of drugs of abuse.

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126 RELATIONSHIP OF SPIRITUALITY, RELIGIOSITY, AND SELF-ESTEEM TO RESILIENCY AMONG SUBSTANCE ABUSERS

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Resiliency is a term used to describe one's ability to adapt despite challenging circumstances. In this study, we hypothesized that resiliency would be positively associated with greater spirituality, religiosity, and self-esteem. The participants were 107 male and female substance abusers entering a residential treatment program. They averaged 34.4 years of age and 11.7 years of education; 55% were African American, 36% white. All had Drug Abuse Screening Test (DAST) scores exceeding 3 (mean = 6.73). Resiliency was assessed using the Dispositional Resiliency Scale. In terms of religiosity, results revealed positive relationships between resiliency and religious well-being (0.39, P < 0.001, Religious Well-Being Scale) and God consciousness (0.29, P < 0.01, Religious Beliefs and Behavior Scale). In terms of spiritual variables, resiliency was positively associated with purpose in life (0.57, P < 0.001, Purpose in Life Scale), hope (0.26, P < 0.001, Hope Scale), existential well-being (0.54, P < 0.001, Existential Well-Being Scale), forgiveness of self and others (0.36 and 0.42, respectively, P's < 0.001, Forgiveness of Self-Others Scale), and serenity (0.46, P < 0.001, Serenity Scale). Finally, resiliency was strongly and positively associated with self-esteeem (0.73, P < 0.001, Rosenberg Self-Esteem Scale). These findings indicate robust relationships between resiliency and spirituality, religiosity, and self-esteem, suggesting the importance of evaluating these dimensions in clinical assessment.

127 STRESS HORMONE RESPONSES TO CORTICOTROPIN RELEASING HORMONE IN SUBSTANCE ABUSERS WITHOUT SEVERE CO-MORBID PSYCHIATRIC DISEASE


Pre-clinical data indicate a crucial role of stress in the acute effects of drugs of abuse, maintenance of self-administration and susceptibility to relapse. Stress system activation may serve as a marker for a neurochemical dysfunction with prognostic significance in patients with addiction. We tested pituitary adrenocorticotropic hormone (ACTH) and adrenal cortisol response to ovine CRH to assess the reactivity of the HPA in 7 controls, 31 polysubstance abusers without depressive symptoms, and 7 polysubstance abusers with depressive symptoms. Compared with normal controls, substance abusers showed lower ACTH and cortisol responses over the course of oCRH stimulation (P < 0.0001). Substance abusers with depressive symptoms showed similar blunted responses. Substance abusers with no previous or current diagnosis of other axis I disorders show blunted ACTH and cortisol responses to oCRH. The finding of a chronically activated HPA axis in this population suggests an overlapping role of central CRH and HPA activation in affective disorders and substance abuse, likely to constitute an endocrine milieu necessary for the maintenance of addictive behavior. This data supports future therapeutic trials with non-peptide CRH receptor I antagonists in these patients.
128 Behavioral effects of GHB alone and in combination with other drugs

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Gammahydroxybutyrate (GHB) is endogenously found in the mammalian brain whose physiological role remains unclear. Exogenously administered GHB readily crosses the blood-brain-barrier and produces a variety of behavioral effects. GHB has been used clinically as an anesthetic agent and as a treatment for alcohol and heroin dependency disorders in Europe, and has gained approval (Xyrem) for the treatment of catalepsy associated with narcolepsy in the USA. GHB is also recognized as a drug of abuse in the USA. GHB is used at rave parties and is often co-abused with other drugs such as alcohol and methylenedioxymethamphetamine (MDMA, Ecstasy). Little is known about how GHB interacts with other drugs. Consequently, the present study was designed to understand the behavioral, sensorimotor and physiological effects of GHB alone and in combination with alcohol and MDMA in male Swiss Webster mice. Psychomotor activity was assessed using automated activity chambers. Sensorimotor and physiological effects were determined using a Functional Observational Battery (FOB). The FOB consisted of assessing effects on core temperature, forelimb grip strength (kg of force), time to completion of an inverted screen task (s), loss of the righting reflex, and hindlimb splay (mm). Both GHB (0.1–1.0 g/kg, ig) and alcohol (2.0–5.0 g/kg, ig) decreased, whereas MDMA (3.0–30 mg/kg, ig) increased psychomotor activity. When alcohol and MDMA were combined with GHB the resulting effects were generally additive. In FOB, both alcohol and GHB produced disruptions in sensorimotor performance and decreased body temperature. The inverted screen task and hind limb splay were most sensitive to GHB and to alcohol’s disrupting effects, whereas the righting reflex and forelimb grip strength were the least sensitive. Alcohol altered GHB’s effects in an additive manner, except for the righting reflex in which superadditivity was obtained. Generally, the suppressant effects of GHB were altered by depressants and stimulants in an additive manner.

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129 Australian adolescent cannabis check-up


Cannabis is the most commonly used illicit drug by adolescents in the US and Australia with few interventions developed for this group. This paper describes the methodology and latest progress of the Australian Adolescent Cannabis Check-up (AACCU). The ACCCU specifically targets adolescents who are not seeking help to manage their cannabis use but are causing concern to their families or community members such as schools. The first of three sessions aims to assist the families to first attend the 2 session AACCU. Where the young person meets criteria for a cannabis use disorder. Almost half (46%) had a history of treatment for a psychiatric disorder and more than a third (36%) had supported themselves through illegal activity in the past 3 months. Around half of the young people were at least somewhat interested in reducing their current levels of cannabis use. Around half of the eligible young people participated in the randomised controlled trial. Participants will be followed-up at 12 weeks following their completion of the AACCU. Self-reported cannabis use will be validated by urinalysis. The hypothesis is that in young people one session of CBT will have significantly reduced their cannabis use and improved their motivation for treatment compared with the DTC. This project is funded by the Commonwealth Department of Health and Ageing’s Illicit Drug Strategy.

130 Attentional bias and craving in cocaine-dependent individuals with and without comorbid schizophrenia

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Cocaine craving has been implicated as a major factor underlying addiction and relapse. From a cognitive viewpoint, craving may reflect, in part, attentional processing biased in favor of drug related cues and stimuli. Schizophrenic individuals (SZ) however, abuse cocaine in high numbers but typically manifest baseline cognitive deficits that impair their ability to manifest biased attentional processing. In particular, it is theorized that a semantic processing deficit among SZ limits their expression of attentional biases. Objectives of this research were to demonstrate an associative link between attentional bias and craving in cocaine dependent patients (COC) and to examine the relationship between semantic processing deficits and craving in a schizophrenic comorbid group (COC+SZ). If attentional bias is a cognitive process that contributes to the persistence of craving, COC+SZ patients should report fewer craving symptoms than COC patients. The present study examined attentional bias and craving in COC (n = 20); COC+SZ (n = 23); SZ (n = 20) as well as individuals with no Axis I pathology (n = 21) using a modified version of the Stroop test to include cocaine-relevant words. To examine the relationship between craving severity and attentional bias, both cocaine groups also completed a clinical measure of cocaine craving. As predicted, only the COC patients demonstrated a Stroop effect on the cocaine-related words. Moreover, only COC patients’ Stroop attentional bias was significantly related to their scores on the clinical measure of cocaine craving. COC+SZ patients did not demonstrate a Stroop effect and manifested significantly fewer craving symptoms than their COC counterparts. These results suggest that COC+SZ patients’ inability to selectively encode their drug-use experience may limit and shape their subjective experience of craving cocaine and underlying motivation for cocaine misuse.

131 Hepatitis C in an upstate New York methadone treatment population: preliminary analysis

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Objective: We report the preliminary results of a study of the prevalence of Hepatitis C (HCV) antibody among patients in an Upstate New York methadone maintenance treatment (MMT) program, and the differential characteristics of HCV+ and HCV− patients. Method: Information was collected from a cross-sectional review of 215 charts of MMT patients for whom HCV status was known. Data were obtained on demographic characteristics, treatment variables, and medical and mental health status. Results: 150 (69.8%)
patients tested positive for HCV and 65 (30.2%) tested negative. The HCV+ group was older (mean 43.5 vs. 39.6 years, \( P = 0.003 \)), but the two groups did not differ significantly in gender, ethnicity, education level, employment, or insurance coverage. However, significant differences emerged in history of injection drug use: 92.3% of the HCV+ group had a history of injection drug use, versus only 39.7% of the HCV− group (\( P < 0.001 \)). While there were no differences in the proportion of each group who used heroin or cocaine at MMT entry, 88.7% of HCV+ vs. only 35.7% of HCV− patients injected heroin (\( P < 0.001 \)) and 29.5% of the HCV+ group vs. only 7.4% of the HCV− group injected cocaine (\( P < 0.001 \)). HCV+ patients had been in MMT an average of 61.2 months vs 30.2 months for HCV− patients (\( P < 0.001 \)). There were no significant differences in the proportion of drug positive urines while in treatment, nor were there differences in alcohol use. History of depression and anxiety diagnoses did not differ between the two groups, nor did the prevalence of psychotic symptom history. HCV+ patients had higher GGT, ALT and AST levels at MMT entry, and they also had a higher prevalence of Hepatitis B coinfection. Conclusions: HCV antibody seroprevalence is somewhat lower in this Upstate New York sample than that reported for other MMT cohorts, and is linked to history of injection of heroin and cocaine, older age, and possibly greater addiction severity as indicated by longer treatment time in MMT.

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132 A COMPARISON OF TWO VOUCHER DELIVERY SCHEDULES FOR THE INITIATION OF COCAINE ABSTINENCE

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The current study examined the effects of two voucher incentive procedures on initiation of cocaine abstinence among 34 methadone maintenance patients (M age = 42, 62% male, 79% minority, dose = 100 mg/day). Patients were exposed to two experimental conditions in counterbalanced order. Both conditions began on a Monday and were in effect for one week. During condition 1, patients could earn a $200 voucher if they provided a cocaine-negative (benzoylcegonine < 300 ng/ml) urine sample on the following Monday. Because of the duration that cocaine metabolite remains in the body, achieving this goal may require 3–5 days of continuous abstinence. Condition 2 offered intermediate reinforcement opportunities during the test week in order to promote early abstinence initiation and maximize the clients’ chances of being abstinent on the following Monday. Specifically, patients were given two opportunities (Wednesday and Friday) to earn a $50 vouchers for 48 h of cocaine abstinence detected by quantitative urine testing methods, followed by an opportunity to earn a $100 voucher for a cocaine-negative urine sample (benzoylcegonine < 300 ng/ml) on the following Monday. These earning opportunities were independent; i.e., continuous abstinence was not required. Seventy-one percent of the sample produced a cocaine-negative urine sample on Monday when the $200 voucher was available, as compared with 53% abstinent on the Monday when the $100 voucher was available. Rates of 2-day abstinence detected on Wednesday were 85% in the group where a $50 voucher was offered and 62% when no voucher was offered. Although the intermediate reinforcement procedure did help patients initiate abstinence over the first 48 h of the experimental week, it did not assist patients in earning the larger, final reinforcement. Results suggest that when large valued start-up bonuses are employed, drug abusers respond to the most immediately available reinforcer, but then have difficulty sustaining or re-initiating behavior change in order to obtain reinforcers offered at a later time. Findings have implications for optimal scheduling of reinforcers in order to both initiate and sustain drug abstinence.

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133 EFFECTS OF BREMAZOCINE AND A NONDRUG ALTERNATIVE REINFORCER ON THE SELF-ADMINISTRATION OF PHENCYCLIDINE (PCP) IN RHESUS MONKEYS: SEX DIFFERENCES

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Sex differences have been demonstrated in drug self-administration during various phases of drug abuse; however, few studies have examined whether the effects of treatments for drug abuse may vary as a function of sex. The purpose of the present study was to compare pharmacological and behavioral treatments in male and female rhesus monkeys self-administering PCP. Eight adult male and 7 female rhesus monkeys orally self-administered PCP concurrently with water on fixed ratio (FR) 16 schedules. Liquid deliveries (0.6 ml) were contingent upon lip-contact responses. Bremazone (0.00032, 0.001, 0.0025, i.m.) was administered for 5 consecutive days with the 4 preceding days serving as a no treatment baseline. Subsequently, the animals self-administered PCP concurrently with water at FR values 4, 8, 16, 32, 64, 128 to obtain demand curves (consumption as a function of number of responses). Saccharin was then substituted for water at the same FR values. Preliminary results indicate that males and females consumed similar amounts (mg/kg) of PCP, and that low doses of bremazone were more effective in reducing PCP intake in female monkeys. Additionally, preliminary results suggest that saccharin functions as a nondrug reinforcer and reduces PCP intake in females. These results suggest that there may be differential treatment effects in males and females, and sex may interact with treatment dose.

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134 ECSTASY USE, ABUSE AND DEPENDENCE: A COMPARISON BETWEEN TREATMENT AND GENERAL POPULATION YOUNG ADULT SAMPLES

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A number of monitoring mechanisms of youths in the US and abroad are detecting alarming increases in the popularity of Ecstasy use. However, little data exist concerning its consequences and risk factors. As part of a NIDA study on the reliability of DSM substance use disorders, 191 young adults were interviewed: 69 young adults 13–29 years of age reported using Ecstasy. Users were stratified by source of recruitment: those in treatment (TX) were compared with community users (GEN POP). The TX sample was slightly younger in age than the GEN POP sample. Using the CIDI-Substance Abuse Module (SAM) to determine use, abuse and dependence on Ecstasy, our data show that the GEN POP sample was more likely to begin their Ecstasy use later, and use fewer drugs than the TX sample. Although both samples reported initiating Ecstasy last in their repertoire of drugs used, the TX sample actually reported ages of onset of all drugs, including Ecstasy, prior to the age of onset of any drug reported by the GEN POP sample. When DSM-IV criteria were applied for abuse, hazardous use was the most commonly reported symptom by both samples and twice as likely to be reported by the TX sample. With the exception of tolerance, all other criteria for dependence were equally reported by the samples. “Continuing to use despite knowledge of physical or
psychological harm” and “withdrawal symptoms” were the two most prevalent dependence criteria reported by both samples, with approximately 60% of the users reporting each. Of special note is our finding of higher rates of Ecstasy abuse among the TX sample compared with the GEN POP sample (47 vs. 18%) but higher rates of dependence among the GEN POP compared with the TX sample (53 vs. 37%). These unique analyses demonstrate the usefulness of assessing abuse and dependence on Ecstasy and their importance and relevance of DSM-V. With a newly funded study from NIDA, plans are underway for a multisite study of these issues, including the reliability and validity of Ecstasy abuse and dependence criteria.

135 IS CASE MANAGEMENT EFFECTIVE IN RE-ENGAGING DISCHARGED METHADONE MAINTENANCE PATIENTS IN TREATMENT?

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Few methadone maintenance treatment programs (MMTPs) provide adequate follow-up of patients upon discharge. A total of 207 former methadone patients were interviewed following discharge at a VA and two community-based MMTPs. Nearly 60% of patients were discharged because they were noncompliant with treatment, dropped out or were suspended from the program, whereas only 7% successfully completed treatment. At three months post-discharge 134 of the 207 patients (65%) had relapsed, and most of those patients (n = 114) were not enrolled in drug treatment. These 114 predominately male African–American patients were randomly assigned to receive either a passive referral for drug treatment (n = 46 passive) or were provided a case manager who assisted them in re-entering treatment (n = 68 enhanced). A total of 94 patients (82%) were followed-up 6 weeks following their 3-month post-discharge assessment. Among enhanced patients 23% successfully re-enrolled in MMT compared to 8% of passive patients (χ^2 = 3.762, df = 1, P = 0.052). Additional enhanced patients would have enrolled in treatment if it were not for significant waiting lists at MMTPs. The findings highlight the importance of engaging former patients in treatment since many patients continue to use drugs following discharge and since MMT has been associated with reductions in opiate use, crime, mortality and HIV seroconversion.

136 THE BIS-PICOLINIUM SALT, BPIDDB, IS A POTENT AND SELECTIVE ANTAGONIST AT NICOTINIC ACETYLCHOLINE RECEPTORS MEDIATING NICOTINE-EOVED DOPAMINE RELEASE IN RAT STRIATUM

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S(−)-Nicotine (NIC) acts as a nonselective agonist at neuronal nicotinic acetylcholine receptors (nAChRs). Very few subtype-selective nAChR antagonists are available for use as pharmacological tools to investigate the role of nAChR subtypes in drug abuse. Alkylation of the pyridino N-atom of the NIC molecule converts it from an agonist to an antagonist (Dvoskin et al., 2000; Dvoskin and Crooks, 2001). As part of a structure-activity analysis, a series of bis-quaternary ammonium dodecanes were synthesized and evaluated in several nAChR subtype assays, including [3H]NIC and [3H]methyllycaconitine (MLA) binding using rat brain membranes to probe the α4β2* and alpha7 nAChR subtypes, respectively, and NIC-evoked [3H]dopa mine (DA) release from superfused rat striatal slices to probe the α3β2* nAChR subtype. The bis-nicotinium, bis-pyridinium, and bis-picolinium analogs (bNDDB, bPDDB and bPiDDB, respectively) exhibited low affinity (Ki = 1.4–33 μM) for the α4β2* subtype, whereas the bis-quinolinium and bis-isouquinolinium analogs (bQDDB and bIQDDB, respectively) showed no activity (Ki = > 100 μM), bQDDB and bIQDDB inhibited [3H]MLA binding (Ki = 1.6 and 13 μM), whereas bNDDB, bPDDB, bPiDDB showed no activity (Ki = > 100 μM). Moreover, bPiDDB potently inhibited NIC-evoked [3H]DA release (IC50 = 2 nM), whereas bQDDB, bNDDB and bPiDDB inhibited release, but with at least 100-fold lower affinity (IC50 = 330, 1000 and 4400 nM, respectively). Furthermore, bPDDB had a 1000-fold higher affinity for the α3β2* subtype compared to the classical nAChR antagonist, dihydroyxy-b-erythroidine (IC50 = 1.0 μM). Thus, bPiDDB exhibited ~10000-fold greater selectivity for the α3β2* compared to α4β2* and α7* nAChR subtypes, providing a novel probe to assess the involvement of α3β2* nAChRs in the reinforcing efficacy of NIC, as well as provide a potential treatment for NIC abuse.

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137 MMPI-2 AND SMOKING HISTORY VARIABLES PREDICT EARLIER SMOKING INITIATION AMONG INCARCERATED MALE SMOKERS

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Age of smoking initiation was investigated as part of a larger study with 314 male incarcerated smokers forced to quit smoking during a state-wide smoking ban. Participants completed questionnaires on smoking history and smoking measures at 1 week prior to the ban, and two follow-up times (4 days and 1 month after the ban). The MMPI-2 had been given at time of initial incarceration and was extracted from the inmate’s chart. Average age was 32.45 years, 26.4% were African–American, median length of sentence was 11 years, and 57.1% were single. Thirty-three percent smoked between 11 and 30 cigarettes per day; 13.8% smoked more, and over a quarter (26.4%) had never tried to quit smoking. For smokers who had tried to quit, 79.9% rated it as “difficult” or “very difficult”, with the majority quitting for 1 month or less (61.5%). The majority of smokers (62.8%) began smoking before age 15 (13.9% by age 10), and 92.6% had started by age 20. Logistic regression was used to determine the probability of younger smoking initiation using the MMPI-2 clinical, validity and MAC-R scales as predictor variables. The overall predictive model was significant (model χ^2 (14, N = 164) = 24.65, P = 0.038), with endorsement of symptoms of stress and somatic complaints (Scale 3) and symptoms of obsessional thoughts and fears (Scale 7) predictive of starting to smoke by age 15, while fewer depressive symptoms (Scale 2) were predictive of starting to smoke at age 16 or older. Overall, this model correctly classified 70.1% of the sample. Logistic regression was also used to determine younger age of smoking initiation using demographic variables. The overall predictive model was significant (model χ^2 (6, N = 262) = 33.00, P < 0.001), with smoking more than 20 cigarettes per day, single, and Caucasian predictive of smoking by age 15. The model correctly classified 71.0% of the participants. Implications will be discussed.

138 SELF-ESTEEM AFTER ABUSE-NEGLECT IN YOUNTHS WITH CONDUCT PROBLEMS: RELATIONSHIP TO SUBSTANCE INVOLVEMENT

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Conduct disorder (CD), abuse-neglect (AN), and low self-esteem (SE) all reportedly precede adolescent substance involvement, but they confusingly co-occur. Attempting to understand associations of these variables, we assessed them in patients and controls. HYPOTHESES: (A) SE will be higher in controls (vs. patients) and in males (vs. females). (B) In both patients and controls more AN will associate with worse SE. (C) Worse SE will predict worse substance involvement.
METHODS. 98 adolescents in treatment for conduct and substance problems, and 102 controls, completed the (a) Colo. Adolescent Rearing Inventory, which quantitates AN, (b) Piers-Harris Self-Concept Scale for SE (reported as T-scores), (c) DISC for CD symptoms, (d) CIDI-SAM for substance-dependence symptoms, and (e) Carroll Self-Rating Scale for depressive dysphoria. RESULTS. (A) SE was higher among controls than patients (mean 62.5 vs. 53.1; P < 0.001). Gender differences were NS. (B) About 2/3 of patients and 1/3 of controls reported at least minimal AN. SE negatively correlated with severity of AN among patients (rho = −0.27; P < 0.008) and controls (−0.23; P < 0.02). (C) After adjustment for patient-control effects lower SE predicted severity of across-drug substance involvement (Beta = −1.4; P < 0.003). (D) Depression scores correlated strongly and negatively with SE (rho = −0.7; P < 0.001). Conclusions. Among youths in treatment for conduct and substance problems, and among controls, higher AN scores are associated with worse SE. Moreover, in both groups worse SE is associated with worse substance involvement. Future studies might seek reductions in later substance problems from treatments that improve adolescents’ SE after AN experiences.

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139 COMPARISON OF MAINTENANCE VERSUS DETOXIFICATION TREATMENT SEEKERS

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Introduction: Although opioid agonist maintenance and inpatient detoxification are two of the most common treatment modalities for opioid dependence, the unique characteristics of patients selecting one of the two options has received little scientific attention. Thus, this study compared the pre-treatment characteristics of those seeking opioid agonist maintenance versus inpatient detoxification for opioid dependence. Method: Detox patients (DP; n = 155) and agonist maintenance patients (AM; n = 203) were compared using variables from the Structured Clinical Interview for DSM-IV E-module and the Addiction Severity Index regarding demographics, drug histories for heroin, cocaine and alcohol and types of detoxification treatments previously sought. Results: Compared to the AM group, the DP group reported significantly more lifetime and daily cocaine (64.3 months, P < 0.001), and alcohol use (86.7 vs. 30.5 months, P < 0.001) and 30.2 days, P < 0.001) and significantly less daily heroin use (28.3 vs. 29.6 months, P < 0.001) prior to treatment entry. No differences existed between the groups for amount of lifetime heroin use. The DP group also reported significantly more lifetime drug treatments (3.6 vs. 2.1, P < 0.001) compared to the AM group. Conclusions: Overall, relative to agonist treatment seekers those seeking inpatient detoxification have more severe and more diverse drug and drug treatment histories yet sought more short-term interventions for their opioid problems.

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140 METHAMPHETAMINE-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF NOVEL GBR 12909 ANALOGS IN SQUIRREL MONKEYS

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The dopamine transporter (DAT) blocker GBR 12909 (GBR) has proven to be a useful tool for the study of brain dopamine systems and is being evaluated as a treatment medication for stimulant abuse. Analogues of GBR with higher affinity and selectivity for the DAT may also have experimental and therapeutic applications. In the present studies, the methamphetamine (MA)-like effects of cumulative doses of GBR and four novel congeners with higher DAT affinity and selectivity (AM2502, AM2506, AM2515, AM2517) were assessed in squirrel monkeys (n = 3–5) trained to discriminate 0.3 mg/kg MA from saline. All compounds produced dose-related increases in responding on the MA-associated lever, with full substitution following doses of 5.6 mg/kg AM2517, 10.0 mg/kg GBR, 17.8 mg/kg AM2515 or AM2502, and 30.0 mg/kg AM2506. No effects on response rate were observed up to doses that substituted for the MA training dose. Thus, despite higher affinity and selectivity at the DAT, congeners were approximately equipotent or less potent than GBR in producing MA-appropriate responding. In time course studies, the onset of action of AM2517 was found to be similar to that of GBR. Co-administration of AM2517 (1.0 and 3.0 mg/kg) or GBR (1.0 and 3.0 mg/kg) with MA (0.01–0.30 mg/kg) produced large leftward shifts in the MA dose-effect curve. In contrast, selective norepinephrine (desipramine, nisoxetine) or serotonin (clomipramine) uptake inhibitors did not significantly enhance the effects of MA. Effects of the novel GBR analogs are consistent with dopaminergic mechanisms of action, in keeping with their selectivity for the DAT in vitro. It is noteworthy that GBR and its analogs differ dramatically in their in vitro binding affinity and selectivity. Their similar potencies in the present studies indicate that factors in addition to their binding characteristics play a major role in the potency of these phenylpiperazines in vivo.

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141 THE STRAW NICOTINE ORAL DELIVERY SYSTEM: SAFETY AND PHARMACOKINETICS OF SINGLE AND REPEAT DOING

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Cigarette smoking is highly addictive, and smokers become dependent on both nicotine and the behavior of smoking. The Straw™ is a novel form of nicotine replacement therapy (NRT) designed to provide both the nicotine and the oral and manual stimuli that many smokers need for a successful quit attempt. Smokers sip a beverage through The Straw™, ingest a full dose of nicotine particles in the first swallow, and then may chew and handle The Straw™. In this safety and pharmacokinetics trial, 24 smokers were randomized to nicotine (4, 8 or 12 mg) or placebo straws. The Straw™ was administered after 9 h of overnight smoking abstinence. Plasma levels of nicotine increased by 5.6 (1.7), 18.9 (7.7), and 19.5 (4.4) ng/ml (mean, S.D.) within 1–2 h in the 4, 8 and 12 mg groups. Cotinine also rose above baseline levels by 51 (42), 79 (66) and 140 (70) ng/ml. The smokers returned 1 week later and received 8 doses of nicotine, once every 90 min. Maximal increases in nicotine were 18.9 (7.8), 33.0 (17.6) and 49.2 (13.8) ng/ml in the 4, 8 and 12 mg groups. Cotinine values increased by 273 (52), 588 (30) and 730 (161) ng/ml. Nicotine and cotinine steadily increased over the 11.5 h session. Single and repeated uses of The Straw™ were generally well tolerated and liked. Only 4 subjects (3 in the 12 mg group) reported The Straw™ tasted bad. Side effects (gastrointestinal distress, lightheadedness) were not severe or unexpected and were consistent with those seen with other NRT products. The results of this trial indicate that The Straw™ will provide sufficient nicotine replacement and safety for use as a smoking cessation product.

142 AN OPEN-LABEL PILOT STUDY ON THE EFFECTIVENESS AND TOLERABILITY OF MODAFINIL FOR COCAINE DEPENDENCE

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Modafinil is an anti-narcolepsy agent that may promote cocaine abstinence by reversing cocaine withdrawal symptoms, including hypersomnia, anergia, depressed mood, hyperphagia, and poor concentration. Severe cocaine withdrawal measured by the Cocaine Selective Severity Assessment (CSSA) correlates with poor outcome, suggesting that reversing withdrawal might be clinically advantageous. Modafinil may also reverse cocaine-induced neuroadaptations affecting the dopamine and glutamate neurotransmitter systems. This abstract presents preliminary results of an open-label pilot study that assesses the tolerability and effectiveness of two dosages of modafinil in cocaine-dependent subjects. Four subjects with severe cocaine withdrawal (based on high CSSA scores) were randomized to either 200 or 400 mg/day of oral modafinil that was instituted during inpatient treatment (10–14 days) and evaluated over 8 weeks of outpatient treatment with urine toxicology, CSSA interviews and a number of other questionnaires to assess mood, adverse events and cocaine use. Two subjects were able to achieve complete cocaine abstinence throughout their outpatient treatment, one dropped out of the study during the inpatient phase (unrelated to study medication) and the other subject continued to use cocaine through outpatient treatment. These results far exceed abstinence rates (10%) that are customarily achieved by high CSSA subjects enrolled in other studies within our center. This is a preliminary report of a larger pilot study (N = 20) that will be statistically analyzed upon completion. There were no significant complaints of intolerability or adverse events. Overall, modafinil appears well tolerated and may represent an effective adjunctive pharmacotherapy in cocaine-addicted patients with severe cocaine withdrawal symptoms.

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143 Regional pattern of increased opioid receptor density in early abstinence from methadone in man: a PET study with 11C-diprenorphine

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Objectives: The aims of this study are to investigate the changes in 11C-diprenorphine binding in the brain resulting from chronic methadone treatment for opioid dependence. Specifically, we hypothesized that early abstinence following a sustained period of methadone treatment would be associated with an increase in 11C-diprenorphine binding. Methods: 18 control subjects (15 m 3 f, 25–56 age) and 10 inpatients in early abstinence (7–10 days since last dose) from methadone (8 m 2 f, 25–45 age) were recruited. All underwent an 11C-diprenorphine PET scan on a brain dedicated ECAT 953b scanner. All subjects were drug free, as confirmed by urine drug screening and the control group had no history of dependence on any drug except nicotine. A Volume of Distribution (VD) image of the 11C-diprenorphine binding was generated. Results: The results show a trend for the mean global VD for the abstinent group (20.8 + 1.7 S.D.) to be higher than in the control group (19.3 + 2.8 S.D.) (t = 1.79; P < 0.09). VD was increased in every brain region studied and achieved statistical significance in four regions. These were the right ventral striatum (30.6 + 4.6 vs. 26.6 + 4.8; P < 0.05), the left ventral striatum (29.9 + 3.9 vs. 26.3 + 4.7; P < 0.05), the left medial temporal region (23.0 + 2.9 vs. 20.7 + 2.9; P < 0.05) and the left putamen (33.1 + 3.3 vs. 29.5 + 4.5; P < 0.05). Conclusions: This preliminary data suggests that opioid receptor levels are increased in early opioid abstinence throughout the brain. The implications of the increases seen in the ventral striatum, which plays a crucial role in drug dependence, are unknown. Since diprenorphine labels mu, kappa and delta receptor subtypes, it cannot be determined whether the increase is due to mu opioid receptors as has been reported in cocaine addiction. Increased opioid receptors levels have now been reported in addiction to a number of substances suggesting a key role for the opioid system. This study also demonstrates that these changes endure after the resolution of the acute clinical signs and symptoms of opioid withdrawal.

144 Differential involvement of calcium calmodulin-kinase II in nicotine’s pharmacological effects in mice

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We recently reported an involvement of CaM-Kinase II in the in vivo spinal antinociceptive effects of nicotine (Damaj et al., 2000). Since a difference between spinal and supraspinal pharmacology of nicotine is suggested in the literature, we compared the effects at the spinal level to the effects mediated at the supraspinal level using two different pain tests in the ICR mice. The effect of CaM-Kinase II inhibitors, KN-62 and KN-93, on nicotine-induced antinociception after intraventricular (i.c.v.) administration in mice was investigated using the tail-flick and hot-plate tests in mice. KN-62 blocked the effects of nicotine in the tail-flick test with an AD50 value of 1 (0.05–1.9) µg/mouse. In contrast, KN-62 at the highest dose tested (20 µg) failed to significantly block the effect of nicotine in the hot-plate test. In addition, a significant decrease of nicotine-induced analgesia in the tail-flick test but not the hot-plate test was observed in CaM-Kinase II heterozygous mice. These results suggest a differential activation of CaM Kinase II by different nicotinic receptors.

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145 Concordance of reported smoking behavior between adolescent smokers and their parents

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Family dynamics affect adolescent smoking behavior. Both ethnic and gender differences seem to exist with respect to the level of parental involvement in adolescent smoking behavior. The present study examined the concordance of self-reported cigarettes smoked per day (CPD) among adolescents as reported by both teens and parents. We hypothesized that differences exist between male (n = 12) and female (n = 25) adolescent smokers, and AA (African American) (n = 7) adolescent smokers and non AA (n = 30) adolescent smokers. Participants consisted of 37 teenage adolescent smokers 15.3 (1.3) enrolled in an accruing smoking cessation study, which involved consent for participation and parental knowledge of their adolescents smoking at least 10 cigarettes per day. Data on parental observation of cigarette consumption were obtained from a Parent/Guardian’s Weekly Treatment Observation Form on the second treatment visit (at 3 days of treatment enrollment) along with CPD disclosed to nursing staff by the adolescent. Two-way χ² analysis demonstrated that female adolescent smokers and their parents had high rates of concordance (χ = 19.3 P = 0.004) males, however, did not (χ = 10.1 P = 0.341). Non-AA adolescents, also had high rates of concordance with parents (χ = 22.3 P = 0.008), while AA adolescent smokers, did not (χ = 2.9 P = 0.577). Given the influence of socio-environmental factors on smoking behavior and cessation, these preliminary findings suggest the need for a closer look at gender and ethno-racial differences in degree of parental monitoring and/or adolescent disclosure of smoking behavior.

146 History of suicide and depression among entrants to heroin dependence treatments

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Aim: To determine the prevalence of attempted suicide, major depression and associated factors among entrants to opiate dependence treatment. Subjects: 331 consecutive entrants to opiate dependence treatment in Sydney, Australia: methadone maintenance (MM, n = 142), detoxification (DX, n = 115), therapeutic community (TC, n = 74). The mean age was 28.6 years, and 64% were male. Procedures: 19 treatment agencies were randomly selected, stratified by modality. All entrants to treatment were approached to complete a structured interview. Results: 31% of entrants had attempted suicide, 13% in the preceding 12 months. Current suicidal ideation was present in 25% of entrants, 24% met criteria for a current DSM-IV diagnosis of major depression, and 17% were using antidepressants. A history of suicide was more common (P < 0.05) among TC entrants (43%) than among MM (30%) or DX entrants (25%). Females were more likely to have attempted suicide, both ever (39 vs. 27%, P < 0.05) and in the preceding year (20 vs. 10%, P < 0.05), and to be using antidepressants (25 vs. 13%, P < 0.01). Entrants with a history of suicide had commenced drug use at an earlier age (13.2 vs. 14.1 years, P < 0.05), were more likely to have overdose (60 vs. 45%, P < 0.05), to have current major depression (38 vs. 17%, P < 0.001) and to be using antidepressants (30 vs. 11%, P < 0.001). Conclusions: Suicide and suicidal ideation is a major clinical issue in opiate treatment, particularly among females.

147 CORRELATES OF SOCIAL PHOBIA IN DEPRESSED ADOLESCENTS WITH CONDUCT DISORDER AND SUBSTANCE DEPENDENCE

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The rate of Social Phobia (SP) in adolescents is estimated to be 13%. Adults with SP have shown high rates of comorbidity with Substance Use Disorders (SUD) and depression, although this has not been fully assessed in adolescents. HYPOTHESIS: We hypothesized that the incidence of SP would be higher in depressed adolescents with SUD and Conduct Disorder (CD) than that reported in the general population, and that SP would be associated with greater severity of depression and SUD, lesser severity of CD, and may also influence drug of choice. METHODS: We analyzed data from a preliminary cohort of 27 depressed adolescents (ages 13–19) with CD and SUD entering a controlled trial assessing the impact of treatment for depression. Subjects meeting DSM-IV criteria for SP were compared to subjects without SP on measures of depression, CD, and SUD. RESULTS: 37% (N = 10) of subjects met DSM-IV diagnostic criteria for SP. Subjects with SP had more severe depression (P < 0.01). No differences were found between the two groups on measures of SUD and CD severity or drug preference in this preliminary sample. We will continue to assess these outcome measures as subject accrual increases. CONCLUSIONS: Depressed adolescents with CD and SUD may have high rates of SP. Social Phobia may also be associated with more severe depressions in such youth.

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148 PERSISTING EFFECTS OF NICOTINE ON COGNITIVE PERFORMANCE IN RHESUS MONKEYS

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Desirable or beneficial effects, other than pleasure or reward, may contribute substantially to the motivation for use of abused drugs. Although this concept is typically considered important in the context of “self-medication” of mental disorders (i.e., smoking rate in schizophrenia) it often receives short-shrift in the context of substance abuse in otherwise healthy individuals. In particular, improvements in attention, learning, memory and motor performance have been observed with many abused drugs such as nicotine, caffeine, cocaine and amphetamine, among others. In addition to acute improvement on attention, nicotine has beneficial effects on visual recognition memory which last at least 24 h in monkeys. To determine if the persisting effects of nicotine benefit additional cognitive domains, rhesus monkeys were trained to perform tests adapted from a human neuropsychological assessment battery (CANTAB; CNeS, Ltd., Cambridge, UK) as well as a bimanual motor skill task (BMS). The battery included tests of learning (paired-associate learning; PAL), memory (delayed match to sample, DMS; self-ordered spatial search, SOSS), reinforcer efficacy (progressive ratio; PR) and vigilance/motor response (reaction time; RT). Animals were trained to stable performance on all tasks and then the effects of challenge with nicotine (0.003–0.056 mg/kg, i.m.; 15 min, 24 h pretreatment) was then determined. Acutely, nicotine speeded BMS performance and reduced inattention errors in the RT task. Dose dependent improvement of motor and memory performance was observed 24 h after nicotine challenge. Therefore nicotine may produce lasting improvement of multiple cognitive domains including attention and memory in particular. Thus, some drug use may be supported by a beneficial effect on skills necessary for everyday life.

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149 THE EFFECTS OF CIGARETTE SMOKING AND NICOTINE PATCHES ON INCENTIVE MOTIVATION


The ability of nicotine to stimulate release of DA within the mesocorticolimbic ‘reward’ pathways is believed to be responsible for its rewarding effects and thus for nicotine addiction and dependence. Chronic smoking is associated with dysfunctional dopaminergic transmission in animals. However, to date few studies have tested predictions concerning the impact of smoking and abstinence on responsiveness to non-drug reward (or ‘incentive motivation’) in humans. Hypothesis: that acutely abstinence regular smokers will show reduced responsiveness to non-drug reward compared both to non-smokers and to smokers who have ingested nicotine via cigarette or patch. Species: Humans. Number of subjects: 47 smokers and 22 non-smokers. Procedure: all participants were tested twice on a simple psychomotor card-sorting task, on each occasion under conditions of reward (financial incentive for fast performance) and non-reward. Smokers were 10 h abistent on one occasion and received nicotine via cigarette or transdermal patch on the other. Statistical analysis and results: ANOVA revealed that during abstinence smokers showed significantly lower reward responsivity both (i) than when tested in the smoking/patch condition and (ii) than non-smokers. This effect appeared to be more pronounced in women than men. There was no difference in reward responsivity between cigarette and nicotine patch conditions: both means of delivery elevated reward responsivity to a level comparable with that of non-smokers. Importance of findings: Diminished motivation to engage in normally rewarding activities might constitute a significant relapse risk in smokers attempting to quit if they have come to depend on nicotine for its drive properties. The present data suggest that nicotine patches are able to ameliorate this deficit, particularly in women. The gender effect merits further exploration as it was not anticipated but may have implications for the individual tailoring of treatment programmes.
150 WISTAR-KYOTO RATS EXHIBIT REDUCED INTRAVENOUS NICO-
TINE SELF-ADMINISTRATION BEHAVIOR: IMPLICATIONS FOR AN ANI-
MAL MODEL OF DEPRESSION

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Diminished interest in rewarding or pleasurable stimuli is a central feature of depression in humans. A principle interest of our lab is the characterization of altered reward that accompanies depression in distinct animal models. Wistar-Kyoto (WKY) rats are an inbred strain of animals that exhibit heightened responses to stressful stimuli and depressive-like behavior in the forced swim test. Since the behavioral state exhibited by WKY rats arises from an endogenous depressive condition, they are ideally suited for simultaneous testing in stimulant reward paradigms. We sought to establish the reward profile for WKY rats as compared to control animals, Wistar rats. WKY (N = 6) and Wistar (N = 8) rats were first trained on an FR1 schedule of reinforcement for food (45 g pellets). While both strains of rats effectively learned the lever-pressing task, the rate of acquisition was distinct and during an 8-min timed test Wistar rats significantly outperformed WKY rats (49.7 ± 5.8 vs. 32.7 ± 3.1, respectively). One week after jugular implant surgery all rats began intravenous nicotine (0.03 mg/kg per infusion) self-administration training on an FR1 schedule. Differences between Wistar and WKY rats in total nicotine infusions (in a 60 min session) emerged on Day 2 and persisted for the remainder of the study. The data reveal that Wistar rats infused significantly more nicotine during a typical session than WKY rats (16.1 ± 3.1 vs. 3.2 ± 0.7, respectively). This significant dissimilarity in responding was remarkably consistent on a day-to-day basis. Overall, the data from WKY rats coincide with the proposed role as an animal model of depression (i.e., diminished reward). In fact, other animal models have reported reduced sweet solution intake as an indicator of the depressive state of the animal. Importantly, recent neurochemical data from this lab indicate distinct baseline, stress-induced, and nicotine-induced serotonin and dopamine turnover ratios in prefrontal cortex and nucleus accumbens between these two strains of rats. This new data may provide an explanation for altered responding for nicotine in the self-administration paradigm.

151 STYRYL BENZENES AND THIOFLAVINS AS PROBES FOR AMYLOID
AGGREGATES

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Chronic alcohol and drug abusers, in particular those who have a history of 'skin popping' cocaine and heroin, may develop amyloidosis in the liver, lungs and kidneys. The ability to detect such deposits may aid in the diagnosis of amyloidosis and the subsequent development of novel therapeutic modalities. Presently, there are few agents able to specifically identify these amylin deposits. The focus of our research was to design and synthesize small molecules that can be used for in vivo identification of amylin deposits. As a basis for this program, we have synthesized and tested agents derived from the histological stains for amyloid, congo red and thioflavin T (Zhang et al., J. Med. Chem. 44:1905–14), against human islet amylin protein (hIAPP) in vitro. As thioflavin T binding to amylin shifts the excitation wavelength from 370 to 320 nm, binding was monitored as the ratio of the emission (450 nm) to excitation wavelengths (320 nm). Our results have shown that thioflavin T bound to 0.5 micrograms of hIAPP with an affinity of 870 nanomolar. Based on these results, we attempted to enhance affinity of thioflavin T for hIAPP by altering its structure. In addition, the binding affinity of several isothiocyanate derivatives of styrylbenzene to hIAPP were investigated. These compounds represent a new class of potential probes for amylin.

152 NUCLEUS ACCUMBENS NEURAL ACTIVITY IS MODULATED BY
PROBABILITY OF COCAINE AND JUICE REINFORCEMENT IN THE
NONHUMAN PRIMATE

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Simultaneous recordings of multiple single neurons were performed in the nonhuman primate nucleus accumbens during performance of a Go-NoGo task for either cocaine or juice rewards on a discreet trial basis. The type of reinforcer (juice or drug) was varied on a trial to trial basis and its availability was controlled within each session by an independent probability generator for drug reward. The probability that a given trial was either juice or cocaine rewarded was varied systematically but never indicated to the animal except on the basis of the past occurrence within the session. The onset of the trial was signaled by the appearance of a green circle or ‘ring’ into which the animal had to move the cursor. Placing the cursor in the ring initiated a go-nogo trial, the reward determined by the color of the target and nontarget stimuli. Behavioral responding to the juice or drug Targets (moving the cursor into the target) was a direct function of the past history of cocaine availability within the session. Responses to the juice reward decreased as the probability of a drug trial increased across sessions as did responding for drug as the probability of juice trials increased. Different neurons in the nucleus accumbens were identified on the basis of their firing during different phases of the task, including segregation with respect to type of reward as well as to different stimuli. The probability of cocaine versus juice reward was inversely related to the firing rate of accumbens neurons such that the lower the probability of cocaine, the higher the discharge rate of accumbens cells during the drug Target response. There was a distinct threshold with respect to dose for this effect, 0.03 mg per infusion did not affect firing or responding as a function of probability of occurrence in the session, but doses of 0.06 and 0.09 mg per infusion produced consistent variations. The findings suggest that accumbens neurons detect the relative likelihood of reinforcing stimuli and alter behavioral expectancy accordingly.

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153 NON-TREATMENT-SEEKING HEROIN USERS—AN EXPLORATION
OF STRATEGIES USED TO MANAGE DEPENDENCE

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Current knowledge of heroin users relies heavily on samples from treatment facilities or criminal justice systems where dependent or ‘problem’ users are heavily represented. We aim to identify characteristics and drug use patterns among those not seeking treatment, and explore their methods of controlling their heroin use. A cohort of 100 heroin users who have never sought treatment for their heroin use were interviewed as part of a prospective study. Demographics, drug use patterns, risk taking and psychological functioning were assessed. The Severity of Dependence Scale (SDS) and other questionnaires were administered. Preliminary results (n = 52): (mean age 29 years), average age of first heroin use was 22 years, with a mean duration of use being 7 years. The frequency of use over the previous 12 months varied widely, ranging from 6-monthly to daily. Twenty-five percent of subjects had experienced a period of daily use lasting at least 6 months; another 31% had a period of daily use lasting at least 1 month, yet only 6% of the sample were using daily at the time of the interview. Those with a history of daily use (> 7 days) scored higher on the SDS than those without (P = 0.065). Most of the sample had a strategy for
managing their heroin use. Coded responses from the semi-structured interview allowed subjects to be allocated into categories related to maintaining control. Strategy categories were: placing limits on use frequency (15%); placing limits on amount of money spent on heroin (8%); limiting involvement with heroin users and culture (14%); maintaining positive state of mind (8%); periodic abstinence (12%); no strategy (19%); and multiple strategies (23%). Subjects with a strategy of financial limits believed that it was less important to avoid dependence ($P < 0.05$) and displayed the least confidence in changing use ($P < 0.05$). Early results suggest that this is a cohort of heroin users who have been able to exert control over, or reduce, their heroin use without requiring treatment, but that different styles of maintaining control may impact differently on drug use outcomes.

154 **GENDER DIFFERENCES, CUE-EXPOSURE REACTIVITY AND NINE-MONTH OUTCOME**

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Gender differences have been shown to be related to the course of cocaine dependence and treatment. And while previous research has shown cue exposure procedures to be somewhat effective at reducing responsivity of substance dependent individuals to drug related stimuli, the few studies that have examined gender differences in cravings and cue-reactivity have yielded equivocal results. We have recently demonstrated that an active cue-exposure procedure that featured cocaine-dependent individuals receiving immediate feedback about their level of physiological arousal following videotaped exposure to cocaine-related stimuli was capable of positively influencing in-treatment (helplessness, abstinence efficacy), as well as, 9-month outcome (i.e., urinalysis) indices (Sterling et al., 2001). The purpose of the current study was to determine whether differential in-treatment or 9-month follow-up outcomes were obtained for male and female study participants. Subjects in this study were 81 individuals (47 male) who met DSM-IV criteria for cocaine dependence and who had consented to be randomly assigned to either the active cue-exposure or control conditions. Participants were compared along a myriad of pre-treatment, in-treatment, and 9-month follow-up measures. While no obvious systematic pattern of differences on pre-treatment indices was observed, male subjects did report significantly more recent work, $t (79) = 3.08$, $P < 0.05$, and significantly less SCL-90R measured somatization, $t (75) = 2.01$, $P < 0.05$, than their female counterparts. Regarding cue-responsivity, we observed that male subjects responded to a greater number of stimuli, $t (39) = 1.98$, $P = 0.058$, and were more successful at establishing control over their responsivity to the cocaine-related stimuli, $t (35) = 1.90$, $P = 0.07$. These results are especially interesting in light of the finding that no gender differences in treatment retention were observed. With respect to nine-month follow-up, no gender differences on measures of addiction severity, psychological functioning or urinalysis were seen. Further examination of the role of gender in the addiction treatment process is needed.

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155 **THE UTILITY OF THE DEAS-MARIJUANA OBSESSIVE COMPULSIVE SCALE (DEAS-MOCS IN AN INPATIENT ADOLESCENT SUBSTANCE-ABUSING SAMPLE**

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The Deas-Marijuana Obsessive Compulsive Scale (Deas-MOCS) is an instrument that detects ‘craving’ and problem marijuana use in adolescent/young adult populations. The instrument has two factors (interference/loss of control and avoidance), which have been shown to be sensitive and specific in identifying problem marijuana users. The purpose of the study was to explore the utility of the Deas-MOCS in an inpatient adolescent substance abusing sample. Sixty (60) consecutively admitted dually diagnosed inpatient adolescents completed the Deas-MOCS and provided quantity/frequency substance use data. Overall, individuals who met the threshold score on the interference/loss of control subscale smoked almost 1.5 times more marijuana joints and 2.8 times more marijuana blunts than those with scores below the threshold. The Deas-MOCS interference/avoidance threshold was moderately correlated with both quantity and frequency of marijuana use (all $r$-values 0.33–0.55 and $p$ values less than 0.01). Additionally, the Deas-MOCS avoidance threshold score was moderately correlated with both quantity and frequency of marijuana use ($r$-values 0.44–0.59 and $p$ values less than 0.01). We concluded that the Deas-MOCS reliably identifies certain dimensions of ‘craving’ and problem marijuana use in dually diagnosed adolescent inpatients.

156 **END-OF-TREATMENT SELF-EFFICACY AND OUTPATIENT DRUG TREATMENT OUTCOMES IN A STIMULANT-DEPENDENT SAMPLE: WHAT’S THE USE?**

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Drug treatment outcomes research has suggested that an addict’s beliefs about the ability to resist drug use (“self-efficacy”) may be an important predictor of treatment success. More specifically, several studies have demonstrated that higher treatment-end perceptions of self-efficacy over the initiation of drug use predict more favorable treatment outcomes at follow-up. However, empirical support for the association has been equivocal; some reported studies have failed to obtain evidence of an efficacy-outcomes relationship. Methodological imperfections, especially inadequate controls for prior drug use, may account for some of the conflicting evidence. This study conducted a methodologically strict test of the efficacy-outcomes hypothesis in a sample of 177 primarily cocaine-dependent individuals. Self-efficacy to resist any cocaine use in high risk situations (Situation Confidence Questionnaire-39) was measured at the end of a 16-week Cognitive-Behavioral and/or Contingency Management treatment program. A series of linear and logistic multiple regressions were conducted to test whether level of self-efficacy at treatment end or increases in self-efficacy during treatment were associated with the number of cocaine-using days or the presence of cocaine metabolites in urine at follow-up. After controlling for gender, and the Employment, Legal, Alcohol, and Family subscales of the Addiction Severity Index, higher self-efficacy was associated with fewer days of cocaine use and with cocaine-free urine at both 26-and 52-week follow-ups. In contrast, only limited support was garnered for the predictive utility of increases in self-efficacy. Most importantly, when including the number of cocaine-using days in the past month at treatment end as an additional control, neither self-efficacy nor increases in self-efficacy significantly predicted any of the treatment outcomes. It is argued that self-efficacy is primarily a cognitive manifestation of recent drug use. Moreover, recent use, rather than self-efficacy, is the more important proximal predictor of treatment success. If true, this implies that all studies examining the efficacy/outcomes hypothesis should control for recent drug use, and that treatment efforts should in part focus directly on the attainment of drug-free days.

157 **DISRUPTION OF THE QUANTITY AND QUALITY OF COMPLEX BEHAVIOR FOLLOWING MORPHINE ADMINISTRATION IN RATS**

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The disruptive effects of morphine were studied in four Long-Evans rats trained to respond under a multiple schedule of repeated acquisition and performance of response sequences. All experimental
sessions began with an acquisition component, which then alternated with a performance component after 40 reinforcers or 20 min, whichever occurred first. During the acquisition component, subjects acquired a different 3-response sequence each session, whereas in the performance component the sequence remained the same. Responding during both components was maintained by food presentation under a second-order FR2 schedule of reinforcement. An incorrect response produced a 5-s timeout, during which responding had no programmed consequence. Increasing doses of morphine decreased both the rate and accuracy of responding in each component when compared to sessions in which saline was administered (e.g., control session). However, accuracy of responding in both components was disrupted at doses of morphine that had little or no effect on response rate, indicating that the quality of behavior is more sensitive to the effects of morphine than the quantity of behavior in rats. In summary, morphine dose-dependently disrupted both the quantity and quality of behavior in rats responding under a multiple schedule of repeated acquisition and performance.

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158 A PROBLEM SOLVING MODEL OF DEPRESSION AND COCAINE USE
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Comorbid major depression is common among those seeking treatment for cocaine dependence. The presence of both disorders is associated with elevated clinical symptoms, more intense cravings for cocaine, and a poorer overall prognosis. This study examined relations among depression, craving and problem-solving ability and their impact on cocaine use in 102 cocaine dependent individuals. It was hypothesized that problem solving would mediate the relation between depression and cocaine use, specifically, that increased depression would affect cocaine use indirectly by reducing self-efficacy and the ability to generate effective coping plans. A second hypothesis was that problem solving would moderate the relation between craving and use such that having better coping abilities would weaken the association between these variables. A series of regression models was used to test the hypotheses, and additional exploratory analyses were conducted. As expected, problem solving fully mediated the relation between depression and use, with self-efficacy emerging as the key problem-solving component. The moderator hypothesis was not supported. Findings are consistent with relapse prevention and self-management models of addiction that emphasize treatment strategies to enhance self-efficacy and coping skills.

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159 THE DURATION AND CORRELATES OF SUBSTANCE ABUSE TREATMENT CAREERS AMONG PEOPLE ENTERING PUBLICALLY FUNDED TREATMENT IN CHICAGO
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Substance use dependence with multiple co-occurring problems is increasingly recognized as a chronic, relapsing condition that may last for decades and require multiple episodes of care over many years before reaching a sustained state of remission. Unfortunately there are very few studies that have examined the duration and correlates of care over multiple years and episodes—referred to here as treatment careers. Data are from 1326 people recruited from a stratified sample of admissions to publically funded treatment programs on Chicago’s west-side and followed up at 6, 18, 24, 36, 48, and 60 months (with over 94% completed). With an average age at the referent intake of 35 (S.D. = 8) years, the sample is 59% female, 87% African American, 7% Hispanic, and 5% white. With an average of 18 years of use (from age of first use at 17 to age 35), the most common dependence diagnoses were for cocaine (64%), alcohol (44%), opioids (41%) and/or marijuana (14%). Using lifetime treatment histories collected at intake and subsequent treatment utilization recorded during follow-up interviews, we estimated the duration of treatment careers in a survival analysis (with people still using or in treatment at the last follow-up treated as right censored). The median time from the date of first treatment admission to the last treatment discharge preceding sustained recovery was 7.1 years. The median length of the treatment career was significantly longer for those presenting with 2+ or 1 prior admission than for those presenting for the first time (9.2 vs. 5.3 vs. 1.3 years). Longer treatment career durations were associated with higher ASI drug composite scores, co-morbid psychological problems, fewer sober/non-using peers, being male, going to methadone treatment, residing in unstable housing, high neuroticism scores and low Agreeableness and Conscientiousness scores on the NEO. The results suggest the need to conduct long-term research on treatment careers, not just individual episodes of care.

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160 THE SYNTHESIS AND EVALUATION OF NEW METHYLPHENIDATE-RESTRICTED ROTATION ANALOGS
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The long term objective of this research is to develop treatment agents for cocaine abuse. An important site of the molecular action of cocaine is the binding site associated with the dopamine transport (DAT) complex where the reinforcing effect of cocaine is thought to be mediated. We have synthesized are a series of restricted rotation analogs of methylphenidate, which have substantial biological activity. In terms of binding to the DAT, as compared to the unsubstituted (Y = Z = H) analog: the ketone, a-alcohol, and a-methylether are less active; the b-alcohol is equipotent; and the b-methylether more potent. The ring substituted (X = 3,4diCl) analog is more potent. The unsubstituted compound has strong discriminative activity in both rats and monkeys. The a-alcohol seems to have little biological activity whereas the a-methyl ether is much more active in terms of locomotor stimulation and drug discriminative in rats. Further biological evaluation of all of these compounds, both in rats and monkeys is in progress and will be discussed in detail.

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161 EFFECT OF ALCOHOL ADMINISTRATION TIME ON THE CORE BODY TEMPERATURE OF HUMAN SUBJECTS OVER 18 H
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Chronopharmacological studies have shown that the response of organisms to drugs can be dependent on time of day the drugs are administered. The aim of this study was to investigate the effect of
alcohol administration time on the core body temperature of 12 human subjects over an extended period of time. Rectal temperature was logged continuously for 18 h using a portable electronic data logger. A within-subjects design was used; subjects logged rectal temperature under alcohol and no alcohol conditions. It was hypothesized that alcohol would have a more potent effect after alcohol administration at 1300 h compared to the 1800 h. It was further hypothesized that rectal temperature would be significantly increased during the sleep phase following alcohol administration, relative to the no alcohol condition. Planned contrasts with trend analysis, were used to analyse the results. The hypotheses were supported. Alcohol significantly decreased core body temperature relative to the no alcohol condition when it was administered in the afternoon. However alcohol did not have a significant impact on core body temperature after it was administered in the evening. Additionally, rectal temperature was significantly increased across the sleep phase (2330–0830 h) following alcohol administration compared to the no alcohol condition. These findings have important implications for researchers conducting behavioural, physiological, and pharmacological studies. Consideration of the time of day measures are examined is necessary as effects could be influenced by the time the studies are performed. Likewise, the findings of this study have implications for public health and workplace safety.

162 COGNITIVE TESTING AFTER INACTIVATION OF THE LATERAL PREFRONTAL CORTEX, A SITE WhOSE FUNCTIONS MAY BE RELEVANT FOR MEMORY SYSTEM REGULATION OF DRUG ADDICTION


Recent studies implicate a role for cognition in regulating reward process, including drug addiction. In particular, it has been suggested that different memory systems are critical for the acquisition, maintenance and reinstatement of drug-seeking and drug-taking behavior. To evaluate how memory systems may regulate drug addiction, it is first necessary to identify the pertinent anatomical sites that may be relevant by means of cognitive testing. Reported here are the effects of bilateral lidocaine inactivation of the lateral prefrontal cortex (PFC). The lateral PFC was examined because anatomical studies have shown that highly organized connections exist between the nucleus accumbens, a brain site that mediates reward, and the lateral PFC. The odor-guided delayed win-shift task was used specifically to assess acquisition of working memory that is lateral PFC-dependent. Also examined was the conditioned cue preference task, which measures basolateral amygdala-dependent conditioned stimulus-reward learning. Results showed that direct infusion of 10 mg lidocaine (n = 5) into the lateral PFC during the delay period significantly blocked the working memory necessary to acquire the task as compared to infusion of saline (n = 5). Analysis of the types of errors made during the test phase revealed that lidocaine treated rats exhibited more between phase errors (P < 0.006) and an equal number of within phase errors (P < 0.053). Lidocaine inactivation of the lateral PFC did not, however, impair conditioned stimulus-reward learning processes in that both saline (n = 4) and lidocaine (n = 4) treated rats showed a conditioned preference for the reward–paired environmental cues. Together, these findings indicate that lidocaine inactivation of the lateral PFC leads to cognitive changes that are both anatomically and behaviorally specific. This cognitively identified site can now be used to elucidate the role of the lateral PFC in regulating addiction-related behavior.

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163 JOB SKILLS TRAINING OUTCOMES IN A THERAPEUTIC WORKPLACE TRAINING PROGRAM

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The Therapeutic Workplace is an employment-based treatment for drug addiction and unemployment. This treatment has two phases. Initially, participants are taught skills they need to perform a data entry job. Participants who acquire the needed skills are hired as employees in an income-producing Therapeutic Workplace business as data entry operators. Throughout both phases participants are paid for attending the workplace and for performance. However, to promote abstinence, patients are required to provide drug-free urine samples to gain daily access to the workplace. In an initial prototype, participants were taught academic skills (e.g., reading, spelling) prior to receiving data entry job skills training. That basic skills training required considerable time and cost to complete. In this study, a more focused jobs skills training program was evaluated in cocaine-dependent methadone patients (N = 6) and in recently detoxified HIV-positive injection drug users (N = 7). Trainees received computerized typing, keypad and data-entry training programs that have three main characteristics. (1) Each program is divided into small steps that gradually increase in complexity. (2) Each trainee continues on a step until the trainee reaches a criterion level of speed and accuracy. (3) Trainees earn and lose monetary vouchers for correct and incorrect responses, respectively, and earn bonus vouchers for completing steps. Preliminary results are available for the typing and keypad programs and show that all trainees who attended the workplace consistently acquired typing and keypad skills. On average, the trainees learned to type all alphabetic keys (upper and lower case) in an average of 47 training h (range 15–103) over an average of 14 weeks (range 5–22), and all keys on the number pad in an average of 27 training h (range 2–53) over 9 weeks (range 2–20). These results show that adults with long histories of chronic unemployment and drug addiction can reliably acquire typing and keypad skills, and do so over relatively short periods of time.

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164 ASSESSING THE INITIATION AND CESSATION OF COCAINE SELF-ADMINISTRATION IN NON-TREATMENT SEEKING, COCAINE-DEPENDENT VOLUNTEERS

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Human laboratory models of cocaine self-administration (SA) are critical tools for assessing factors that influence cocaine-seeking behavior. Two inpatient studies were designed to evaluate two novel procedures: one targeting the ability to stop taking cocaine once cocaine SA was initiated (Cessation model) and a second focusing on the ability to refrain from initiating cocaine SA when in a state of abstinence or primed with cocaine (Relapse model). In the Cessation model (Study 1), participants sampled cocaine (0, 12.5, 25 or 50 mg/70 kg IV) and then chose between additional injections of that dose and increasing amount of money ($1, $4, . . . $16) over six successive trials. Each cocaine dose was evaluated under three inter-trial-intervals (15, 30 min, and a self-selected interval). In the Relapse model (Study 2), participants sampled cocaine (0, 15 or 30 mg/70 kg IV) 1 day and on other days chose between that dose and decreasing amounts of money ($19, $16, . . . $1) over seven trials. At each SA dose, participants were administered 0, 15 or 30 mg/70 kg cocaine 30 min prior to the first choice trial to assess the effects of cocaine priming on cocaine SA. The choice to take cocaine was dose-dependent in both procedures. The
Cessation model yielded nearly all cocaine choices when active cocaine was available and little relationship between the choice to take cocaine and the alternative reinforcer. In contrast, cocaine-taking in the Relapse model was moderate, negatively related to the monetary alternative, and potentiated by cocaine. These studies advance current methodology for assessing cocaine-taking behavior and provide a human laboratory illustration of cocaine-induced ‘priming’ of cocaine SA. Supported by NIDA R01 DA05196, T32 DA07209, K05 DA00050.

165 DEVELOPMENT AND APPLICATION OF A CHIRAL ASSAY FOR THE D- AND L-ISOMERS OF MODAFINIL IN SERUM

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Modafinil is a novel stimulant approved by the FDA for use in the treatment of narcolepsy and idiopathic CNS hypersomnia. Its pharmacology suggests utility for other indications including treatment of cocaine dependence. In order to investigate the potential interactions of modafinil and cocaine, we developed and validated an HPLC method to measure the separate enantiomers of modafinil in human serum samples. D- and L-modafinil were separated following organic extraction from serum on a β-cyclodextrin column, then detected by UV absorbance spectroscopy. Validation studies included determination of specificity, precision, accuracy and recovery. Inter- and intra-day assay variability (CV) typically ranged from 3 to 4%. The limit of quantitation (0.5 mg/ml) was well below the concentration found in serum samples obtained from patients receiving therapeutic trials of modafinil. Neither cocaine nor its major metabolites co-eluted with the enantiomers of modafinil. An example of apparent stereoselective disposition is presented as D-modafinil was eliminated more rapidly than l-modafinil from serum samples collected from a volunteer after receiving 200 mg twice daily of racemic modafinil for 5 days. Overall, the validation data support the use of this method for human pharmacokinetic studies of modafinil in the presence of cocaine co-administration.

166 SEX AND HORMONAL INFLUENCES ON PAIN RESPONSIVITY IN HUMANS

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Although most studies show that women have higher subjective pain ratings in response to painful stimuli, less consistency exists across studies with regard to sex differences in the ability to discriminate painful stimuli. This study evaluated both the emotional and sensory aspects of pain in normally-menstruating women (NMW) at five menstrual cycle phases, in women maintained on oral contraceptives (OCW), and in men (M). All participants completed 10 sessions (two sessions per ‘phase’). During the cold pressor test (CPT), participants immersed the forearm into water (4 °C); latency to first pain report (threshold) and latency to withdraw the arm from the water (tolerance) were measured. During the mechanical pressure test (MPT), weights were placed, one at a time, upon the fingers. Two primary dependent measures obtained from the MPT were P(A), ability to discriminate between two stimuli, and B, willingness to report pain. Preliminary results suggest that both pain threshold and tolerance during the CPT were greater in NMW, compared to OCW and M. In contrast, for the MPT, B values were greater in M, indicating greater stoicism, compared to the two groups of women. Ability to discriminate pain, however, was similar across groups. Pain tolerance increased in an orderly fashion across the menstrual cycle in NMW, and was greatest during the late luteal phase. No systematic changes across menstrual phase in P(A) and B were found for NMW during the MPT. These results suggest that for mechanical pressure pain, men and women do not differ in the ability to discriminate pain, but willingness to report pain is lower in men. However, NMW appear to have a greater tolerance for cold pressor pain, particularly during the late luteal phase. Future studies will examine the effects of morphine as a function of sex and hormonal status.

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167 MALE-FEMALE DIFFERENCES AND FAMILY ATTENTION IN EARLY INHALANT TRANSITIONS: EVIDENCE FROM THE PACARDO STUDY OF ADOLESCENTS IN LATIN AMERICA

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Mainly from US studies, current evidence suggests protective influence of parental supervision on early initiation of drug use. We seek to estimate how inhalant drug use might depend upon two inter-related aspects of family attention, with separate estimates for males and females. Our study data are from anonymous self-report questionnaires administered for recent NIDA-sponsored PACARDO surveys of school-attending adolescents in nationally representative samples drawn within Panama, five countries of Central America, and the Dominican Republic. Standardized multi-item sets were used to assess response variables (e.g., ages at first inhalant use), with separate scales for family supervision (FS) and communication (FC). Among 5121 male and 5621 female students, 635 reported use of inhalants. Based upon the polytomous form of multiple logistic regression, and with attention to classroom-clustered samples, among boys, occurrence of inhalants use was found to be associated with higher FS levels and, independently, with higher FC levels, but among girls, the association was present for FS but not for FC. Boys with the lowest supervision were about 2–2.5 times more likely to have used inhalants as compared to boys in the two upper tertiles (P < 0.05); for FC, boys with the lowest communication were about 1.5–2 times more likely to have used inhalants as compared to boys in the two upper tertiles (P < 0.05). A similar magnitude of association was found for girls with the lower supervision scores (P < 0.05), but not with respect to communication (P > 0.05). Next steps include consideration of exposure opportunity as an intermediate step, and consideration of other potential intermediary variables such as affiliation with drug-using peers, or others influenced by family attention. A long-term goal is new insights for design of evidence-based prevention strategies for boys and girls.

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168 HEAVY MDMA USE IS ASSOCIATED WITH INCREASED IMPULSIVITY

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Methylenedioxymethamphetamine (MDMA) popularly known as “ecstasy” decreases CNS serotonin levels in animals, and blunts
response to serotonergic challenge in humans. Since lower serotonin function is associated with increased impulsivity, we hypothesized that heavy MDMA users would have increased impulsivity as measured by behavioral laboratory and questionnaire measures of impulsivity. Method—Sixteen current MDMA users and 20 non-drug using controls were recruited and completed behavioral laboratory and questionnaire measures of impulsivity. An analysis of variance (ANOVA) was performed comparing heavy MDMA users, casual users, and controls. Results—Heavy MDMA users were significantly more impulsive on both a behavioral laboratory and a questionnaire measure of impulsivity than non-drug using controls. Within MDMA using subjects, there was a significant positive correlation between the quantity of self-reported MDMA use and behavioral laboratory measured impulsivity. Implications—Heavy MDMA users show greater impulsivity, which is correlated with the level of self-reported MDMA use. The increased impulsivity did not appear to be solely related to concomitant drug use. In light of the known effect of MDMA on serotonin, it is possible that MDMA increases impulsivity in regular, frequent MDMA users.

169 DEVELOPMENTAL COCAINE ALTERS FUNCTIONAL COUPLING IN CENTRAL DA SYSTEMS

D. Dow-Edwards and S. Melnick, State University of New York, Downstate, Brooklyn, NY Postnatal cocaine administration to the SD rat (a model of third trimester human exposure) has been shown to alter brain function and behavioral responses to dopaminergic drugs when tested in adulthood. This study tested the hypothesis that cocaine exposure during postnatal day (PnD) 11–20 alters the functional relationships between components of the mesolimbic and nigrostriatal dopamine systems. During PnD11–20, 40 male rats received either water or 50 mg/kg cocaine daily. On PnD60, subjects were challenged with either saline or 5.0 mg/kg SKF82958, a selective full D1 receptor agonist, and were monitored for locomotor activity and videotaped to allow for behavioral assessments for 75 min. Thirty minutes after the drug challenge, the 2-deoxyglucose method of Sokoloff was carried out. Rates of metabolism in components of the nigrostriatal and mesolimbic systems were examined using Pearson Product Moment Correlations which revealed that in the nigrostriatal system of the controls, rates were highly correlated and that the cocaine-treated rats showed much lower degrees of correlation. For example, there was a significant difference in the correlation between the somatomotor cortex—caudate@1.6 in the two groups (Linear regression analysis). These data suggest that function in components of the nigrostriatal and mesolimbic systems is strongly linked and that this relationship is significantly weaker in the cocaine-treated rats compared to the controls.

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170 DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF FLUOXETINE IN SMOKING CESSATION TREATMENT WITH NICOTINE PATCH AND COGNITIVE BEHAVIORAL TREATMENT: FINAL REPORT

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Smoking cessation attempts are often complicated by nicotine withdrawal symptoms. Fluoxetine’s antidepressant and anorexiant properties and capacity to attenuate compulsive behavior suggest that it might facilitate smoking cessation treatment. In a double-blind randomized trial of fluoxetine for smoking cessation, 150 daily-smokers were assigned to placebo (n = 48), 20 mg (n = 51), or 40 mg fluoxetine (n = 51). All participants received group cognitive-behavioral therapy (6 weeks) and transdermal nicotine patch (10 weeks). After 14 weeks, 43.9% of the placebo group, 53.8% of the 20 mg fluoxetine group, and 64.7% of the 40 mg fluoxetine group had quit smoking. Participants with a history of major depressive disorder were significantly more likely to quit smoking in the fluoxetine groups (75%) than the placebo group (28.6%). Findings suggest fluoxetine is efficacious in smoking cessation, particularly for people with major depressive disorder histories.

171 COCAINE-MEDIATED, SIGMA RECEPTOR-DEPENDENT SUPPRESSION OF ANTITUMOR IMMUNITY IS DUE TO INDUCTION OF IL-10 AND TGF-B

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In this study, we show that cocaine suppresses host immune reactivity against lung cancer. To determine the effect of cocaine on tumorigenicity in vivo, mice were pre-treated for two weeks with i.p. injections of cocaine (5 mg/kg) or diluent control (saline) five times per week. Fourteen days following the initiation of cocaine or diluent injections, 5 x 10^5 Lewis Lung Carcinoma (3LL) or 105 Line 1 alveolar carcinoma (LC12) tumor cells were implanted subcutaneously. Following implantation of tumor cells, mice continued to receive cocaine injections five times per week. There was significant enhancement of 3LL and LC12 tumor growth in cocaine-treated mice but administration of a specific sigma 1 receptor antagonist (BD1047) was able to block the accelerated tumor growth. The immune inhibitory cytokines, interleukin 10 (IL-10) and transforming growth factor-beta (TGF-b) were significantly elevated at the tumor site following cocaine administration and neutralizing antibodies for these cytokines reversed the cocaine-mediated enhancement of tumor growth. Both antigen presenting cells (APC) and T cells from cocaine-treated mice showed limited capacities to generate alloseactivity. APC from cocaine-treated mice revealed diminished capacity to produce IL-12 both constitutively and in response to CD40 ligation. Our findings suggest the cocaine promotes tumor growth by inhibiting antitumor immunity by a sigma 1 receptor-mediated, cytokine-dependent pathway.

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172 (−)-6-B-PROPYLNICOTINE ANTAGONIZES THE ANTILOCOCIC EFFECTS OF NICOTINE

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We have identified a region of limited bulk tolerance on nicotinic acetylcholine (nACh) receptors associated with the 6-position of nicotine (Eur. J. Pharmacol. 1996, 31, 875–888). For example, 6-methylnicotine binds at nACh receptors with an affinity comparable to nicotine, and produces nicotine-like antinociceptive (mouse tail-flick assay), locomotor (mouse), and discriminative stimulus (rat) effects with nicotine-like potency. We explored this region further by preparing and evaluating additional 6-alkyl analogs of nicotine. Whereas (−)-6-ethylnicotine retained activity and potency, the (±)- and (−)-6-n-propyl analogs—although binding at nACh receptors with about 10-fold reduced affinity (K_i = 20–25 nM)—failed to display nicotine-like actions in the functional assays. In fact, (−)-6-n-propylnicotine antagonized the antinociceptive effects of nicotine in a dose-related fashion (AD50 = 4.9 μmol/kg). (−)-6-n-Butyl-nicotine (Ki = 21
nM) behaved in a similar manner (AD50 = 9.2 umol/kg). However, (--)-6-n-propylnicotine failed to antagonize either the locomotor or discriminative stimulus effects of (--)-nicotine. There are currently few competitive nACh receptor antagonists available and the most widely used is dihydro-beta-erythroidine (DHBE). DHBE antagonizes the antinociceptive and discriminative stimulus effects of nicotine, but not nicotine’s effect on locomotor activity. The noncompetitive nACh receptor antagonist mecamylamine antagonizes all three actions. (--)-6-

173 IMPACT OF MATERNAL PSYCHOPATHOLOGY AND PARENTING ATTITUDE ON DYSREGULATION IN CHILDREN OF WOMEN WITH SUBSTANCE USE DISORDER

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This study examined the relation between maternal psychopathology and child dysregulation (cognitive, emotional, behavioral) in a sample of substance abusing (SUD+) and non-abusing (SUD−) women and their children (n = 207). Fifty three percent of the children were female, ranging in age from 1–9 years, with non-significant differences in the mean age between the children in the SUD+ and SUD− groups of mothers. There were no significant differences in mean age, SES, ethnicity, and education between the SUD+ and the SUD− women. The results of moderation analyses revealed that maternal psychopathology assessed in adolescence (age 14–18) did not predict child dysregulation. However, parenting attitude assessed at age 19–23 predicted child dysregulation (assessed contemporaneously, but independently) (β = −0.19; P = 0.008). In addition, parenting attitude moderated the association between maternal antisocial behavior (ASB) and child dysregulation (β = −0.16; P = 0.05). These findings indicate that parenting attitude in interaction with ASB in young adult SUD women, relative to adolescent psychopathology, is a better predictor of child dysregulation. In conclusion, given that dysregulation is typically an antecedent to ASB which is, in turn, a precursor to substance abuse, the quality of parenting may be a mechanism that places children of SUD mothers at high risk for developing early-onset SUD themselves.

174 CHARACTERIZING WITHDRAWAL FOR METHAMPHETAMINE DEPENDENCE USING TWO SELF-REPORT MEASURES: PRELIMINARY ANALYSIS

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Objectives: Given the increasing rate of methamphetamine dependence, it is important for treatment providers to understand the progression of withdrawal and mood symptoms that may emerge during the early phase of withdrawal as opposed to the later stages of withdrawal. To our knowledge this syndrome has not been examined in a group of methamphetamine dependent individuals who were continuously monitored. To address this critical issue we examined self-report levels of depression in two samples of methamphetamine dependant individuals. Methods: In order to measure depression symptomology comparatively between two groups of methamphetamine dependant participants, the BDI and BSI were administered at two different periods of time. Tests were given during the first 3 days of abstinence to evaluate the early phase of withdrawal, while these same scales were completed in a separate population after seven to 14 days of abstinence to examine persistent symptoms. Results: Our results indicate that methamphetamine dependant individuals initially showed mild to mild moderate depressive symptoms; however, the symptoms resolved within 3 days. Conclusions: In contract to earlier research, it appears that regardless of when withdrawal symptoms emerge, these symptoms eventually seem to resolve themselves rather than progress to more severe mood disturbances. Future studies may want to examine whether these mood states remain resolved over greater periods of time and whether quantity or quality of methamphetamine used effects this resolution.

175 PERSONAL AND CONTEXTUAL FACTORS THAT AFFECT RETROSPECTIVE SELF-REPORTS OF SUBSTANCE USE AND HIV RISK BEHAVIORS

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Survey studies that assess retrospective self-reports of substance use and HIV risk behavior often do not allow for direct evaluations of validity. Further, reliability estimates and indicators of convergent validity are expensive and may not be feasible in intervention research or large clinical trials. Because sensitive self-reports are vulnerable to self-presentation and other demand biases, personal characteristics and contextual factors that may negatively affect self-report must be addressed. This study examined the effects of anonymity, gender, and erotophilia on the quality of self-reported alcohol, drug, and sexual behaviors. A sample of 155 male and 203 female undergraduate students were randomly assigned to an anonymous and a confidential (i.e., non-anonymous) assessment condition. Gender, erotophilia, frequency reports on substance use, sexual behaviors, illegal activity, and perceived item threat were assessed by questionnaire. χ² and ANOVA tests indicated that data quality (item refusal, frequency behaviors, terminations) was strongly affected by experimental condition and gender. Terminations and item refusals were more frequent in the confidential condition and among women. Logistic regressions indicated that self-reported engagement in drug, alcohol, and HIV risk behaviors was positively related to both perceived question threat and erotophilia. Path analyses suggests that question threat mediates the effects of anonymity manipulations and gender on data quality (item refusal, termination), and that erotophilia mediates the effects of gender on incidence and frequency self-reports. The present study provides clear evidence that non-anonymous assessment conditions can lead to reduced data quality, and suggestive evidence than non-anonymous conditions may lead to underreporting of the incidence and frequency of drug, drug, alcohol, and HIV risk related behaviors. Limitations of anonymous assessments and their generalizability to larger surveys of substance use (NCTOPPS) and sexual risk behaviors are discussed.

176 EFFECTS OF A SINGLE 50% INCREASE IN DAILY METHADONE DOSE ON HEROIN CRAVING AND MOOD IN LOW-VERSUS HIGH-DOSE METHADONE PATIENTS

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Clinical experience suggests that a considerable part of methadone patients occasionally urge for extra methadone for different reasons. This study sought to assess the acute-on-chronic effects of a single 50% increase in patient’s daily methadone dose on heroin craving, mood and opioid-related symptoms. A randomized, double-blind, placebo-controlled, counterbalanced crossover design was used to test the safety of this increase and the hypothesis that low-dose patients (20–60
177 Novel trisubstituted hydroxy piperidine analogues for the dopamine transporter

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In our ongoing effort to develop pharmacologically active agents for the dopamine transporter (DAT), we designed novel trisubstituted hydroxy piperidine derivatives. In designing these new compounds, we wanted to explore the effect of introduction of polar groups such as hydroxy and amino into the piperidine ring of our previously developed lead compound, 4-[2-(bis(4-fluorophenyl)methoxy)ethyl]-1-benzylpiperidine. The introduction of an hydroxyl group at the 3-position gave rise to racemic trans hydroxy compounds. Biological evaluation of the racemic trans isomer mixture indicated low nanomolar activity at the DAT with high selectivity for the DAT compared to the activity at the serotonin and norepinephrine transporters. Consequently, the racemic mixture was separated into pure enantiomers and the activity of each enantiomer is currently being evaluated. All compounds are characterized for their binding at the dopamine, serotonin and norepinephrine transporters. Synthesis, measurement of biological potency, and preliminary characterization of activity in studies on in vivo locomotor behavior and drug discrimination will be presented.

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178 Meso-transdiene, a potent, selective antagonist at alpha3-containing nicotinic receptors


Lobeline (LOB), a nicotinic acetylcholine receptor (nAChRs) antagonist, alters presynaptic dopamine (DA) storage and release via inhibition of the vesicular monoamine transporter (VMAT2) and inhibition of the DA transporter (DAT). To determine if defunctionalization of LOB affords greater selectivity at its sites of action and if C2-C6 stereochemistry is important for activity, the present study determined the effect of LOB and defunctionalized analogs, cis-meso-transdiene (MTD) and trans-meso-transdiene (tMTD) at nAChRs, VMAT2, DAT and the serotonin (5-HT) transporter (SERT) using rat brain. LOB was 3-orders of magnitude more potent than MTD or tMTD in inhibiting [3H]nicotine ([3H]NIC) binding to striatal membranes (Kd = 0.016, 11 and 12 μM, respectively); LOB inhibited NIC-evoked 86Rb+ efflux from thalamic synaptosomes, but MTD did not (IC50 = 0.73 and > 10 μM, respectively). Furthermore, LOB inhibited [3H]methyllycaconitine binding to whole brain membranes, but MTD and tMTD did not (Kd = 6.6, > 100 and > 100 μM, respectively). In contrast, MTD was 5- and 60-fold more potent than LOB in inhibiting NIC-evoked [3H]norepinephrine release (IC50 = 21 and 95 nM, respectively) and NIC-evoked [3H]DA release (IC50 = 30 nM and 1.8 μM, respectively). Surprisingly, MTD was only 6-fold more potent than tMTD in inhibiting NIC-evoked [3H]DA release. Thus, defunctionalization of LOB affords greater potency and selectivity for inhibition of z3β[2] and z3β[4] nAChRs. LOB, MTD and tMTD were equipotent in inhibiting [3H]methyllycaconitine binding to vesicle membranes (Kd = 5.5, 1.3 and 5.2 μM, respectively), indicating that these structural modifications did not alter interactions at VMAT2. In contrast, MTD and tMTD were more potent than LOB in inhibiting [3H]DA uptake (IC50 = 1.5, 0.85 and 90 μM, respectively) and [3H]-5-HT uptake (IC50 = 23, 1.2 and 77 μM, respectively), indicating that LOB defunctionalization enhances the inhibitory potency at DAT and SERT, with no change at VMAT2. Thus, the defunctionalized LOB analog, MTD has high affinity and selectivity for z3[3]-containing nAChRs.

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179 Coerced treatment: characteristics of methamphetamine users and treatment outcomes

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Policy makers have responded to the increase in the prevalence of methamphetamine (MA) use and the associated social costs (such as crime and child abuse and neglect) by mandating a growing number of MA users to substance abuse treatment via the criminal justice system (CJS) and/or child protective service (CPS) agencies. This analysis uses natural history interview data from 350 clients treated for MA use in Los Angeles County to: (1) describe those who were pressured by CJS and/or CPS to enter treatment; (2) look at the differences between clients who were pressured into treatment and those who were not; (3) compare treatment characteristics for pressured and non-pressured MA users; (4) examine differences in treatment outcomes for the pressured and non-pressured treatment groups. Selected results include the following: 63% of the sample had at least one pressured treatment episode. A higher proportion of females than males experienced at least one pressured treatment episode and non-Hispanic Whites and Hispanics were significantly more likely to have entered treatment under pressure than were African-Americans or people from other ethnic groups. Focusing on a target treatment episode, those who were pressured into treatment were less likely to have residential treatment than those who were not pressured. Yet, clients who were pressured into treatment had longer, but less intense (measured in h/month), target treatment episodes than non-pressured clients. Differences in outcomes between the pressured and non-pressured groups include a significant increase in the odds of relapse within 6 months of discharge for the pressured group when length of treatment is held constant. Findings may assist policy makers and treatment providers in better understanding the characteristics and treatment needs of MA users entering treatment through pressure from CJS or CPS, and in turn allowing optimal development and provision of appropriate services.
This study examined differences in the stages of change readiness and treatment eagerness scale among probation-referred substance using offenders of domestic violence. Two groups of male substance dependent offenders (N = 69) were evaluated at the onset of treatment for treatment compliance, motivation to change, alcohol-related problems, depression and domestic violence-related problems. Sixty nine male offenders who met DSM-IV criteria for substance dependence participated in the study. Differences were assessed between substance dependent offenders with a domestic violence arrest (SADV +, N = 30) versus substance dependent offenders without a domestic violence arrest (SADV −, N = 39). The Socrates, Conflict Tactic Scale (CTS), Michigan Alcohol Screening Test (MAST), and Beck Depression Inventory (BDI) were administered. Results indicate that substance dependent offenders of domestic violence have different stages of change readiness than substance users without a domestic violence arrest. The findings illustrate the importance of integrating motivational interviewing interventions and assessments among substance users with co-occurring domestic violence offenses.

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**Past-week heroin craving reports by heroin abusers: preliminary normative data and individual differences using a novel questionnaire**

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The first aim of this ongoing study is to establish normative data on a new past-tense version of the Heroin Craving Questionnaire (HCQ) that asks subjects to report the extent of craving ‘in general during the past week’ (whereas the current version asks about craving ‘right now’). The second aim is to determine whether individual difference characteristics are related to past-week craving scores. After an initial phone interview, heroin abusers (n = 95; 67 men and 28 women ranging from 18 to 50 years old) have been screened for participation in opioid research studies. Participants provide complete medical and psychiatric histories, blood and urine samples for routine laboratory testing and drug toxicology, EKG, and clinical interview for DSM-IV diagnoses. They complete questionnaires that assess past-week heroin craving (45 items, each scored on a 7-point Likert scale), personality characteristics (short form of the Tridimensional Personality Questionnaire), and lifetime/current drug use. All participants have met criteria for current opioid dependence. Individual HCQ total scores range from 69 to 312 with sample mean = 215 and S.D. = 45 (possible range, 45–315; indifference score = 180). Participants who smoke < 10 cigarettes per day (n = 21) report significantly less heroin craving than those smoking 11–60 cigarettes per day (n = 74). Participants with current medical or psychiatric problems (n = 28) report significantly less heroin craving than otherwise healthy heroin abusers (n = 67). Unexpectedly, illicit drug use variables are not significantly related to past-week craving. African-American participants (n = 79) report significantly more heroin craving than Caucasians (n = 15). Correlation analyses indicate that individuals with TPQ scores indicating higher novelty seeking and reward dependence and lower harm avoidance, report more past-week heroin craving. These preliminary findings suggest that several non-heroin factors (tobacco smoking, health, ethnicity and personality) may influence reports of recent heroin craving.

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**Delayed release morphine and methadone for maintenance therapy in opioid dependence**

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Aims: The study compared the efficacy and tolerability of once-daily delayed release morphine sulphate capsules with once-daily administration of methadone oral solution. Primary outcome measures were retention in treatment, consumption of illicit substances and adverse drug effects of study medication. Design: In the 14 weeks of the trial patients received in a double blind, double dummy cross-over design either methadone (D−/L+racemat) or delayed release morphine (morphine sulfate). After a titration period of 1 week at the beginning of each treatment phase, a stable dose was required for a treatment period of 6 weeks. The dose ranged from 55 to 100 mg for the methadone phase and from 200 to 800 mg for the delayed release morphine phase. Participants: 64 subjects (6 females and 58 males) who met DSM IV criteria for opioid dependence and were seeking treatment. Findings: Retention rate in both groups was very good, only nine patients (14%) withdrew from the study with no significant difference between medications. There was a statistically significant difference between the groups in the final dose to which patients were titrated (P = 0.031) with more patients needing higher dose levels when treated with morphine. There was a significant difference in craving for heroin (P = < 0.001) and nicotine (P = < 0.001) in the last two weeks of treatment in favour of morphine. Conclusions: Both substances were effective and safe for the treatment of opioid dependence, no serious adverse event occurred. Delayed release morphine could be an effective and well tolerated medication in maintenance treatment and the once-daily dosing allows treatment conditions similar to methadone.

**Non-reactive cognitive measures of attention and attitude in cigarette smokers**

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Some of the motivation to continue smoking may result from cognitive tendencies to focus attention on cigarette-related events that in turn activate powerful cigarette-related affective responses. These reactions may be difficult to access through highly reactive self-report measures. As an alternative, two reaction time measures of cognitive bias were utilized: (1) the dot-probe attentional task, in which attentional bias toward smoking cues is indicated by faster reaction times when the probe appears in the location of a smoking picture on the prior screen, and (2) the implicit attitude task, where pictures which evoke either positive or negative affect reduce reaction times to categorize adjectives with similar valence. These tasks were given to smokers entering treatment, smokers not entering treatment, past smokers, and non-smokers. In addition, before and after the tasks, measures of subjects’ drug related affects (e.g. high, craving and withdrawal) as well as measures of their current mood states were obtained. The greatest attentional bias was exhibited by current smokers; past smokers and non-smokers displayed similar levels of bias. Smokers in this large sample exhibited a range of affective responses (positive and negative). Importantly, bias scores were uncorrelated with (pre-task) subjective...
measures of high craving or withdrawal, suggesting that they may represent an independent and useful source of variability for outcome prediction.

184 Characterization of profound sex differences in opioid-potentiated inflammation: pharmacological and immunological investigations

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A series of experiments was conducted to assess whether male and female rats differ in their sensitivity to the immunomodulatory effects of opioids using a model of chemically-induced cutaneous inflammation, the contact hypersensitivity response. Male and female CDF rats were sensitized on the ventrum with 2,4-dinitrofluorobenzene (DNFB) on 2 consecutive days. Four days later they were administered either selected doses of mu opioid receptor agonists or vehicle (6 animals/group) and 1 h later challenged on the pinna with DNFB. Measurements of pinna thickness were performed from 12 to 192 h after challenge. Results indicate significant proinflammatory effects of morphine (2.5–25 mg/kg), buprenorphine (0.01–1.0 mg/kg) and etorphine (0.001–0.01 mg/kg) (all P < 0.001) and that across all drugs tested females displayed a markedly potentiated and prolonged inflammatory response compared to males (all P < 0.001). In another set of experiments, mRNA levels of early molecular mediators of inflammation were assessed at 3 and 6 h post-challenge using RT-PCR to determine which cytokines underlie the observed sex differences. Preliminary analyses suggest that opioids induce a complex, differential pattern of cytokine expression in males and females that may underlie these sex differences. These results have implications for the understanding of sex differences in immune function and guiding opioid analgesic selection for use in males and females.

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185 Elucidating the role of the HPA axis in cocaine dependence: double-blind placebo-controlled hydrocortisone and cocaine infusions in humans

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Hypothalamic-pituitary-adrenal axis hormone, cortisol, has been demonstrated to maintain cocaine self-administration in rodents. In higher primates and humans the relationship between the HPA axis function and cocaine dependence is more complex, with positive reinforcing (cocaine-like), negative and no effects reported. To elucidate this relationship further, we have designed a double-blind placebo-controlled infusion study with varying doses of hydrocortisone and one low dose of cocaine (0.2 mg/kg), both administered as an IV bolus. Blood cortisol assays are obtained immediately prior and 5, 10, 15, 30, 60, 90 and 120 min following the bolus administrations. Computerized behavioral ratings for craving and high (Likert-type scale, range 0–3) are initiated 2 min pre-infusion and collected every minute until 20 min post infusion. In the preliminary analysis of the data from five individuals with cocaine dependence (mean age ± S.D.: 43.6 ± 5.2 years; 2 females and 3 males; 4 African-American and 1 Caucasian; ASI Drug Score = 0.14 ± 0.13), both hydrocortisone (0.5 mg/kg) and cocaine, but not placebo administration, resulted in significant elevations (P < 0.01; Friedman ANOVA test) in plasma cortisol levels (also reported in other abstract). However, cortisol elevations produced by hydrocortisone were greater than those produced by cocaine (P < 0.05; Wilcoxon matched pairs test). Only cocaine, but not cortisol or placebo, produced significant increases in behavioral ratings for craving and high (P < 0.01; Friedman ANOVA test). Since exogenous hydrocortisone administration at 0.5 mg/kg did not appear to model the kinetics of plasma cortisol elevations produced by cocaine, more experiments are underway in our laboratory with lower doses of the corticosteroid. The data generated by those experiments will be presented.

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186 Brain stimulation reward in C57BL/6J mice

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The rewarding effect of electrical brain stimulation is thought to occur through the activation of brain circuitry involved in natural and drug-induced reward. The potentiation of brain stimulation reward by drugs of abuse has been used successfully to investigate neurobiological mechanisms involved in drug abuse. To date, the majority of studies have been done in the rat. The purpose of this study was to determine if brain stimulation reward could be established in the C57BL/6J mouse and if morphine and amphetamine would potentiate brain stimulation reward. Methods: The lateral hypothalamus of 12 C57BL/6J male mice was implanted with monopolar electrodes. Following surgery, mice were allowed access to brain stimulation on an FR1 schedule of reinforcement. Each quarter-turn of the operand (wheel) delivered a 200 ms train of 0.1-ms rectangular cathodal pulses. Initial current intensity and frequency was 70 μA and 100 Hz, respectively. Mice were then trained on a rate-frequency protocol wherein current was fixed but frequency was decreased across 19 fixed intervals. Rate-frequency curves were quantified in terms of the frequency that maintained half-maximal rates of responding. Following stable performance morphine (0, 1, 3 or 5.6 mg/kg, s.c.) or amphetamine (0, 1, 2 or 4 mg/kg, i.p.) was administered 15 min prior to the session. Three saline days were run between each drug dose. Results: Rate-frequency curves were established in all mice. Morphine and amphetamine potentiated brain stimulation reward as demonstrated by shifting the rate-frequency curve to the left. Ordinarily dose-effect functions were found for both drugs. Morphine and amphetamine decreased half-maximal frequency (increased sensitivity) by 40–45%. A subset of morphine treated mice were unresponsive to morphine (no histological foundation was identified). Conclusion: Electrical stimulation of the lateral hypothalamus maintains high rates of behavior in the C57BL/6J mouse and drugs of abuse such as morphine and amphetamine potentiate rewarding brain stimulation. Overall, this study demonstrates that brain stimulation reward and rate-frequency protocols can be used in mice to study the reward potentiating effects of abused drugs and that the behavioral phenotypes of genetically engineered animal models can be explored using this protocol.

187 Methadone levels exceed those of its main metabolite in spot urines from methadone-maintained outpatients


Urine assays for methadone and its main metabolite EDDP have been suggested for clinical applications such as detection of missed doses or diversion of medication. Any such applications will require data on those substances’ urinary excretion profiles. The few published data (e.g. that EDDP: methadone ratio increases to >1.0 in the first 4 weeks of daily maintenance) are mostly from 24-h urine collection on closed wards. It is not known whether they would generalize to a more realistic outpatient collection schedule—spot urines at predose trough. We determined concentrations of methadone and EDDP in 1093 spot
urine specimens collected 3 × per week in 27 outpatients during up to 17 weeks of observed methadone ingestion (35–80 mg/day). Semi-quantitative analyses were done by homogeneous enzyme immunoassay (CEDIA). The median EDDP:methadone ratio was only 0.71, denoting greater-than-expected excretion of unchanged methadone. There was no evidence that the ratio changed over time. Concentrations of methadone were more variable than those of EDDP (coefficients of variation 74 and 57%, respectively), perhaps due to an unmeasured factor such as urine pH. As expected, methadone and EDDP concentrations significantly increased with dose, and (in one patient whose attendance was poor) significantly decreased following missed doses. However, all specimens had >100 ng/ml EDDP, all but one had >100 ng/ml methadone, and all but 28 had >300 ng/ml methadone, suggesting that these typical cutoffs are unlikely to detect one or two missed doses. Detailed time-course data will be presented.

188 CHRONIC TREATMENT WITH ANTIDEPRESSANTS DOES NOT AFFECT TOLERANCE TO OR DEPENDENCE ON MORPHINE

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Opioids and antidepressants are often co-administered particularly in the treatment of severe, chronic pain. This study investigated the possible effects of antidepressants on the development of tolerance to and dependence on morphine in pigeons. Tolerance was indicated by reduced sensitivity to the rate decreasing effects of morphine, expressed as a shift to the right in the morphine dose effect curve. Dependence was indicated by enhanced sensitivity to the rate decreasing effects of naltrexone, expressed as a shift to the left in the naltrexone dose effect curve. White Carneau pigeons responded under a fixed ratio 20 schedule of food presentation and, on different occasions, received imipramine or desipramine for 6 weeks. During weeks 4–6 pigeons also received increasing doses of morphine (10, 32 and 56 mg/kg, each for 4 days, and 100 mg/kg for 9 subsequent days). Chronic administration of morphine alone produced tolerance and dependence as indicated by a 10–16 fold shift to the right in the morphine dose effect curve and a 210–350 fold shift to the left in the naltrexone dose effect curve. Administration of imipramine or desipramine alone did not alter sensitivity to the rate decreasing effects of morphine or naltrexone. Moreover, coadministration of imipramine or desipramine with morphine did not change the development of tolerance to or dependence on morphine, as indicated by sensitivity to morphine and naltrexone, respectively. While the coadministration of antidepressants and opioids might enhance pain treatment, perhaps through attenuation of associated pathology (e.g., depression), the combination does not appear to confer a reduction in tolerance or dependence liability.

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189 IMPACT OF PROPOSITION 36 ON PATIENT SERVICES AND OUTCOMES

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We conducted secondary analyses of data collected in the California Treatment Outcome Project (CalTOP) to provide an early indication of the impact and outcome of Proposition 36. Passed in November 2000 and implemented in July 2001, Proposition 36 mandates that drug-abusing adults convicted of nonviolent offenses can receive community-based drug treatment in lieu of incarceration. The ongoing CalTOP includes assessments of patients admitted to 44 providers across California on their drug use and drug-related problems at intake, discharge, 3-month follow-up, and 9-month follow-up (Addiction Severity Index is administered at intake and 9-month follow-up). Additionally, all services received by the patients during treatment are recorded. As of September 2001, 8,042 patients have been admitted to CalTOP, some were admitted under Proposition 36. Preliminary analysis of the 8,042 patients showed: 45% female; 53% white, 17% African American, 24% Hispanic, and 6% other; 20% aged 18–25, 32% 26–35, 48% older than 36 years; and 47% were on probation or parole at the time of intake. About 31% reported methamphetamine, 28% alcohol, 13% cocaine/crack, 14% heroin, and 11% marijuana as their primary drug problem. Further analysis will include data collected through April 2002. We will compare patient characteristics across two comparable periods covering pre- and post-implementation of Proposition 36, and will assess treatment outcomes among three groups: Proposition 36 cases, non-Proposition 36 cases, and pre-Proposition 36 cases to address (1) the level of severity in drug use and criminality among Proposition 36 patients, (2) if there have been changes in the service mix before and after Proposition 36 implementation, and (3) whether the three groups have comparable rates of treatment completion, retention, and outcomes. The impact of Proposition 36 on California’s substance abuse treatment system will have major implications for future policy and practice, especially for states that are planning similar initiatives.

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190 HEPATITIS C KNOWLEDGE ASSESSMENT AND COUNSELING WITHIN THE CONTEXT OF SUBSTANCE USE TREATMENT

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Approximately 4 million individuals are infected with Hepatitis C in the U.S., with intravenous substance users [IVDUs] considered the group to be at highest risk. This study examined the feasibility of integrating Hepatitis C counseling into a substance abuse research clinic’s HIV counseling program. It was hypothesized that a relationship would exist between subjects’ HIV knowledge and Hepatitis C knowledge. Secondly, IVDUs were expected to have higher knowledge levels [HIV and Hepatitis C] than non-intravenous drug users. Treatment-seeking substance abusers [N = 110] completed an HIV/Hepatitis knowledge assessment instrument at study intake. Correlational analysis revealed a significant positive relationship between HIV and Hepatitis C knowledge. ANOVA results indicate significant differences between IVDUs and non-IVDUs on HIV (P < 0.028) and Hepatitis C (P < 0.002) knowledge with IVDUs having higher knowledge scores. Overall, subjects had proportionally less knowledge of Hepatitis C than HIV risks and prevention strategies. Findings indicate that Hepatitis C counseling should be integrated into substance use treatment programs; existing HIV counseling programs may serve as a vehicle for this integration.

Several preclinical studies in rodents suggest that there are sex differences in response to cocaine and that these differences appear to be related to fluctuations in the ovarian hormones of females. Female rhesus monkeys have menstrual cycles that are remarkably similar to human menstrual cycles in both duration and hormonal variations. Therefore, data obtained in monkeys should be an ideal model for assessing the effects of cocaine across the menstrual cycle in humans. The present study assessed the acute effects of intravenous...
cocaína (0, 0.25, 0.50 and 1.0 mg/kg) in 5 female rhesus monkeys during 4 phases of the menstrual cycle: menses, midfollicular, periovulatory and midluteal. To limit the effects of stress, all animals were trained to enter prime chairs and while restrained they received fruit and treats. Similarly, during the 2 h experimental sessions, females were in the prime chairs and their feet were restrained in shoes so that repeated blood samples could be obtained from the leg veins. Hormone levels for estradiol and progesterone were measured each session before cocaine administration. Cocaine plasma levels were measured at 5, 15, 30, 45, 60 and 90 min after cocaine administration. Similarly, levels of cortisol and luteinizing hormone (LH) were measured before, 15, 30 and 60 min after cocaine administration. Within 5 min of cocaine administration, behavioral changes such as increased motor activity, mydriasis and refusal of treats were observed. These effects typically resolved in 15–30 min and were dose-related. Results on cocaine, cortisol and LH plasma levels as a function of cocaine dose and menstrual cycle phase will be presented.

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192 Repeated examination of morphine conditional place preference while testing across doses of morphine

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It has previously been demonstrated that the ‘drug-state’ of a rat during tests of conditional place preference (CPP) alters the magnitude of place selection. More time is spent in the drug-paired chamber when rats are tested in the presence of the conditioning drug as compared to tests in the absence of drug, even though rats receive the same drug during conditioning (Bespalov et al. (1999) Psychopharmacology 141:118–122). Therefore, it was of interest to examine whether the intensity of the “drug-state” would consistently influence expression of morphine CPP. Using a two-compartment CPP chamber, one environment was consistently paired to a particular dose of MS (0.56, 1.8, or 5.6 mg/kg s.c.) or SAL and the alternate environment was paired to SAL. Rats were then tested in the presence of a range of MS doses (SAL, 0.56, 1.8, 5.6, and 10 mg/kg MS). Pairing sessions (3 drug, 3 SAL) were interspersed between tests, MS doses were tested in counterbalanced order, and three dose-effect curves were completed for each group. The control group (SAL/SAL) did not exhibit CPP throughout the study. The group paired with SAL/0.56 MS did not exhibit CPP when tested in a “drug-free” state in the first dose-effect curve. However, these rats did exhibit CPP when tested with all MS doses. Furthermore, in subsequent dose-effect curves, this group did exhibit CPP in “drug-free” tests. For the remaining groups (SAL vs. 1.8 or 5.6 MS) CPP was expressed in both the presence and absence of MS. The greatest magnitude of CPP was exhibited by rats that received pairing with the intermediate dose of 1.8 mg/kg MS, irrespective of the dose of MS administered during tests. In general, the dose of MS administered during tests did not alter the expression of CPP. The highest conditioning dose of MS (5.6 mg/kg s.c.) produced CPP consistently lower than that produced by 1.8 mg/kg MS. Therefore, place selection was influenced only by the dose of MS used during pairing, not the dose of MS administered during testing.

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193 Social support and service use in a homeless drug-abusing population

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The relationship between social support and service use in the homeless drug abusing population has received little systematic study. A hypothesis that social supports may facilitate access to services was examined in a NIDA-funded epidemiologic study of service utilization of 300 drug and 100 non-drug abusing homeless individuals in St. Louis, Missouri selected from a variety of public settings (shelters, day centers, and homeless rehabilitation programs) including the streets. The Composite International Diagnostic Interview/Substance Abuse Module (CIDI/SAM) provided detailed assessment of drug use disorders. Social support was measured using questions from a previous NIAAA-funded study by this group as well as with the Arizona Social Support Interview Schedule. The CIDI/SAM Treatment Module, services items created for this study, and service use information gathered from agencies serving the homeless in St. Louis provided service utilization information. Multivariate logistic regression analyses demonstrated cocaine use disorder, less family contact, being bothered by family problems, and spending free time alone or with individuals in shelters to be associated with substance abuse service use. Cocaine and opiate use disorders and being bothered by family problems predicted mental health service use. Cannabis use disorder, greater family contact, more friends in the area, and spending free time with their children and other shelter guests but without individuals on the streets predicted use of homeless services. Spending free time with their children predicted health service use. Social support, particularly that of family, may play a role in service use, but further study is needed to draw conclusions about causal directionals.

194 Subregional upregulation of prodynorphin mRNA expression in the primate striatum after high, but not low, dose cocaine self-administration

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Several lines of evidence suggest that the striatal dynorphin system is important to the actions of cocaine. In the current study, the effects of cocaine self-administration (SA) on prodynorphin (PDYN) mRNA expression were examined in monkeys. A particular advantage of the primate model is the very close homology to humans. The effects of cocaine were studied at initial and chronic phases of SA. Adult Rhesus monkeys self-administered food or cocaine (0.03 or 0.3 mg/kg per inj) on a fixed interval schedule (FI-3 min) for 5 or 100 days and were sacrificed 1 h after the final session. The PDYN mRNA expression was analysed at the rostral and caudal level of the precommissural striatum using in situ hybridization histochemistry. We found a specific upregulation of the PDYN mRNA levels in the limbic innervated patch compartment of the dorsal caudate and dorsal putamen during the initial phase of the high dose cocaine SA. After 100 days of the high dose exposure both the patch and the sensorimotor connected matrix compartments of the dorsal caudate and putamen were increased, in particular the rostral level of the caudate. There were no significant changes in the corresponding striatal regions of the low dose cocaine-exposed primates, neither during the initial or the chronic phases of SA. Moreover, cocaine SA failed to alter the PDYN mRNA expression in high- or low-expressing PDYN cell populations in the nucleus accumbens shell or core during any condition studied. These results are consistent with previous rat and human cocaine studies where increases of the PDYN transcript have been found predominantly in the dorsal striatum. Overall, the most pronounced activation of the PDYN transcript was evident after high dose exposure in the caudate nucleus, initially only in the limbic-related patch compartment and chronically in both limbic- and sensorimotor-related compartments. The temporal alterations in the PDYN gene expression of the caudate nucleus may mirror a change in drug responsivity, the transition to drug dependence.
**195** Behavioral couples therapy with substance-abusing men: the effectiveness of bachelor’s- and master’s-level counselors  
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The purpose of this study was to examine whether bachelor’s-level counselors (N = 5), as compared to master’s-level counselors (N = 5), could deliver manualized Behavioral Couples Therapy (BCT) to substance-abusing men and their intimate partners (N = 40) with equal compliance and achieve comparable patient outcomes. Male substance-abusing patients, being treated in an outpatient program, and their intimate partners were randomly assigned to receive BCT from either a bachelor’s-level or a master’s-level counselor. Equivalency testing revealed that, in comparison to master’s-level counselors, bachelor’s-level counselors were equivalent in terms of adherence ratings to a BCT treatment manual, but were rated lower in terms of competence of treatment delivery. However, partners who received BCT from the bachelor’s- and master’s-level counselors reported equivalent levels of (a) satisfaction with treatment, (b) marital happiness during treatment, and (c) dyadic adjustment and percentage of days abstinent at posttreatment, 3-, 6-, 9-, and 12-month follow-up. These findings suggest that BCT can be delivered by master’s- and bachelor’s level treatment providers with equal effectiveness. Because the majority of treatment providers in community-based substance-abuse treatment programs have bachelor’s degrees or less formal education, these findings suggest paraprofessional treatment providers could be used to deliver BCT, which, in turn, could allow this effective intervention to be adopted in these settings more readily.  
**196** Interaction of paroxetine and MDMA in humans  
A double-blind, randomized clinical trial was carried out to study the influence of paroxetine (a selective serotonin reuptake inhibitor and a potent inhibitor of hepatic CYP 2D6 isoenzyme) in the pharmacological effects and the pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). The local Ethics Committee (CEIC-IMAS) and Spanish Medicines Control Agency approved the study protocol. A group of 10 recreational users of MDMA were included. Subjects were randomized to receive during 3 days paroxetine (20 mg once a day) or matched placebo. Three h after the last paroxetine/placebo administration, subjects were given a pharmacological challenge with MDMA (100 mg oral). Study evaluations included physiological, subjective and psychomotor effects. Blood samples were drawn to determine MDMA and metabolites. Paroxetine reduced the physiological (blood pressure and heart rate) and subjective effects (euphoria) induced by the MDMA challenge. Paroxetine produced a slight increase MDMA plasma levels but reduced by half the formation of 4-hydroxy-3-methoxymethamphetamine (HMMA).  
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**197** Morphine in pellets, but not morphine, deltorphin II or U50,488H in osmotic pump, potentiates oral salmonella infection and inhibits intestinal transit in mice  
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We have previously shown that 75-mg morphine slow-release pellets markedly enhance susceptibility to oral Salmonella typhimurium infection. The present study examined the differential effects of morphine, 82 and kappa opioid receptor agonists administered via an Alzet’s osmotic minipump oral Salmonella infection and on gut transit. C3HeB/FcJ mice were implanted s.c with either a morphine pellet or a minipump administering morphine, deltorphin II (82) or U50,488H (x) followed by inoculation with oral Salmonella. To quantify Salmonella replication, 48 h later, Peyer’s patches (PP), mesenteric lymph nodes (MLN) and spleens were harvested from 5 mice per group. Tissue homogenates were prepared and the number of Salmonella colonies enumerated by agar plate counts. The results show that morphine-pelleted mice had a significant increase in bacterial burden with approximately 106 Salmonella in PP, 104 in the MLN and 103 in the spleen. There were no detectable bacteria in mice receiving morphine by minipump at doses of 1–10 mg/kg per day, doses which we have shown to be immunosuppressive (Rahim et al., 2001). In comparison, mice implanted with a minipump infusing deltorphin II at 0.5 mg/kg per day had a low level (~102) of bacteria in spleens of 2/5 mice. Similarly, in mice receiving U50,488H at 2 mg/kg per day 1/5 mice had a low level of bacteria in the spleen. To examine the effect of opioids on gut transit, 48-h drug-treated mice were administered intragastric charcoal. Charcoal transit was evaluated after 20 min. Morphine pellets inhibited gut transit by 38.3% while mice receiving morphine by minipump at doses of 1–25 mg/kg per day showed only a dose-dependent 7–17% inhibition. Deltorphin II and U50,488H (0.1–10 mg/kg per day) did not suppress gut transit. The present studies indicate that a predominantly mu agonist, morphine, given by slow-release pellet potentiates Salmonella infection and inhibits gastrointestinal transit. In contrast, morphine in pumps slightly inhibits intestinal transit but does not sensitize to Salmonella infection. A 82 and a kappa agonist have minimal effects on either parameter.  
This work was supported by NIDA grants DA06650, DA11143 and DA13429.  
**198** Translycypromine (TCP) inhibition of nicotine metabolism  
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Nicotine is the active component of tobacco responsible for the dependence producing properties of cigarette smoking. Nicotine dependent individuals smoke cigarettes in order to maintain central nicotine concentrations. In humans, 70% of nicotine is metabolized to cotinine by the polymorphic hepatic enzyme cytochrome P450 2A6 (CYP2A6). Smokers with CYP2A6 null alleles (*2 or *4) smoke significantly fewer cigarettes per day than do homozygous wild-type smokers (Rao et al., 2000). Chemical inhibition of CYP2A6 may provide a useful strategy to decrease nicotine clearance and reduce the number of cigarettes smoked. Furthermore a treatment that increases nicotine bioavailability could develop oral nicotine as a form of nicotine replacement therapy. Translycypromine (TCP) (Parnate®), a reversible MAO inhibitor, is a competitive inhibitor of CYP2A6 (Ki = 0.04–0.15 μM). We hypothesized that co-treatment with TCP would decrease the systemic clearance of nicotine and increase the bioavailability of oral nicotine resulting in a significant increase in mean plasma nicotine concentrations. DSM-IV tobacco dependent subjects participated in this placebo controlled single blind testing of 3 doses of TCP: Phase 1 (4 females, 5 males) TCP (2.5 mg t.i.d); Phase 2 (6 females, 3 males) TCP (1.0 mg t.i.d); and Phase 3 (3 females, 4 males) TCP (1.8 mg t.i.d). The latter study phase included an oral tyramine challenge test to establish the safety of tyramine in TCP treated subjects. TCP 2.5 mg t.i.d. after single (76%) and multiple (75%) dosing regimes (8 days) significantly increased plasma nicotine after oral nicotine (F = 3.44, P < 0.05) but had no effect after subcutaneous
nicotine. CYP2A6 activity was reduced since the nicotine/cotinine ratio increased after single (78%) and multiple (56%) doses vs. placebo \((F = 3.81, P < 0.05)\). In prior to TCP the mean ± S.D. dose of tyramine to increase systolic blood pressure by 25 mmHg (PD25) was 479 ± 119 mg. After TCP (1.8 mg t.i.d) for 7 days the mean PD25 was 179 ± 126 mg. TCP in daily doses less than 1/3 those used to treat depression could represent a new treatment for tobacco dependence when given in combination with oral nicotine.

199 TREATMENT-RELATED PREDICTORS OF INFANT OUTCOME IN PREGNANT DRUG-DEPENDENT WOMEN

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Pregnant drug dependent women tend to fare poorly in standard care settings, and more intensive services are often recommended to meet their needs. Unfortunately, empirical data to support such models of care are limited. The present study examined the relationship between Estimated Gestational Age (EGA) on admission to treatment, use of pharmacotherapy (i.e., methadone maintenance), and days attending treatment during the antenatal period and a variety of maternal and infant birth outcomes using regression analyses. Subjects were 217 pregnant opiate and/or cocaine dependent women admitted to a comprehensive program that provided residential and intensive outpatient care during pregnancy and postpartum. Demographically participants were 28.2 years of age (S.D. 4.2), 81% were African American and 56% had less than a high school education. Over half (51%) of the women entered treatment during their third trimester of pregnancy. EGA on admission, however, was unrelated to any maternal or infant birth outcomes. After controlling for EGA on admission, days attending treatment were significantly related to six outcome measures (NICU length of stay, infant birthweight, infant birth length, EGA at delivery, fetal growth ratio (FGR) and risk for premature delivery). Interestingly, this relationship held true only for women receiving methadone maintenance therapy (i.e., 63% of delivery sample). Study findings support medical benefits of comprehensive treatment for methadone-maintained pregnant women. Future studies should examine the specific components of treatment that may contribute to this relationship. These data also confirm that treatment is associated with improved birth outcomes even when such treatment is not sought before the third trimester of pregnancy. Clinical and economic implications of study findings will be discussed.

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200 GENDER DIFFERENCES IN COCAINE-INDUCED LOCOMOTOR AND STEREOTYPIC BEHAVIOR

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There is accumulating evidence which suggests that male and female humans and animals respond differently to psychomotor stimulants. To extend our understanding of sex effects in drug-induced psychomotor activity, the present study examined the relationship of dose and gender on the behavioral effects of cocaine. Male and female rats were given a single injection of cocaine (5, 15, 20, and 30 mg/kg) of cocaine or saline. Total locomotor, ambulatory, and rearing behaviors were measured for a total of 3 h post-injection. Stereotyped scores were measured at 30 min, 1 and 2 h. In male and female rats, there is a linear relationship between dose and behavioral activity which peaks at 20 mg/kg. Overall, female rats had greater total, ambulatory, rearing, and stereotypic counts at 5, 15, 20, and 30 mg/kg of cocaine as compared to males. Females also have a longer-lasting and prolonged period of motor activation. Taken together, our data suggests that there are dose and gender effects on cocaine-induced behaviors, which may highlight differences in the pattern of cocaine abuse or relapse between males and females.

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202 ARE JUDICIAL STATUS HEARINGS A KEY COMPONENT OF DRUG COURT? MULTI-SITE GENERALIZABILITY IN FOUR DRUG COURTS


In prior work (Marlowe et al., in press), we experimentally examined different schedules of judicial status hearings in a misdemeanor drug court. Participants were randomly assigned to attend status hearings either every 2 weeks or only as needed. Otherwise, participants received the same treatment and case management, random weekly urinalyses, and rewards and sanctions in the program. Findings revealed no between-group differences in counseling attendance, drug abstinence or criminal activity during enrollment in the program or at 6-month follow-up. However, significant interaction effects indicated that individuals who met DSM-IV criteria for Antisocial Personality Disorder or who had a history of prior substance abuse treatment achieved better outcomes when assigned to more frequent hearings. One serious shortcoming of this prior study was that it was conducted in a single jurisdiction, with a single drug court program, and a single judge. The current study was designed to evaluate the generalizability of these findings across four additional adult drug courts, serving both misdemeanor and felony offenders and located in both urban and rural communities. To date, 112 participants have been randomly assigned to either bi-weekly \((n = 55)\) or as-needed \((n = 57)\) status hearings. Similar to our previous findings, preliminary analyses revealed no significant effect of increased hearings on counseling attendance, urinalysis-confirmed abstinence, or criminal activity during the first 12 weeks of the program. The current cell sizes required us to combine samples across courts and jurisdictions and prevented us from examining interaction effects at this time; however, future analyses will examine outcomes separately for felony versus misdemeanor and urban versus rural samples and will allow us to examine the generalizability of our prior interaction effects.

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203 OFFICE VERSUS NARCOTIC TREATMENT PROGRAM-BASED BUPRENORPHINE FOR OPIOID DEPENDENCE

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Is the effectiveness of buprenorphine maintenance treatment of opioid dependence diminished during treatment in a primary care clinic (PCC), when buprenorphine is provided for unobserved home use and counseling provided by primary care nurses, in comparison to treatment in narcotic treatment programs (NTP) when medication administration is directly observed (DOT) and traditional drug counseling (DC) provided? We compared treatment outcomes in patients enrolled in two clinical trials of buprenorphine; one performed in a PCC and one in a NTP. Comparable daily buprenorphine doses were prescribed in both trials, but patients in the PCC received 4–5 take-home doses per week and medical management provided by
primary care nurses while patients in the NTP received all buprenorphine doses under DOT and DC. Primary outcomes were retention in treatment and urine toxicology for opioids via weekly testing. The subjects in the PCC (n = 84) and NTP (n = 99) were similar on mean age (38 versus 37 (P > NS), male sex 74% (P > NS), white 66% versus 75% (P > NS), employed 61% versus 46% (P > NS), mean years of opioid use 11 versus 10 (P > NS) and prior methadone treatment 50 versus 38% (P > NS). Fewer patients in the PCC than the NTP reported injection use 45 versus 59% (P < 0.05). With respect to outcomes, fewer patients were retained in treatment for 12 weeks in the PCC compared with the NTP, 39/84 (46%) versus 70/99 (71%), P < 0.001. There were no differences in the proportion of patients with 3 weeks, 36/84 (43%) versus 43/99 (43%), P = NS, or 6 weeks, 22/84 (26%) versus 20/99 (20%), P = NS, of opioid negative urine toxicologies. There were no differences in the proportion of patients with 8 weeks of opioid positive urine toxicologies, 8/84 (10%) versus 10/99 (10%), P = NS, between the PCC and NTP. We conclude that office-based buprenorphine treatment of opioid dependence is associated with decreased treatment retention, yet provides similar rates of abstinence as NTP-based care.

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204 Office-based prescription study with buprenorphine

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Introduction: Since 1999 buprenorphine has been registered in EU-countries for the treatment of opioid dependence. We conducted an office based treatment study, with standardized supervision through a specialized addiction center. Methods: 120 opioid dependent subjects (DSM IV:304.0) were enrolled at the addiction clinic of the University of Psychiatry, Vienna for a study period of 3 weeks with a continuation of 12 weeks at general practitioners office. Induction onto buprenorphine took place during the first 5 days until reaching sufficient dosing. Supervised urinalysis was undertaken weekly during the first month with a continuation on a 2 weekly basis over the study period. Structured rating instruments for withdrawal, craving and physical condition were applied. Results: A retention rate of 58% was achieved after 15 weeks investigational period, the drop out analysis showed a significant gender difference regarding age (P < 0.015) and onset of dependence (P < 0.040). The mean daily buprenorphine doses (without induction period) was 16 mg (range: 8–28). A significant reduction on heroin consumption (P < 0.01) as well as cocaine consumption (P < 0.05) was evaluated. In addition a significant improvement in physical and psychological wellbeing could be shown. Discussion: Buprenorphine is a medication which showed efficacy as well as well acceptance and safety for opioid dependent patients when treated in GP’s office in collaboration with a specialized center.

205 Psychostimulants differentially redistribute VMAT-2

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The vesicular monoamine transporter-2 (VMAT-2) sequesters monoamines into synaptic vesicles. We have demonstrated rapid (<1 h) changes in vesicular dopamine (DA) uptake, VMAT-2 ligand (dihydrotetrabenazine; DHTBZ) binding, and VMAT-2 immunoreactivity in response to drug treatment. Specifically, administration of the DA releasing agent, methamphetamine (METH), rapidly decreased vesicular DA uptake and DHTBZ binding in vesicles prepared from both the striatum and hippocampus of treated rats. In contrast, treatment with the DA reuptake inhibitors, methylphenidate (MPD) and cocaine, abruptly and reversibly increased striatal vesicular DA uptake and DHTBZ binding. Administration of the D2 agonist, quinpirole, increased striatal vesicular DA uptake as well. Neither cocaine, MPD nor quinpirole altered vesicular DA uptake when assessed in vesicles prepared from the hippocampus of treated rats. In addition, results indicate a differential redistribution of VMAT-2 within striatal synaptic terminals after cocaine, MPD or METH treatment. Cocaine and MPD shift striatal VMAT-2 protein from a synaptosomal/plasmalemmal membrane- to a non-plasmalemmal membrane-associated compartment. In contrast, METH treatment results in a shift of striatal VMAT-2 from a non-plasmalemmal membrane-associated compartment to a location that is not retained in the preparation of the synaptosomes. These data demonstrate that psychostimulants acutely and differentially affect the subcellular localization of VMAT-2 in a brain region-specific manner. Mechanisms underlying these phenomena will be discussed.

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206 Recovery from opioid abuse

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Long-term outcomes among opioid users treated in outpatient methadone programs found 28% were in recovery based on both biological and self-report measures of no drug use, less than daily use of alcohol, and no arrests or illegal activity during the year before follow-up. Patients’ background, index treatment experience, and reasons for long-term recovery from opioid abuse were examined to determine factors associated with these improvements. Subjects included 432 admissions to 18 outpatient methadone treatment programs in eight cities who completed a 5-year follow-up interview as part of the national Drug Abuse Treatment Outcome Studies (DATOS). Group differences (i.e., recovered vs. unrecovered) in background, index treatment experience, and reasons were identified using Analysis of variance (ANOVA), and odds-ratios were calculated to serve as indicators of the relative discrimination. Those who were in recovery offered pronounced reasons for their improvement in contrast with those who were not. Personal motivation, treatment experiences, religion/spirituality, family, and a job/career were significant discriminators. The importance of community supports is highlighted by the emphasis recovering patients place on the availability of family and close friends on the one hand and the relative absence of problems in relating effectively to family and friends on the other. Findings suggest the importance of family and peer supports to maintaining the gains achieved through drug abuse treatment, and indicate important pathways in the recovery process that can be targeted for strategic interventions.

207 Predictors of drinking outcomes among alcoholics

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Objective: Predicting outcomes for individual patients entering substance abuse treatment has long been a clinical goal in the addictions field. Attempts to identify pre-admission predictors of treatment outcomes have often relied on short-term outcomes and bivariate analyses. This study assess the extent to which baseline measures can
predict post-treatment outcomes. Methods: A longitudinal design was used to examine pre-admission predictors of drinking frequency for alcoholics. The study investigated two types of predictors: measures of alcoholism severity and psychosocial measures. The ASI was administered at both baseline and follow-up. The baseline study sample consisted of 248 applicants, of whom 219 (88%) were retrieved at 3-month follow-up, and 173 (70%) at 12 months. Results: Frequency of drinking diminished substantially and significantly between intake and the two follow-ups. The proportion of outcome variance accounted for by alcohol severity was 6% for both the 3-and 12-month data. The proportion of outcome variance accounted for by the psychosocial predictors (in addition to the severity control) was approximately 30% at each follow-up. Those who drank less often at 3-month follow-up were more likely at intake to have reported high treatment motivation, have a history of positive engagement with 12-step groups, have serious medical problems, be a parent, have a sibling, and have few family members with psychological problems. Those who drank less often at the 12-month follow-up were more likely at baseline to have reported high treatment motivation, extensive 12-step involvement, positive quality of family life, illegal drug use, and few psychological problems. Conclusions: The considerable predictability of drinking outcomes based on intake information suggests that clinicians could adjust treatment strategies based on knowledge about which clients are likely to succeed or fail.

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208 STUDENTS AT RISK: COLLEGE STUDENTS WHO BINGE DRINK AND USE OTHER SUBSTANCES

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Binge drinking college students experience and inflict significant drinking-related consequences. In an intervention study with binge drinkers at a large northeastern University, we examined the additional risk resulting from concurrent substance use hypothesis. Students who use additional substances will drink more as well as suffer greater drinking-related consequences than non-substance using binge drinkers. Method: Freshman/sophomore students are voluntarily screened for binge alcohol use in the campus Health Center when presenting for routine medical care. Subjects are randomly assigned to one of three brief interventions (12-step, Motivational, and CBT). Data collected at baseline, 1, 6 and 12 months, include: Time-Line Follow-Back, Alcohol Dependency Scale (ADS), Rutgers Alcohol Problem Index (RAPI), Beck Depression Inventory (BDI) and Brief Symptom Inventory (BSI). Results: The sample (N = 206) included: 59% freshmen, 63% female, 86% Caucasian, and 95% living on campus. At baseline, 36% (n = 74) reported using drugs (predominantly marijuana) in addition to alcohol over the last 30 days. These subjects were more likely to be male (46% of the males vs. 30% of the females, P < 0.05). They also reported significantly more drinking in the previous 30 days as measured by total drinks (M = 74.6 vs. M = 39.3, P < 0.01), drinking days (M = 9.6 vs. M = 6.7, P < 0.01), binge episodes (M = 7.9 vs. 4.7, P < 0.01), and time spent drinking (M = 39.4 h vs. M = 23.6 h, P < 0.01). These subjects also scored significantly higher on the ADS (M = 11.7 vs. M = 7.7, P < 0.01), RAPI (M = 10.5 vs. M = 7.6, P < 0.01), BDI (M = 8.9 vs. M = 6.3, P < 0.01), and ADS (M = 60.3 vs. M = 55.3, P < 0.01). Of the subjects assigned to the Motivational and CBT interventions who attended at least one group session (N = 84; 58%) subjects reporting other drug use were more likely to attend (68.4% vs. 51.7%, P < 0.05). Conclusion: College binge drinkers who use additional substances are at risk for heavier drinking, as well as its concomitant problems. A protective factor for this group may be that they are more likely to attend interventions offered for their drinking than their non-drug using peers.

209 THE RANKING OF FIVE SUBSTANCE USE DISORDER DIAGNOSTIC INSTRUMENTS BY THE NATIONAL DRUG ABUSE CLINICAL TRIALS NETWORK

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With the current emphasis on blending research and clinical practice, the identification of a substance use disorder diagnostic instrument with the highest degree of acceptance to both practitioners and researchers is of considerable importance. After a protracted series of initiatives to select a single SUD diagnostic instrument, 36 university-based addiction researchers and 62 community-based treatment providers of the National Drug Abuse Clinical Trials Network’s (CTN) participated in a process in which they ranked five widely recognized SUD diagnostic instruments for their suitability in community-based clinical trials. These instruments were: Structured Clinical Interview for DSM-IV (SCID), Composite International Diagnostic Interview—second edition (CIDI-2), Diagnostic Interview Schedule for DSM-IV Diagnosis (DIS-IV), Diagnostic Statistical Manual-IV Checklist (DSM-IV Checklist), and Substance Dependence Severity Scale (SDSS). To inform the ranking process, a table comparing the instruments along 26 dimensions of relevance to practitioners and researchers, and a narrative description of each instrument, was prepared and distributed within the CTN. Participants ranked each instrument from one (highest) to five (lowest) based on their appraisal of the each instrument’s suitability for CTN studies. A significant difference was observed across the five diagnostic measures F(4384) = 20.0, P < 0.001, with the SCID receiving the highest mean rank (2.24) followed by the CIDI (2.59), DIS (2.94), DSM Checklist (3.40) and the SDSS (3.83). Following the presentations and discussions about these data and the relative merits of the five instruments, the Steering Committee of the CTN selected the CIDI for adoption. The reasons for this selection and the implications for practice/research collaboration will be discussed.

210 BIRTH OUTCOMES AS A FUNCTION OF ADDICTION SEVERITY

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This study explored the relationship between various measures of addiction severity in pregnant drug abusers and two birth outcomes: (1) weight in grams; and (2) head circumference. Subjects were 54 women with DSM-IV substance dependence diagnoses who were receiving treatment at the Center for Perinatal Addiction (CPA), a model treatment program for pregnant and parenting women and their children. Subjects were primarily African-American (86%), with a mean age of 29 years of age. The prevalence of alcohol use disorder was (58%), cocaine (89%), cannabis (58%) and heroin/other opioids (23%). Variables included in a discriminate function analysis predicting neonatal outcomes were amount of cigarettes smoked per day, ASI drug severity (t-score), ASI alcohol severity (t-score), and the MacAndrews Scale (MacR), Addiction Potential Scale (APS) and Alcohol Acknowledgement Scale (AAS) scales from the MMIP-2 (t-scores). The mean weight of the infants was 2844.23 g (S.D. = 789.29). Of the candidate variables, only smoking status predicted infant weight (Wilks’ Lambda = 0.004). None of the variables predicted head circumference. While prenatal exposures to alcohol and illicit drugs can and does have devastating effect on unborn children, the implications of cigarette smoking during pregnancy are often down-
played or ignored. These data suggest the need for smoking cessation programs for pregnant drug-dependent women.

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211 Discriminative stimulus effects of sedatives, anxiolytics and anticonvulsants in diazepam-dependent and non-dependent rhesus monkeys

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The pharmacological selectivity of discrimination assays sensitive to GABA(A) modulation was examined in non-dependent and diazepam-dependent rhesus monkeys. Sedative, anxiolytic and anticonvulsant compounds varying in mechanism of action were studied including: non-selective benzodiazepine (BZ) site ligands flunitrazepam and abecarnil; a five-selective BZ QH II 66; 5-HT1A agonist buspirone; histamine antagonist diphenhydramine; sodium channel blocker valproic acid; GHB; and ketamine. In non-dependent monkeys (n = 5) discriminating midazolam, BZ site ligands substituted for midazolam with the following rank order potency: flunitrazepam > abecarnil > QH II 66. Non-GABA(A) ligands did not substitute for midazolam. Pretreatment with valproic acid shifted the midazolam dose-effect curve to the left (6-fold), pretreatment with diphenhydramine shifted the midazolam dose-effect curve to the right (3-fold), and pretreatment with buspirone, GHB or ketamine had no consistent effect. In diazepam (5.6 mg/kg per day) dependent monkeys (n = 5) discriminating flumazenil, none of the compounds substituted for flumazenil. Pretreatment with flunitrazepam, abecarnil or QH II 66 shifted the flumazenil dose-effect curve to the right; non-GABA(A) ligands did not modify the flumazenil discriminative stimulus. The results indicate that, despite differences in affinity or efficacy at BZ receptor subtypes, flunitrazepam, abecarnil and QH II 66 are qualitatively similar to other positive GABA(A) modulators in these discrimination assays. The results further indicate that, despite evidence for functional interactions between some non-GABA(A) ligands and midazolam, these discrimination assays differentiate drugs on the basis of mechanism of action (e.g. GABA(A) modulation) and not functional endpoint (e.g. sedation).

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213 Assessment of brain dopaminergic function using two-color BOLD fMRI

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Emerging literature suggests that retinal blue cone response (but not that of the other cones) is specifically influenced by altered dopaminergic conditions, including cocaine withdrawn states. BOLD fMRI is a rapid, non-invasive method for assessing response to visual stimuli; the differential BOLD response to isolated stimulation of individual color cone groups therefore may provide insight into dopaminergic transmission in the brain. Initial studies (N = 37) showed that (a) BOLD response to red and blue light is log-linear over 3.5 orders of magnitude of light intensity, and (b) the slope of the blue light response is 1.8 times that of the red light, implying different neural processing for the two colors. A further study (N = 15) showed time-dependent augmentation of V1 BOLD signal change in response to red, but not blue light, in response to low doses of oral t-amphetamine, and a smaller study (N = 8) showed significantly lower blue and higher red response to low intensity stimulation in cocaine-withdrawn individuals relative to controls. These studies confirm that dopaminergic drugs modify the differential BOLD response. Differential measurements avoid a major complication in the use of fMRI in the study of acute cocaine and amphetamine intoxication BOLD changes, by allowing the separation of the neuronal effects of the drug from the profound cerebral vascular effects of dopaminergic drugs, which also influence the BOLD signal. We describe the implementation of a second generation measurement system, designed to make this a routine, high quality assay, by improving the sensitivity and time resolution of the technique, and improving subject acceptance. Initial studies used alternating boxcar stimuli were limited to one differential measurement every 8 min. To adequately correlate these measures with the rapid behavioral changes during acute drug response, we have a target resolution of at least one measurement per minute. To achieve this we are using a simultaneous measurement of red and blue light response using an event related paradigm using pseudorandom multicolor photic stimulation. This new protocol, coupled with the change to a 4T MR scanner (increasing the size of the BOLD effect and image SNR) will provide an objective measure of neural changes during response to drugs of abuse.

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214 Ecological momentary assessment of crack cocaine relapse risk

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This was a feasibility study to determine whether ecological momentary assessment techniques could be used to acquire real-time and near real-time information about relapse risk in a homeless, crack cocaine dependent population. Aims of the study were to develop a cellular phone assessment of cocaine lapse and relapse and test the feasibility of a computerized momentary assessment of cocaine use behaviors and related risk factors. Participants were 31 clients from an outpatient substance abuse treatment program in a community agency that serves the homeless. They were repeatedly surveyed by cellular phone eight times per day over a 2-week period. Participants were assessed for location, activities, associates, feelings, cravings, and coping strategies related to cocaine use. Feasibility findings were: 81% of subjects completed 2-week assessment period, 63% of total possible calls were initiated, 2% of initiated calls were disconnected, 100% of all questions were answered from completed calls. Out of seven positive urine results, only three were reported by the subject via the cellular phone survey. Obstacles were: complicated programming of assessment, unreliable cellular technology, participant response burden, call back failure, and minimal lapse/relapse events. Implications of this research include: cellular phone technology lacks reliability for adequate sampling, need for increased assessment time frame or target more active users to increase lapse/relapse events, and reduce frequency of calls per day to lessen response burden. Ecological momentary assessment using cellular phone technology has the potential to become a useful research/intervention tool if obstacles are overcome.

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215 Family history and other characteristics of heroin-dependent males in Israel

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Background: Various lines of investigation support the concept of an inherited vulnerability to drug dependency, while emphasizing the importance of social and environmental influences and their interactions. Objectives: The present investigation compares the characteristics of heroin dependent Jewish men in Israel to members of the general population, with a focus on the nature of family history of substance abuse problems. Methods: This case-control study compares 64 heroin-dependent Jewish male residents of Jerusalem with a community sample of 131 randomly selected Jerusalem residents with no drug use disorder. Univariate and multivariate models are employed to appraise the independent associations between heroin dependence and exposure variables such as family history of substance misuse and exposure to legal psychoactive substances. Results: The case group is characterized by heavy tobacco and alcohol involvement. Nearly 70% of the cases report an alcoholic and/or drug problem in at least one first-degree relative compared with 10% of controls (odds ratio = 14.5, adjusted for socio-demographic and other potential confounders). Cases with a positive family history have, on average, higher alcohol consumption levels and higher heroin-use severity scores, as compared with cases with no such history. Conclusions: Familial aggregation of drug and alcohol problems, along with smoking at a young age, is the strongest predictor of heroin dependence in this population. Better understanding of the components underlying this familial aggregation can lead to improved treatment and prevention strategies.

216 Drug counselors’ attitudes on empirically supported treatment manuals

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We assessed attitudes about empirically supported treatment (EST) manuals, among community and research drug counselors with a revised version of Najavits et al. (2000) survey, ‘What do you think of treatment manuals’. The questionnaire consisted of 15 questions, now related specifically to substance abuse manuals, asking respondents to provide short answers and rate statements about the usefulness of these manuals on a 7-point Likert-type scale. Subjects were 40 drug counselors (22 from the community and 18 from research). We evaluated the differences in attitudes between these two types of counselors, hypothesizing that research drug counselors would report more favorable attitudes. 35% of the sample was Master’s level, 25% Doctoral, 15% Certified Alcohol and Drug Counselors, and 22.5% had no post-secondary degree or certification. Community counselors had more years of substance abuse treatment experience than research counselors: 9.02 (4.94) versus 5.68 (2.83) (t = 2.49, df = 37, P < 0.05). Additional results revealed that both types of counselors rated the overall usefulness of EST manuals as high: 5.29 (1.23), and while our main hypothesis was not supported, there was a trend toward more favorable overall attitudes for those involved in research as opposed to the community drug counselors: 5.67 (0.84) versus 4.95 (1.43) (t = 1.85, df = 36, P = 0.07). Furthermore, years of experience was significantly associated with community counselors’ attitudes toward substance abuse EST manuals; the more experience they had, the less favorable their attitudes (r = -0.46, P < 0.05). Finally, research counselors found manual components such as a ‘solid theoretical rationale and empirical support for the treatment’, ‘detailed descriptions of specific techniques’, ‘session by session plans’, and ‘indications for reexamine/altering the treatment’ to be more useful than community counselors (all P < 0.05). Findings suggest the importance of evaluating both community and research counselors attitudes specific to training and administration of EST manuals.

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217 The effect of race, neighborhood, and social network on initiation of injection drug use

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Objective: To determine the extent to which individual-level factors (race, social network, injection practices) and contextual-level factors (neighborhood racial composition, poverty, education, and employment levels) contribute to adolescent initiation of injection drug use (<21 years of age) among a population of injection drug users (IDUs) in Baltimore, Maryland. Methods: Street-recruited IDUs from 12 neighborhoods (15–30 years) who initiated injection <5 years prior study entry underwent HIV testing and a risk survey including high-risk practices, and social characteristics. Generalized Estimating Equations was used to estimate the contribution of individual- and contextual-level factors on adolescent initiation while adjusting for the correlation between individuals within neighborhoods. Results: Of 144 IDUs, most were female (60%) and black (63%). In a model including
individual and contextual factors, adolescent initiates were less likely to be black (AOR = 0.05), report early sharing of injection equipment (AOR = 0.37), and more likely to have dropped out of school (AOR = 2.05) and report an early high-risk network following initiation of injection (AOR = 0.98) than young adult initiates. Adolescent initiates were also more likely to come from neighborhoods with a high minority composition (AOR = 3.95) and less likely to come from a neighborhood with a high poverty level (AOR = 0.28) than young adult initiates. The probability of a black adolescent who lived in a low poverty and low minority composition neighborhood initiating IDU was 29% compared with 84% for a black adolescent coming from a high poverty and high minority composition neighborhood. The probability of a white adolescent living in a low poverty and low minority neighborhood initiating IDU was 88% compared with 96% for a white adolescent coming from a high poverty and high minority composition neighborhood. Conclusions: These data suggest that while individual factors play a role in age of initiation of injection and high-risk behavior soon after initiation, social processes within neighborhoods also play an independent role. Public health efforts to reduce adolescent initiation and subsequent high-risk networks should consider the individuals' connection to their social environment.

218 ROLE OF THE DopAMINE RECEPTOR ON THE ABUSED SOLVENT TOLUENE-INDUCED REWARDING EFFECT IN MICE

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Toluene and many toluene-containing products are abused via inhalation. Previous investigations have used the place preference paradigm to evaluate the rewarding effects of commonly abused drugs such as morphine, cocaine, and amphetamine. A conditioning paradigm of toluene inhalation was developed in order to estimate the rewarding effect in mice. Conditioning sessions (five for toluene: five for air) were conducted twice daily for 5 days using a newly developed novel sealed inhalation shuttlebox (15 × 30 × 15 cm: w × l × h), which was divided into two compartments of equal size. One compartment was white with a textured floor, and the other was black with a smooth floor. All conditioning sessions were 20 min in duration, and a minimum of 7 h separated each session. Test sessions were carried out 1 day after the final training session in the drug-free state. Uninjected mice were placed on the ‘neutral’ platform of the shuttlebox, and allowed free access to both compartments of the shuttlebox. The time spent in each compartment during a 1200 s session was measured using a digital video camera. Toluene inhalation (2500–6000 ppm) produced a significant conditioned place preference in mice. These rewarding effects of toluene were abolished by pretreatment with dopamine D1 receptor antagonist SCH23390. These results suggest that the conditioned place preference procedure using a newly developed novel sealed inhalation shuttlebox offers an important tool for studying the rewarding effect of abused solvents. Furthermore, the activation of D1 receptors may play an important role in the expression of the toluene-induced rewarding effects.

219 RELIGIOUSNESS AND ALCOHOL, DRUG, AND TOBACCO USE AMONG 10TH GRADE ADOLESCENTS

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The negative consequences of adolescent substance abuse (ASA) are profound and not only affect individual adolescents and their families, but the effects ripple throughout society. Adolescents who misuse substances are more likely to suffer from poor school functioning, impaired relationships, legal problems, deterioration of physical health, among many other problems. Society pays the costs in increased criminal activity, violent behavior, and increased health care. As a result, researchers are examining a large number of factors that may affect adolescent’s use of substances. Recent work has suggested that religiousness may be a protective factor for ASA, and a call to further understand the circumstances under which religiosity serves to reduce the risk of ASA has been issued. The current study investigated the relation between religiousness and drug, alcohol, and tobacco use among 200 10th graders participating in a 4-year longitudinal investigation of adolescent relationships. Participants completed a computerized version of the Drug Involvement Scale for Adolescents (DISA) which assessed alcohol, drug and tobacco use, as well as a demographic questionnaire that included ratings of religious affiliation and level of religious investment. With all wave one data collected (n = 200), preliminary analyses (n = 85) demonstrate religiousness was negatively correlated with both alcohol use (r (84) = −0.34, P < 0.01) and drug use (r (84) = −0.22, P < 0.05), but not associated with tobacco use. Multiple regression analyses were employed to examine the association between religiousness and substance use when accounting for a number of other factors associated with ASA. The results suggest religiousness may be an important predictor of alcohol use, but not of drug use. For drugs it was the association between religiousness and parental monitoring that best explained use. Implications of these findings and suggestions for future research will be presented. Supported by NIDA grant 1F31DA15030-01(SAB) and NIMH grant 50106 (WF).

220 NEIGHBORHOOD CHARACTERISTICS AND RISK OF FATAL DRUG OVERDOSE IN NEW YORK CITY

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Background. Neighborhood-level factors have been associated with individual morbidity and mortality. We hypothesized a relation between characteristics of New York City (NYC) neighborhoods and fatal drug overdoses. Methods. We carried out a multilevel case-control study using Community Districts (n = 59) as neighborhood units. We used 1990 US Census data for the following neighborhood-level variables: income distribution (Gini coefficient), racial distribution (percent of residents African-American (AA)), socioeconomic status (SES) (percent of residents with less than high school education). We used the 1996 NYC housing and vacancy survey to assess neighborhood housing quality (percent of residents in public housing). We analyzed records from the Office of the Chief Medical examiner of NYC on all accidental fatal drug overdoses (cases) and persons who died of non-drug related accidents (controls) in 1996. Results. Among 740 cases and 1036 controls, cases were more likely than controls to be young, AA, and male. In separate hierarchical models, Gini coefficient (P = 0.003), percent less than high school education (P < 0.001), and percent public housing (P = 0.01) were associated with a greater likelihood of fatal drug overdose. Percent AA was not associated (P = 0.5) with likelihood of fatal drug overdose. All models adjusted for neighborhood-level income in quadratic form, neighborhood level of drug use, and individual age, race, and sex. Discussion. Neighborhood income distribution, SES, and housing quality were all predictors of fatal drug overdose in models adjusted for levels of drug use and neighborhood income. Public health efforts to reduce fatal overdoses should target neighborhoods with evidence of contextual disad-
Comparing the SCID and CAAPE for assessing dual diagnoses

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Generating an accurate and complete diagnosis is challenging under typical circumstances. The challenge is even greater when dual diagnoses (i.e., both substance use and mental health disorders, DDx) are suspected. About 20 persons with reported DDx were assessed using both the SCID (Structured Clinical Interview for DSM-IV), which is used frequently in research, and the CAAPE (Comprehensive Addictions and Psychological Evaluation, Hoffman, 2000), a newer interview designed to assess DDx. Two interviewers assessed ten respondents each; five from a research site and five from comparison sites to control for any differences in symptomology and functioning at different sites. Inter-interviewer reliability was established prior to this study. The interviewers were blind to respondents diagnoses of record. The order of presentation of the interviews was counterbalanced. The SCID was burdensome taking 2 or more h to administer. The PTSD module was particularly difficult for many of the respondents. The substance use modules contain several questions that lack specificity. Finally, establishing which diagnosis was primary was difficult without additional targeted questions. The CAAPE was less burdensome. The average administration took 45 min. Some of the CAAPE mental health modules required additional questions to support diagnoses and it did not include a module for psychotic disorders. The CAAPE more thoroughly assessed DSM-IV substance abuse/dependence criteria and was specific enough to allow the interviewers to establish reliable and complete substance use diagnoses. In addition, each of the mental health modules explicitly asks whether psychiatric symptoms occurred when not using substances. Recommendations concerning the use of these interviews as well as broader implications for assessment of DDx will be discussed.

Sexual and injection risk behaviors in the CSAT methamphetamine treatment project: Baseline data


The Methamphetamine Treatment Study is an eight-site randomized clinical trial designed to compare the Matrix Model of treatment for methamphetamine dependent individuals with ‘Treatment As Usual’ at each site. Data on sexual and injection risk behaviors were collected at treatment entry using the Texas Christian University AIDS Risk Assessment. Of the 1016 subjects, 55% were female, 60% Caucasian, 17% Hispanic, 17% Asian or Pacific Islander, 3% Native American, 2% African–American; and their mean age was 32.8 (S.D. 8.0) years. Subjects had a mean of 2.1 (S.D. 6.0) sexual partners in the past 6 months and 24% (245) had unprotected sex with an individual who was not their spouse or primary partner. Of the 649 subjects who reported unprotected sex in the past month, they had unprotected vaginal sex a mean of 10.6 (S.D. 12.4) times and unprotected anal sex a mean of 0.44 (S.D. 2.33) times.

Outcomes after a brief outpatient detoxification with buprenorphine in young heroin users

D.H. Gandhi, J.H. Jaffe, S. McNary, G. Kavanagh, and M. Hayes, University of Maryland School of Medicine and Center for Addiction Medicine, Baltimore, MD

There is little research into outcomes following a very brief detoxification in young opioid users. Despite the general belief that detoxification is typically followed by a rapid relapse, many opioid users, especially young, new initiates to heroin, appear to seek repeated brief detoxifications before they commit to opioid maintenance or longer-term recovery oriented treatments. Under current United States regulations, physicians who do not have a special registration with the DEA are limited to treating withdrawal with opioids for a maximum of 3 days. This study examines the outcomes after such a 3-day outpatient detoxification using buprenorphine in 18–25 year-old heroin users in Baltimore. About 119 subjects enrolled in the study and agreed to be contacted after detoxification at 1, 3, and 6 months. Although follow-up rates were 79.8, 54.6 and 47% at 1, 3 and 6 months, there were no significant differences in demographics or drug use characteristics between subjects who could and those who could not be contacted at 6 months. Engagement in aftercare was generally poor. Based on self report, 46.3% of the follow-up sample were currently not using heroin at 1 month, 58.5% at 3 months, and 62.5% at 6 months. However, only 18.2, 31.6 and 40% of those tested at 1, 3 and 6 months respectively, had a negative urine test. There was a significant reduction from the baseline in the mean Addiction Severity Index drug use composite score, as well as the mean number of days of heroin and cocaine use during past 30 days, that was sustained over the three follow-up points. Overall, the findings suggest a possible role for brief outpatient detoxification as part of an interim harm reduction strategy, particularly for young heroin users who may not yet be ready or able to engage in more intensive, long-term abstinence-oriented or opioid substitution treatments.

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This study was funded by The Abell Foundation.

Long-term blind label methadone withdrawal after at least 6 months of open label methadone maintenance—A pilot study

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Ten subjects who completed an opiate abuse treatment project at The Treatment Research Clinic and who expressed interest in withdrawing from methadone were consented for the outpatient pilot study. Double blind procedures were used with only the pharmacist and primary investigators being privy to dose reductions. At each visit withdrawal symptoms were monitored by the dispensing nurse and the subjects completed the Subjective Opiate Withdrawal Scale. Subjects experiencing excessive discomfort were maintained at the current week’s dose until symptoms subsided and then reduction was reinstituted. Urine screens were collected at each visit. Clinical management sessions were scheduled bi-monthly. The final phase was a placebo condition lasting from 7 to 21 days. Six subjects completed the study. The number of urine samples ranged from 23 to 55; the number of opiate positive urines ranged from 0 to 15. Three subjects were dropped because of unmitting use of opiates and one departed. Among six subjects who completed the 6 month withdrawal protocol, the number of placebo days was 7 to 18. Preliminary evidence suggests that this method of methadone dose reduction is feasible and may lead to improved outcomes relative to traditional shorter, open label methadone withdrawal.

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Do baseline client characteristics predict subsequent satisfaction with drug abuse treatment?

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Hypothesis: It is expected that drug abuser characteristics describing baseline demographic, criminal, social, psychiatric, and drug use histories will predict subsequent satisfaction with drug abuse treatment. Procedures: In-depth baseline and post-treatment surveys based on the Addiction Severity Index and Mental Health Statistical Improvement Program satisfaction scale were conducted with 495 substance abusers. Analyses: Correlation and linear regression techniques were used to test the associations. Results: Post-treatment satisfaction was found to be predicted by baseline demographic variables (being older, married, no religious affiliation), fewer incarcerations and convictions, less lifetime and recent drug use and treatment involvement, fewer problems with family and friends, and fewer psychiatric difficulties. Implications: The results may identify a subgroup of drug abusers for whom a different treatment approach may be indicated, such as tailored preparatory program.

226 EFFECTS OF NICOTINE ON THE RELATIVE REINFORCING STRENGTH OF FOOD AND COCAINE IN MONKEYS TRAINED UNDER CONCURRENT FR30 SCHEDULES OF FOOD AND COCAINE AVAILABILITY

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Epidemiological data reveal a positive correlation between tobacco and cocaine use. The present study evaluated the effects of nicotine (NIC) on the relative reinforcing strength of food and cocaine (COC) in rhesus monkeys trained to ‘choose’ between food delivery or i.v. injections—saline or COC—under concurrent fixed ratio 30 (FR 30) schedules; i.e., food was delivered after 30 consecutive responses on one lever whereas saline or COC was delivered after 30 consecutive responses on the alternative lever. Daily sessions consisted of three 30-min cycles separated by 10-min timeout periods. Under these conditions, the distribution of behavior was related to available i.v. dose: when saline, 0.01 and 0.032 mg/kg per inj COC were available 2, 44, and 87% of responses, respectively, occurred on the lever leading to i.v. injection. NIC was studied by administering cumulative doses 10 min before successive cycles of the session. Administration of NIC (0.032–1.0 mg/kg) during saline availability had no effect on the distribution of behavior; i.e., responding occurred almost exclusively (82–98%) on the lever leading to food delivery. During availability of 0.01 mg/kg per injection COC, pretreatment with NIC (0.01–1.0 mg/kg) increased the reinforcing strength of COC relative to food; i.e., the average percentage of responding on the lever leading to i.v. injection increased from 44 to 78% with a corresponding decrease in responding on the lever leading to food delivery. In contrast, pretreatment with NIC (0.01–0.1 mg/kg) during availability of 0.032 mg/kg per injection COC did not change the relative reinforcing strengths of food and cocaine, i.e., the distribution of responding on the two levers was not altered by NIC pretreatment. These results indicate that the effects of NIC on the relative reinforcing strength of COC and food depend on the unit dose of cocaine available for self-administration.

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227 EFFECTS OF ETHANOL ON COCAINE DRUG DISCRIMINATION IN RATS

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Ethanol and cocaine are frequently abused in combination. The ability of ethanol and other GABA(A)-active compounds to alter the discriminative stimulus effects of cocaine was tested. Male Sprague–Dawley rats were trained to discriminate cocaine (10 mg/kg, i.p.) from saline using either single-dose or cumulative dosing methods. In single-dose testing, ethanol (0.1–0.5 g/kg) dose-dependently decreased cocaine-lever responding following the training dose of cocaine. In cumulative dose testing, ethanol (0.5 g/kg) produced a rightward shift in the cocaine dose-effect curve. Ethanol (0.1–1.0 g/kg) failed to substitute for cocaine and the highest dose (1.0 g/kg) completely suppressed responding in both single-dose and cumulative-dose testing. Indirect GABA(A) agonists diazepam (benzodiazepine site) and pentobarbital (barbiturate site) did not block the discriminative stimulus effects of cumulative doses of cocaine. The GABA(A) antagonist pentylenetetrazol (10–40 mg/kg) did not substitute for cocaine. These findings suggest that ethanol can modulate the discriminative stimulus effects of cocaine, and that these effects of ethanol may not be mediated by ethanol’s actions at the GABA receptor.

228 DISCRIMINATIVE STIMULUS PROPERTIES OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, ‘ECSTASY’) IN RECREATIONAL DRUG USERS

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Last year the preliminary results of a study on the discriminative stimulus (DS) properties of 3,4-methylenedioxymethamphetamine (MDMA or ‘Ecstasy’) in humans was reported. The study is now completed with 12 participants. The study consisted of three phases: a training phase, a test-of-acquisition phase, and a test phase for a total of 17 sessions. Recreational MDMA users were trained to discriminate among a serotonin (5-HT) agonist and releaser, metachlorophenylpiperazine (mCPP), a psychomotor stimulant, d-amphetamine, and a placebo based on the subjective effects produced by each. During testing, two doses of MDMA (1.0 and 1.5 mg/kg) were administered to determine whether MDMA shared DS properties with mCPP or d-amphetamine. At the 1.0 mg/kg dose of MDMA, five participants discriminated MDMA as d-amphetamine and seven as mCPP; at the 1.5 mg/kg dose of MDMA, half of the participants discriminated MDMA as d-amphetamine and half mCPP. For each MDMA dose, the subjective effects of the two groups were compared. Clear differences were noted, particularly at the lower MDMA dose where those who discriminated MDMA as d-amphetamine reported more psychomotor stimulant-like effects than the group that discriminated MDMA as mCPP.

229 ROUTES OF ADMINISTRATION OF OXYCONTIN DIFFERENTIATE BETWEEN ABUSERS AND DECEDENTS: ANALYSIS OF POST-MORTEM TOXICOLOGY RECORDS BY DEA

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In order to reliably document the scope of the abuse and deaths associated with the consumption of the opioid analgesic product OxyContin, DEA requested autopsy, toxicology, and investigative reports on all deaths induced by, associated with, or related to oxycodone for 2000 and 2001 from the participating members of the National Association of Medical Examiners. Medical Examiners in 31 states supplied us with 1117 records as of January 15, 2002. A total of 824 complete records were received with 293 additional summary statements provided. Of the 824 complete records received by DEA, 123 deaths were positively verified to be associated with the single product entity, OxyContin; 189 deaths were categorized as ‘most likely’ associated with OxyContin because the toxicologies lacked the presence of acetaminophen or salicylates and a specific pill or prescription could not be verified or documented. These data suggest that 38% of all oxycodone positive toxicology reports are likely related
to a specific single entity product- OxyContin. In addition, 15% of all oxycodone positive toxicology reports received were verified to be OxyContin. More than 40% of the toxicology reports also reported the presence of a benzodiazepine. Approximately 40% contained an opiate in addition to oxycodone. And approximately 30% contained an antidepressant. These three pharmaceutical products are part of the ‘standard pharmaceutical protocol’ in many published chronic pain treatment strategies. Surprisingly, while the DEA and DAWN systems have documented the intravenous and insufflation administration of crushed OxyContin tablets associated with abuse typographies less than ten deaths can be documented to involve intravenous administration of the product. The vast majority of deaths from OxyContin have been documented to involve oral consumption of a prescribed pain medication.

230 Methamphetamine-induced neurotoxicity: sex differences and the effect on subsequent methamphetamine reward

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Experiment 1 determined if there are sex differences in the amount of methamphetamine-induced neurotoxicity produced in dopamine (DA) terminals of the nucleus accumbens (NAcc) in rats. Experiment 2 examined the effects of methamphetamine-induced neurotoxicity on the rewarding effect of subsequent administration of methamphetamine assessed by the conditioned place preference (CPP) paradigm. It was predicted that due to a depletion of DA, methamphetamine-induced neurotoxicity would decrease methamphetamine CPP. In both Experiments 1 and 2, rats were treated with a neurotoxic regimen of methamphetamine (10 mg/kg, s.c., every 2 h for a total of four injections) or saline. In Experiment 1, female (n = 20) and male (n = 19) Sprague-Dawley rats were administered the neurotoxic methamphetamine treatment or saline. 2 weeks later, DA, DOPAC, 5-HT, and 5-HIAA concentrations in the striatum (Str), NAcc, and prefrontal cortex (PFC) were measured using HPLC-EC. Results showed that regardless of drug treatment, females had significantly lower concentrations of 5-HT in the PFC; however, the amount of neurotoxicity measured by depletion of DA or 5-HT was not significantly different between males and females. In Experiment 2, male rats (n = 60) were administered the neurotoxic methamphetamine treatment or saline and then conditioned with methamphetamine (0.1, 0.3, or 1.0 mg/kg, s.c.) or saline using a four-trial CPP procedure. Additionally, locomotor activity was measured during the conditioning sessions for trials 1 and 4. Overall, methamphetamine neurotoxicity treatment increased locomotor activity. Methamphetamine-induced neurotoxicity also enhanced methamphetamine reward, since CPP was demonstrated with 0.3 and 1 mg/kg methamphetamine for rats with methamphetamine neurotoxicity, but only with 1 mg/kg methamphetamine for saline controls. These results suggest that the amount of neurotoxicity produced by methamphetamine is similar between females and males, and that methamphetamine-induced neurotoxicity increases methamphetamine reward.

231 Substance use patterns and antisocial behavior in clinical family pedigrees

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Research has suggested that there are two sub-types of antisocial behavior (ASB) that are frequently comorbid with substance use disorder (SUD). One type, termed adolescent-limited (AL) shows a peak in SUD and conduct disorder (CD) in late adolescence and subsequent diminishing symptoms. The other type, called life-course persistent (LCP) involves symptoms that do not subside, but carry on into adulthood. These subtypes may have different etiologies with the LCP form purportedly displaying a stronger familiarity and a more heritable form. Current research efforts have focused on identifying risk factors that may differentiate these subtypes. Hypothesis: We hypothesized that adolescents with parents meeting DSM criteria for ASPD would be at increased risk for LCP ASB and would show different patterns of substance use than adolescents with unaffected parents. Method: About 265 male adolescent probands in treatment for SUD and ASB, their siblings, and parents were assessed regarding their substance use patterns using structured diagnostic interviews. Results: Adolescents with at least one parent with ASPD showed greater substance dependence. SUD in their relatives showed stronger familial patterns and greater comorbidity substance dependence (e.g. dependence on multiple substances). Conclusions: Although longitudinal data is necessary to validate these results, our findings suggest that differential familial patterns of substance use may be a useful method of discriminating LCP and AL subtypes.

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232 A preliminary trial of selegiline hydrochloride versus placebo for smoking cessation

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We studied the safety and efficacy of the monoamine oxidase-B (MAO-B) inhibitor selegiline hydrochloride versus placebo for smoking cessation in cigarette smokers with a history of smoking quit attempt failures. Forty subjects with DSM-IV nicotine dependence were randomized to: (1) selegiline hydrochloride (SEL, 5 mg po bid) or, (2) matching placebo (PLA) for a total of 8 weeks. All participants received individual smoking cessation counseling emphasizing motivational enhancement and relapse-prevention strategies. Outcome variables included treatment retention, smoking cessation rates, expired breath carbon monoxide levels and medication side effects. SEL significantly enhanced trial endpoint (Week 8) 7-day point prevalence smoking cessation rates in comparison to placebo [SEL, 9/20 (45.0%); PLA, 3/20 (15.0%), 2 = 4.29, df = 1, P < 0.05], and smoking cessation rates during the last 4 weeks of the trial [SEL, 6/20 (30.0%); PLA, 1/20 (5.0%), 2 = 4.33, df = 1, P < 0.05]. About 6-month follow-up 7-day point prevalence smoking cessation rates were substantially reduced compared to trial endpoint and not significantly different between study groups [SEL, 4/20 (20.0%); PLA, 1/20 (5.0%), 2 = 2.06, df = 1, P = 0.15]. Treatment retention during the trial was not significantly different in the SEL versus PLA groups (P = 0.13). SEL treatment led to a reduction in depressive symptoms, and was well tolerated in cigarette smokers. The results of this preliminary study suggest that selegiline (10 mg/day) is safe for use, and significantly enhances smoking cessation rates compared to placebo, in nicotine-dependent cigarette smokers.

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DISRUPTIONS IN RESPONDING FOLLOWING ADMINISTRATION OF FLUMAZENIL TO MONKEYS TREATED CHRONICALLY WITH FLURAZEPAM

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Dependence can develop during chronic treatment with positive GABA modulators, although the effects produced by repeated administration of specific drugs or termination of treatment on complex behavioral processes have not been fully elucidated. In the current study, the effects of daily treatment with the positive GABA modulator flurazepam, as well as termination of treatment, were examined in three old-world monkeys responding for food presentation under a multiple schedule of repeated acquisition and performance of conditional discriminations. For 20 consecutive days, monkeys received 3.2 mg/kg per day of flurazepam p.o. 30 min before experimental sessions. On day 21, flurazepam treatment was discontinued; instead, monkeys received a dose of 1 mg/kg of flumazenil 15 min before the session. On subsequent days, monkeys did not receive drug. Acutely, flurazepam (0.56–18 mg/kg, p.o.) did not alter response rates or increase the number of errors. Moreover, there was no change in either dependent variable during chronic flurazepam treatment. When flumazenil was administered after termination of flurazepam treatment, this dose, which was ineffective when administered acutely, decreased mean response rates to <50% of control in the acquisition component and to <75% of control in the performance component. Errors were not reliably increased by flumazenil. Despite the fact that a small dose of flurazepam was administered chronically, sensitivity to the rate-decreasing effects of flumazenil increased following termination of treatment, suggesting that dependence developed to flurazepam. Moreover, the general disruption in responding that was produced by flumazenil was not accompanied by disruptions in the quality (accuracy) of behavior.

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NO DIFFERENCES BETWEEN HEROIN- AND ALCOHOL-DEPENDENT PATIENTS IN TCI HIGHER-ORDER TRAITS

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Background: Some Temperament and Character Inventory (TCI) traits have been related to substance dependence. Hypothesis: Heroin-dependent patients and alcohol-dependent patients differ in TCI higher-order traits. Method: Participants suffered a severe substance dependence (DSM-IV) involving a single substance (heroin or alcohol); all of them were undergoing treatment in a closed addiction unit after detoxification failure in outpatient facilities. After assessment with the TCI, International Personality Disorder Examination (IPDE), and Addiction Severity Index (ASI), we compared two groups of participants: the 51 inpatients with heroin dependence only, and a second group (n = 51) obtained by randomization of the 140 inpatients diagnosed with alcohol dependence only. Both groups presented comparable sex and age profiles. TCI dimensions were analyzed using the t-test or Mann–Whitney test. Results: No group differences in TCI higher-order traits were found. Only TCI facets were discriminatory. Heroin-dependent participants were more ‘exploratory’ (t = –2.03, P < 0.04), while alcohol-dependent patients were more ‘fearful’ (t = 3.16, P < 0.02), ‘sentimental’, (t = 2.17, P < 0.02) ‘compassionate’ (t = 2.28, P < 0.02) and presented more ‘transpersonal identification’ (t = 2.23, P < 0.02). Conclusion: Heroin- and alcohol-dependent patients differ in TCI, but not in TCI higher-order traits.

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INTIMATE PARTNER VIOLENCE AMONG WOMEN IN METHADONE MAINTENANCE TREATMENT

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Background: Intimate partner violence (IPV) among drug-involved women is a serious public health concern. However, no studies have been conducted on IPV with representative samples among women in methadone maintenance treatment programs (MMTPs). This study assesses prevalence of IPV among a random sample of 416 women recruited from MMTPs and examines associations between the women’s drug use and IPV after adjusting for sociodemographics and partners’ drug use. Methods: Data were collected during face–face interviews with women in MMTPs, who participated in a 3-year, NIDA funded study which examined the co-occurrence of IPV and drug use over time. Results: The majority (87%) of the women reported experiencing physical or sexual IPV during their lifetime using the Revised Conflict Tactics Scale and about one half (47%) experienced such IPV in the past 6 months. One-fifth (20%) reported severe IPV in the past 6 months. Logistic regression analyses indicated that women’s use of marijuana, crack cocaine and/or heroin were not significantly associated with IPV in the past 6 months, after adjusting for sociodemographics and partners’ drug use. Women, however, who indicated that their partners used both crack cocaine and heroin in the past 6 months were more likely than the women who did not report drug use for their partners to report any IPV (OR = 3.3, CI = 1.7–2.7) sexual IPV (OR = 2.1, CI = 1.1–4.1), physical IPV (OR = 4.2, CI = 2.2–8.3), and severe IPV (OR = 5.2, CI = 2.5–11.1) in the past 6 months. Significant associations were also found between partners’ use of crack cocaine only and IPV, but not for partners’ use of heroin only. Conclusion: Prevalence estimates of IPV among this random sample of women in MMTPs are much higher than estimates in the general populations of women and exceed estimates found in other non-random samples of women in drug treatment programs. Perpetrators’ drug use is a stronger indicator of IPV than women’s drug use.

MOTIVATION FOR TREATMENT: COMPARISON OF MARIJUANA AND COCAINE-DEPENDENT TREATMENT SEEKING INDIVIDUALS


Motivation is an important component of substance abuse treatment compliance. However, differences in motivation between distinct groups of substance abusers have not been elucidated. The primary objective of this study is to compare whether marijuana and cocaine-dependent individuals seeking treatment in a clinical research setting differ in their desire to reduce or terminate drug use. It is hypothesized that marijuana-dependent individuals may be less motivated to become fully abstinent than cocaine-dependent individuals. Three separate questionnaires addressing different aspects of motivation are being administered: the Stages of Change Scale (SC); Circumstances, Motivation, and Readiness for Treatment Scale (CMR), and the Marijuana and Cocaine Reasons for Quitting Scale (MJCQR). Thus far, five marijuana-dependent participants and 6 cocaine-dependent participants have completed the questionnaires; 40 participants in each group are anticipated by the time of data presentation. Initial analyses of the CMR suggest that marijuana-dependent participants have significantly lower scores on the Motivation subscale than cocaine-dependent participants, indicating lower levels of motivation for quitting. These data reinforce our hypothesis that marijuana patients may be less interested in terminating drug use, and therefore may be harder to engage in treatment and less likely to commit to an abstinence maintenance program. Findings from this study may emphasize the clinical significance of using motivational interventions in the treatment of marijuana-dependent individuals.
237 Neurochemical interactions between dopamine uptake inhibitors and cocaine in awake squirrel monkeys

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Dopamine transport (DAT) inhibitors have recently drawn interest as potential substitute agonist pharmacotherapies for cocaine addiction. Selective DAT inhibitors have been shown to reduce cocaine self-administration in several species. Characterization of the neurochemical effects of the drug interactions that occur during these studies could reveal the mechanism underlying the behavioral attenuation, but there have been no comprehensive studies. In the present study, two tropanones (RTI-177 and FECNT) and one phenylpiperazine (GBR-12909) were administered to awake squirrel monkeys at doses known to alter cocaine self-administration. The drugs were administered (i.m.) both alone and before a subsequent dose of cocaine while changes in striatal dopamine were assessed with in vivo microdialysis. All drugs tested elicited similar increases in extracellular striatal dopamine, but the onset of this action was slower for GBR-12909 than for any of the tropanones. Interactions between DAT inhibitors and cocaine produced sub-additive effects on extracellular dopamine levels. These results suggest that DAT inhibitors reduce cocaine-self-administration by reducing the effect of cocaine on extracellular dopamine.

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238 Mild opioid deprivation increases the degree that opioid-dependent outpatients discount delayed heroin and money

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A growing literature suggests that excessive temporal discounting of delayed rewards may underlie the etiology of substance abuse problems. Little is known, however, about how drug deprivation may affect temporal discounting of delayed rewards by drug dependent individuals. This study sought to examine the extent that opioid deprivation affects how opioid-dependent individuals discount small, medium and large quantities of delayed heroin and money. 13 opioid-dependent individuals maintained on buprenorphine completed a hypothetical choice task in which they choose between a constant delayed reward amount and an immediate reward amount that was adjusted until they expressed indifference between both outcomes. The task was completed for three values of heroin and money rewards under conditions of opioid deprivation and satiation. Across conditions, hyperbolic functions provided a good fit for the discounting data. Degree of discounting was significantly higher when subjects were opioid deprived. Consistent with previous findings, degree of discounting was higher for heroin than money and inversely related to the magnitude of the reward. Opioid deprivation increased the degree to which subjects discounted delayed heroin and money. Understanding conditions that affect how drug-dependent individuals discount delayed rewards might help investigators understand the myopic choices made by such individuals and develop interventions that improve outcomes.

239 Antagonism of a3ß4 nicotinic receptors as a strategy to reduce opioid, stimulant, and nicotine self-administration


18-Methoxycoronaridine (18-MC), a novel iboga alkaloid congener, has been found, in rats, to decrease the i.v. self-administration of morphine, cocaine, methamphetamine and nicotine as well as the oral self-administration of nicotine and alcohol. Recent studies of 18-MC’s mechanism of action have revealed that it blocks a3ß4 nicotinic receptors. The present study shows that a combination of a low dose (i.e., ineffective alone) of 18-MC with a low dose of another agent known to block a3ß4 nicotinic receptors will reduce morphine, methamphetamine and nicotine self-administration. The other agents tested include dextromethorphan (DM; the active ingredient in most over-the-counter cough medicines), mecamylamine (MEC; a nonspecific nicotinic antagonist), and bupropion (BUP; an antidepressant already in use for the treatment of smoking). Not only are combinations of 18-MC with each of these agents effective, but DM-MEC, DM-BUP, and MEC-BUP combinations are similarly effective. Although 18-MC, DM, MEC and BUP all have other actions (e.g., opioid agonist/antagonist effects of 18-MC; NMDA antagonist effects of DM; a4ß2 nicotinic antagonist effects of MEC; dopamine reuptake blockade by BUP), the one common action of all these agents is to block the a3ß4 nicotinic site. Furthermore, ongoing in vivo microdialysis studies suggest that these agents may indirectly modulate the mesocorticolimbic dopamine pathways involved in drug self-administration via actions in other brain regions having high densities of a3ß4 receptors (e.g. the medial habenula and the interpeduncular nucleus). Considered together, all of these results suggest that antagonism of a3ß4 nicotinic receptors may represent a novel strategy to reduce multiple forms of drug addiction. Because there are no agents available that are specific for a3ß4 receptors, the use of combinations of low doses of unrelated agents that act at this site may be a practical way of enhancing therapeutic efficacy (attributable to additive effects at the a3ß4 site) while reducing side effects (attributable to actions unique to each agent).

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240 What does adolescent relapse look like?

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Relapse after adolescent substance abuse treatment is well documented in the literature. The purpose of this study was to empirically examine relapse to marijuana and other drugs and to assess the impact of alcohol on relapse. Follow-up data from 571 adolescents who had participated in outpatient treatment at four sites and 150 adolescents who had participated in residential treatment were examined. Adolescents from both samples reported alcohol and marijuana as their primary drugs of abuse. Measures selected for the cluster analysis were: (a) days of any use, (b) days of cannabis use, (c) days of heavy use, (d) days used caused problems, (e) days of opioid use, and (f) days of cocaine use. After conducting the cluster analysis on a split half group of the adolescents who participated in outpatient treatment, four relapse clusters were produced. The four group solution yielded a group of adolescents who maintained abstinence and reported no substance related problems (17%), a group who reported using marijuana weekly and little or no heavy use or problems (53%), a group that reported using over a third of the time and heavily almost weekly (18%), and a group who reported using almost daily, frequent heavy use, and many associated problems. Using discriminant analysis to predict the group membership for the second random half of the outpatient group and the group treated in a residential setting, the relapse cluster was able to explain over 95% of the variance in the joint distribution of the above measures of use and problems. When we examined whether there was a significant difference between the four groups with regard to days of alcohol use, heavy alcohol use, and alcohol use in the environment, we found that there were significant
differences with higher relapse associated with more alcohol use by the adolescent and those in his or her environment. These results suggest that adolescents who are low or minor relapers are more like abstainers than those who relapse to a higher degree. Future research should seek to understand more about adolescents in the higher relapse groups and evaluate interventions targeted to address their relapse over longer time periods.

241 Factors associated with marijuana use among injured drinkers in the emergency department setting

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The relationship between alcohol use and injury among emergency department (ED) patients is well established. Besides alcohol, the most commonly used substance among injured ED patients is marijuana as it is seen as enhancing alcohol’s effects. The purpose of this study was to examine the factors associated with marijuana use among injured drinkers in the ED. The sample consisted of 376 injured patients who screened positive for hazardous drinking (obtained a score of eight on the Alcohol Use Disorders Identification Test- AUDIT) and had positive blood alcohol levels. Patients completed an interview while in the ED. Participants were 81% male, 75% white, 77% single with a mean age of 31 years. 54% of the patients were marijuana users. Using multiple regression analysis, controlling for gender and age, the AUDIT (B = 5.89, t = 2.43, P = 0.02), positive alcohol-related expectancies (B = 4.64, t = 2.16, P = 0.03), and risk-taking behavior (B = 6.60, t = 2.57, P = 0.01) significantly predicted 17% of the variance in the frequency of marijuana use, F(6368) = 12.42, P < 0.01, R² = 0.17). We conclude that alcohol-related variables and risk-taking behavior are useful in understanding the frequency of marijuana use among injured ED patients. Interventions focused on changing marijuana use among injured drinkers should concurrently address these factors in order to be effective.

242 Drug and alcohol use and sexual risk behavior among school-based adolescents in Mexico

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Objective: To describe the associations between adolescent drug and alcohol use and sexual risk behavior among school-based youth in Mexico. Methods: Presented are data from the International Study of Adolescent Health and Problem Behavior. School-based adolescents in Mexico, in grades 7 through 12 (N=1203), were surveyed in 1998. Logistic regression analysis compared the use of alcohol with that of other illicit drugs, including heroin, cocaine, amphetamines, ecstasy, barbiturates, tranquilizers, marijuana, LSD and other narcotics. The relationship between illicit drug use and sexual behavior was also investigated. Results: Controlling for gender and age, the use of alcohol during three defined time periods (lifetime, during the past 12 months, and during the past 3 months) was associated with the use of other illicit drugs during the same time period. The adjusted odds ratios for the 3 time periods were 5.24 (95% CI: 3.34 – 8.22), 4.16 (2.66 – 6.51), and 3.00 (1.88 – 4.79), respectively. In addition, students who had used other illicit drugs five or more times in their lifetime were more than twice as likely to have had sex than those who had used other drugs fewer than 5 times (aOR = 2.27; 95% CI: 1.10 – 4.69 adjusted for gender, age and lifetime alcohol frequency). Conclusions: The investigation of sexual risk factors associated with substance use in an international setting has the potential to provide unique insights as to the underlying nature of these behaviors, which cannot be gleaned from the study of adolescents in the United States alone. The significance of these findings with respect to substance abuse and HIV prevention efforts will be discussed.

243 Conditioned taste avoidance produced by self-administered cocaine is correlated with both drug intake and rate of self-administration

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I have previously demonstrated that the individual differences in conditioned taste avoidance induced by self-administered cocaine were correlated with the drug intake in 1-h sessions (Gomez, Brain Res Prot 8:137-142; 2001). These data suggested that the conditioned effect is related to the reinforcing properties of the drug. However, rats showing higher cocaine-maintained rates of responding may have developed stronger saccharin avoidance simply because they took more drug. In the current study, the amount that could be self-administered in a single session was therefore limited to 1 mg/kg (seven injections of 0.15 mg/kg per inj cocaine) an amount taken by all rats, albeit at different rates. Even this low dose of cocaine produced a conditioned taste aversion in the rats that showed high rates of cocaine-maintained responding, but not in rats that showed low rates of behavior (correlation of –0.54; P < 0.05). The possibility that the differences among rats in the development of taste aversion was due to the differences in rate of cocaine self-administration was tested by giving cocaine non-contingently as a rapid iv bolus. A dose of 1 mg/kg iv cocaine did not produce conditioned saccharin avoidance although doses of 3 and 5 mg/kg did so. Thus, neither the difference in rate of drug self-administration nor the amount of cocaine taken can explain the correlation between cocaine self-administration and conditioned saccharin avoidance. These results suggest that rats showing stronger cocaine-induced conditioned avoidance may be more sensitive to the reinforcing properties of the drug. This conditioning paradigm may be a tool to investigate the anticipation of drugs of abuse.

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244 Chemotaxis of rat thymic and human leukocytes by the delta-selective non-peptidic opioid SNC 80


Opioids like morphine, represent a major source of relief for most chronic moderate to severe nonmalignant pain. However, opioid abuse may lead to infections such as hepatitis and AIDS because opioids have been associated with suppressing various parameters of immune function including antimicrobial resistance, antibody production, monocyte-mediated phagocytosis, and both neutrophil and monocyte chemotaxis. We have previously reported immunopotentiating properties of non-peptidic opioid receptor selective agonists and antagonists. In this study, we evaluated the effects of the non-peptidic delta-opioid receptor agonist (+)-4-((2S, 5R)-4-allyl-2, 5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N, N-diethyl-benzamide (SNC 80) on chemotaxis of rat thymic and human peripheral blood mononuclear cells by using a modified Wilkinson chamber. We observed that SNC 80 at concentrations of 10^-10, 10^-9, 10^-8, 10^-7, and 10^-6 M, significantly (P < 0.01) stimulated rat thymic (1.3, 1.55, 1.58, 1.75, and 1.8-fold increases, respectively) and human leukocyte (1.13, 1.37, 1.43, 1.7, 1.83 fold-increases, respectively) chemotaxis, compared with untreated control. Checkerboard assays demonstrated that SNC 80
induced chemotaxis, rather than chemokinesis, on rat and human leukocytes. The effects of SNC 80 on chemotaxis of rat and human leukocytes were antagonized by naloxone, indicating that the modulation of chemotaxis by SNC 80 is via a classic opioid receptor. The development and use of non-peptidic opioids like SNC 80 could have an immediate impact not only as potent analgesics, but in immunomodulation. This work was supported by grants I-32914-N from Consejo Nacional de Ciencia y Tecnología and CN-285-00 from Universidad Autónoma de Nuevo León, México, to RGF, and NIDA/NIH Grants DA12095, to RJW.

245 Efficacy of sertraline in depressed, recently abstinent, cocaine-dependent patients

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About 60 depressed (Hamilton score >15), cocaine-dependent individuals (41 M/19 F; 43 AA/14 H/3 C) with a mean age of 36.2 years (range: 18–52) were entered into a 12-week clinical trial in which they received either the serotonin reuptake inhibitor sertraline (200 mg/day) or placebo. During weeks 1–2, patients were housed on a drug-free residential unit where they were induced onto the study medication. Patients then participated on an outpatient basis during weeks 3–12 while continuing to receive study medication. Patients participated in a day substance abuse treatment program during weeks 1–3 and underwent weekly cognitive behavioral treatment (CBT) during weeks 4–12. Self-reports of mood were obtained once weekly and urine samples were collected thrice weekly. Groups did not differ on retention and baseline characteristics. Preliminary analyses indicate that the rate of neither relapse to cocaine use (log rank = 1.5, P < 0.2) nor increase in cocaine-positive urines over time (z = 0.8, P < 0.4) differed between groups. In addition, decreases in depression scores over time did not differ between groups. These results suggest that sertraline is not more efficacious than placebo in treating either depressive symptoms or cocaine dependence in this population receiving CBT.

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246 Multi-parameter models of the effects of drugs on response rate under multi-component multiple variable interval schedules of reinforcement

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The functional analysis of behavioral drug effects has suffered as a discipline because of a lack of good mathematical models of operant responding. A 2-parameter model originally derived from the Matching Law (Herrnstein, 1970) to account for response rate as a function of reinforcement rate in single response alternative procedures has been shown to provide a good description of response rate under multi-component multiple variable interval (multi VI) schedules of reinforcement, both in the absence drugs and in the presence of a variety of drugs. Data from several published papers concerning the effects of drugs on multi VI schedules are reanalyzed to explore how well the 2-parameter model and variants with three and four parameters describe the published results. It is shown that an exponentiated form of the model describes the effects of drugs on responding better than the original 2-parameter model. With the addition of a fourth parameter the model also describes well the type of relationship between response rates in the drug and no-drug conditions that the Rate Dependency Hypothesis is usually invoked to explain. A preliminary study concerning the effects of amphetamine and pimozide on responding under a nine-component multi VI schedule supports the findings from the reanalysis of the published data. It is suggested that the four parameters of the mathematical model can be used to devise a classification system for the behavioral effects of drugs under a standardized multi VI schedule, some attempts to formulate the classification scheme are discussed.

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247 Tiagabine increases negative cocaine urines in methadone-stabilized cocaine abusers

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This study evaluates the efficacy of tiagabine at high dose (24 mg/day) and low dose (12 mg/day) against placebo in increasing cocaine free urines on methadone-stabilized cocaine users during a 10 week outpatient clinical trial. The 45 treatment seeking subjects were predominately Caucasian (75.6%), males (77.8%) with an average age of 38 years (S.D. = 6.5) and never married (53%). The first 2 weeks’ mean proportions of opiates and cocaine negative urines were 28 and 42%, respectively. Subjects were initially stabilized on methadone during these 2 weeks and then received tiagabine for the following 8 weeks. Baseline assessments included SCID, ASI, urine toxicology and opiate withdrawal scale. Urine toxicology was performed thrice weekly. Treatment retention was over 80% for all treatment groups. At weeks 8–10 cocaine negative urines increased by 14% with high dose tiagabine, by 2% with the low dose of tiagabine and decreased by 17% with placebo (Hierarchical Linear Modeling, Z = 2.07, P = 0.03). The Odds ratio of having negative cocaine urines rose in the high dose group from 0.9 to 1.7 at the end of the trial. Tiagabine at 24 mg/day was well tolerated among these methadone-stabilized patients with only one reporting headache. Tiagabine appears to be a promising GABAergic medication that moderately improves cocaine negative urines.

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248 Indian boarding schools during the ‘Holocaust’ era and their impact on current alcohol use among five tribes of Plains Indian adults

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Thousands of American Indians attended Indian Boarding Schools during what has been called the Indian ‘Holocaust’ Era (1890–1965). Experiences of attending boarding schools are said to have resulted in a multigenerational legacy of chronic trauma and unresolved grief. There is wide-spread belief that this ‘historical unresolved grief’ contributes to high rates of alcoholism and other social problems among American Indians. Only one work, published in 1998, has tested the relationship between boarding school attendance and alcohol use. No significant association was found. However, after dividing the sample into three groups (those that did not attend boarding school, those that attended from 1 to 2 years, from those that attended 3–12 years), 10 of 14 analyses revealed higher and more problematic consumption among
the group attending boarding school for 1–2 years. Data from a fifth tribe were recently collected and are being added to our database; analysis continues.

Funding provided by the NIAAA (RO1 AA09440 and RO1 AA11685) and the NIH Office for Minority Health Research.


Previous results from our team have shown that opiate dependent women who received substitution during pregnancy and early post partum. Two studies were identical with respect to birth, neonatal withdrawal syndrome (NWS) and perinatal patterns of the infant, whether they received oral methadone or sublingual buprenorphine treatment. Even though, demographic issues need to be better discussed. Social status, polydrug abuse medical and psychiatric items appear meaningful compared to the type of substitution chosen. Moreover, this population seem to be older, with less education and longer obstetrical history in face of a witness population. Despite few differences concerning NWS age of maximum and late premature newborn, both the methadone and buprenorphine regimen had a group of severe cases grouping several harmful factors with poor or very poor results. Consequences for a future guide line of indications for ‘liberal-managed’ buprenorphine treated pregnant women or for ‘in-center’ methadone maintained ones will be discussed.

250 METHODS FOR EARLY PHASE MEDICATION DEVELOPMENT TRIALS EXAMINED USING THE AGONIST APPROACH FOR COCAINE DEPENDENCE

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Medication development is costly. Scientific rigor varies in early phases. Problems stem from design and method. Efficiency and diminished risk can be achieved. We explored designs/methods while examining agonists to treat cocaine dependence. Method: We conducted three studies with common procedural features and the premise that early phase clinical trials can benefit from human lab strategies. All three studies used: (1) a priori ‘completer’ strategy decreasing ‘missing data’; (2) narrowly defined inclusion criteria for homogeneity; (3) identical intake/in-study evaluation for comparability; (4) rigorous medication compliance monitoring; (5) double-blind randomized method. Two studies were reversal design variants using dextro-amphetamine. A third study examined an incremental design with two methamphetamine dosing preparations. Results and Discussion: Trends toward benefit of the agonist approach were evident. The designs/methods proved practical in the outpatient research context. Rigorous standardized design and method are recommended in early phase trials. NIDA PS0-9262.

251 ENVIRONMENTAL ENRICHMENT DECREASES INTRAVENOUS SELF-ADMINISTRATION OF COCAINE, BUT ALSO DECREASES RESPONDING FOR NON-DRUG REINFORCERS

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Previous research has shown that rats reared in an enriched environmental condition (EC) self-administer less amphetamine at low unit doses than cohorts reared in an isolated condition (IC). The present experiments examined operant responding for intravenous cocaine, as well as non-drug reinforcers in EC and IC rats. EC and IC rats were trained to respond for sucrose pellets before beginning i.v. cocaine self-administration. Specifically, sucrose responding was assessed under an FR5 schedule at both 85 and 100% of free-feed body weight. A separate group of EC and IC rats were habituated to operant chambers for 6 sessions before assessment of responding for cue-light novelty. Results showed that, as with amphetamine, EC rats self-administer less cocaine at low unit doses than IC rats during acquisition. However, subsequent studies revealed that IC rats have much greater rates of spontaneous responding in the absence of any reinforcement contingency or prior training. Furthermore, IC rats respond at greater rates for non-drug reinforcers (sucrose and novelty) than EC rats. These results suggest that environmental enrichment decreases incentive salience of stimuli associated with positive reinforcement.

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252 POST-DISCHARGE ABSTINENCE RATES FOR WOMEN WITH LONG-TERM RESIDENTIAL TREATMENT IN THREE NATIONAL STUDIES: RWC/PPW, NTIES, AND DATOS

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This analysis compares post-discharge abstinence rates obtained in three national studies of women in long-term residential treatment (LTR). In the first study, 6-month abstinence data (n = 1181) were assessed for women who received LTR in CSAT = s Residential Women and Children/Pregnant and Postpartum Women (RWC/PPW) program. In the second study, 9-month abstinence data on average were assessed for women tho received LTR in CSAT = s National Treatment Improvement Evaluation Study (NTIES), (n = 424), and in the third study, 6- and 12-month abstinence data women were assessed for women who received LTR in NIDA = s Drug Abuse Treatment Outcomes Study (DATOS), (n = 239). The clients = length of stay in treatment (LOS) was controlled in the analysis and the association of abstinence with parent/pregnancy status was assessed. In all three studies, post-discharge abstinence rates were strongly related to LOS. Despite varying clientele, treatment programs, and follow-up intervals women who received LTR of 6 months or longer showed consistently high post-discharge abstinence rates, ranging from 68–71% in the three studies. Between-study differences were largest for women with LOS under 1 month, (ranging from 18% abstinent in DATOS to 43% in RWC/PPW), but diminished as LOS increased. Length of follow-up interval and client pregnancy/paternity status both showed only slight associations with post-discharge abstinence. Parenting and pregnant women with the longest LOS ranged from 62 to 71% abstinent.

253 MAXIMIZING SUPPRESSION OF HEROIN CRAVING: A RANDOMIZED-GROUP, DOUBLE-BLIND COMPARISON OF TWO METHADONE INDUCTION SCHEDULES

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Recent data indicate that early treatment response predicts long-term success, which suggests that methods to improve early treatment response are important. This study is designed to assess whether self-reported heroin craving decreases within and between days during induction onto methadone and whether the magnitude of craving...
suppression depends on the dose sequence. Heroin-dependent volunteers are randomly assigned to receive one of two 15-day methadone induction schedules that are matched for cumulative dose; only the dose sequence differs. Participants can earn $5 for each drug-free urine sample (collected each weekday). The first schedule (STEPWISE, n = 13 to date) escalates methadone doses during week 1 (from 28 mg on day 1 up to 84 mg on day 6) then tapers the dose (to 56 mg) during week 2. Group assignment is stratified for sex, ethnicity and route of heroin use. Test sessions occur on protocol days 1, 2, 5, 7, 10, 11 and 15 (which correspond to methadone dose-effects that are compared within and between groups); subjective and physiological effects of methadone are evaluated 30 min before and 2 h after the daily dose. Trough methadone plasma levels (independent of group assignment) positively correlate with heroin craving questionnaire scores (r = 0.93, P < 0.005). Consistent with predictions, ANOVAs indicate that methadone decreases heroin craving within each session, Pre/Post methadone F[6,144] = 24.69, P < 0.0001, and across induction days, F[1,24] = 14.55, P < 0.0001, and that the magnitude of heroin craving suppression by methadone diminishes by week 2, Day X Pre/Post F[6,144] = 5.07, P < 0.001. Heroin craving scores decrease significantly more in the STEPWISE relative to the RAPID methadone induction protocol, Group X Day X Pre/Post F[6,144] = 3.44, P < 0.001. Rated monetary values of daily methadone doses parallel the pharmacological doses. Supported by NIH/NIDA R29 DA11079 and Joseph Young, Sr. Funds from the State of Michigan.

254 UNDERSTANDING SOME OF THE HEALTH CONSEQUENCES OF METHAMPHETAMINE USE

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While anecdotal evidence suggests that there are negative health consequences of methamphetamine (MA) use, little systematic research has been conducted on these potential consequences. This study investigates the effect of cumulative MA use on health, using several measures of health and of cumulative MA use (based on monthly natural history data since age 14). Analyses were conducted on data from an ongoing study of MA users; the analysis sample consists of 352 individuals between the ages of 18 and 52 for whom data were complete. Compared to general population data from the National Health Interview Survey (NHIS), fewer MA users report their health as ‘Excellent’ or as ‘Very good’ (42, versus 68% of the general population between the ages of 18 and 64). Preliminary analyses suggest that there are interactive effects of age and cumulative MA use on self-reported health. First, OLS regression analysis of a global measure of health (1 = Excellent to 4 = Fair or poor), controlling for other significant predictors (early sexual abuse and having any serious health conditions prior to drug use), indicates that those who are older (over age 34) and have more intensive cumulative use (more than 35 months in which MA was used for at least 20 days) report significantly worse health than does the reference group (age 34 or younger and 35 months or less in which MA was used for at least 20 days). Second, logistic regression analysis of having developed any of a number of serious health conditions after beginning illegal drug use, controlling for other significant predictors (early sexual abuse, parental drug use, and education level), indicates that, compared to the reference group, members of all other groups are more likely to have developed a serious health condition. Moreover, the odds of having developed a serious health condition increase monotonically among groups, moving from younger people with more intensive use, to older people with less intensive use, to older people with more intensive use. Results suggest that the health consequences of MA use intensify with age; thus, intervention early in either the life course or the use career may minimize the individual and social costs of MA use.

255 4-[2-BIS-(4-FLUOROPHENYL)METHOXYMETHYL]PENNYLHIPPERIDINES AS POTENTIAL COCAINE ABUSE THERAPEUTICS

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We have designed and synthesized analogues of GBR 12909 (1-[2-bis-(4-fluorophenyl)methoxy]ethyl)-4-(3-phenylpropyl)piperazine) in order to further study the pharmacological effects of this molecule. The intention was to find ligands with potential as treatment agents for the abuse of cocaine and other stimulants. Reduction in the incidence of this type of drug abuse is expected to be concomitant with a reduction in the HIV epidemic. Our hypothesis was that structural modification of GBR 12909 might alter the affinity and selectivity of this molecule for the DAT (dopamine transporter) and SERT (serotonin transporter). In order to explore structure-activity relationships in the GBR piperazine molecule, we have simplified the molecular structure and reduced the basicity of the compound by changing the piperazine ring to a piperidine ring. These new piperidine analogues were tested for affinity at the DAT and SERT present in rat caudate membranes using [3H]RTI-55 as radioligand. Our results have shown that several analogues display affinity for the DAT in the subnanomolar range. These new analogues may be worthy of exploration as both, pharmacological tools to further study the DAT and new treatment agents.

256 ADDICTION HISTORY, TREATMENT UTILIZATION, AND SERVICE NEEDS AMONG SUB-GROUPS OF DUALLY DIAGNOSED PATIENTS

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Hypotheses: Individuals with co-occurring substance use and mental disorders are heterogeneous with regard to types of mental disorders and substances used. The hypothesis of this study is that addiction history, treatment utilization, and service needs vary among subgroups of dually diagnosed patients by diagnosis and gender. Procedures: This study will examine relationships among addiction history, treatment utilization, and service needs among 300 adult (humans) who are receiving residential drug treatment. In-depth interviews are conducted at the time of treatment admission. Results: 36% of the sample has a psychotic disorder and 64% has a mood disorder. Statistical Analyses: χ² and ANOVA tests were performed to test differences between diagnostic groups. Significant differences were found with regard to ethnicity, with a higher proportion of whites among those with mood disorder (51 vs. 31%) and a higher proportion of African Americans with psychotic disorders (41 vs. 31%, P < 0.05); a higher proportion of psychotics who were dependent on cannabis (56 vs. 41%, P < 0.05); more years of regular cocaine use among individuals with mood disorder (13.7 vs. 11.0, P < 0.05); more use of opiates (non-heroine) among those with mood disorders (31 vs. 29%, P < 0.05); more use of tranquilizers among those with mood disorders (32 vs. 21%, P < 0.05). Regarding treatment participation, individuals with mood disorders had a higher number of prior treatments for alcohol use (1.8 vs. 1.2, P < 0.01), were more likely to have been treated in short-term inpatient modalities (31 vs. 11%, P < 0.01), and had more episodes of outpatient mental health treatment (5.8 vs. 4.0,
Pregnant smoking is the leading preventable cause of low birth weight in the United States. Although many women quit smoking in their first trimester, approximately 20% continue to smoke beyond this time, particularly those from low SES backgrounds. Novel interventions of increased intensity are clearly needed for the more resistant and heavily addicted pregnant smoker. A randomized clinical trial is in progress incorporating parent education about recognizing and appropriately responding to signs of abuse in their children.

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outreach and education for this population to reduce transmission rates and for increasing resources to make Hepatitis testing more accessible to methamphetamine users.

261 OXYCONTIN USE IN INDIVIDUALS SEEKING SUBSTANCE ABUSE TREATMENT

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The illegal use or abuse of OxyContin, a prescribed pain medication, has been sensationalized in the media. To investigate the prevalence and nature of the use of OxyContin in patients entering substance abuse treatment programs, the Drug Evaluation Network System (DENS) was utilized. The DENS is an ongoing electronic data collection system that uses the Addiction Severity Index (ASI) to provide information on patients entering substance abuse treatment programs in seven U.S. cities. Questions on OxyContin (also called Oxy’s, OC’s) were added to the DENS system. ASI assessments on 260 patients, collected between October and December 2001 revealed that only ten patients (3.8%) reported use of OxyContin in the past 30 days and/or in their lifetime. All of the OxyContin users also reported use/misuse of other substances. In fact, only 1 of the 10 OxyContin users reported ‘Opiates/Analgesics’ as their primary substance problem. This presentation will include data collected up to 1 week prior to the conference and will describe patients’ background characteristics as well as the nature and severity of their substance use, health and social problems. To date, the prevalence of OxyContin use among individuals seeking substance abuse treatment does not indicate a major problem; however, this study cannot rule out the possibility of an emerging problem in individuals who are not currently seeking substance abuse treatment.

262 BARRIERS TO WORK AND EMPLOYMENT OUTCOMES AMONG SUBSTANCE-ABUSING WOMEN ON WELFARE: FINDINGS FROM THE CASAWORKS FOR FAMILIES PROGRAM


States face a special challenge moving women with substance abuse problems from welfare to work under the requirements of the 1996 federal Temporary Assistance to Needy Families program (TANF). In prior work, Danziger and colleagues found that a simple, summary index of fifteen potential barriers to employment faced by these women was an excellent predictor of 12-month employment status among welfare dependent women. This study used the ASI and TSR to construct a similar ‘employment barriers index’ modeled after the Danziger work and examined its predictive utility among 342 substance abusing women on welfare in 11 locales around the nation. These women received a multi-service intervention (CASAWORKS for Families) designed to support female welfare recipients’ efforts to achieve stable employment by overcoming substance abuse and other potential major barriers to work. Substance abuse treatment was integrated with employment-related services, and services for domestic violence, parenting skills, and other needs. A repeated measures design with no formal control group was employed during the initial developmental phase. Findings indicated that almost all 15 barriers were quite prevalent among the CWF sample at admission, particularly lack of transportation (85%), low work experience (78%), major depressive symptoms (70%), and legal problems (74%). Further, all substance abusing women on TANF were experiencing multiple potential barriers to work at admission, the average number being 7. Few single barriers predicted employment, but replicating the earlier findings of Danziger, there was a significant relationship between the number of barriers experienced at both baseline and 6 months and the likelihood of employment at 12 months. The conceptual framework of potential barriers to work appears to be promising based on these findings but analyses eventually (in a second phase) with a control group will provide a clearer picture of the utility of this approach.

263 CALIFORNIA STATEWIDE DRUG COURT EVALUATION

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The Drug Court Partnership (DCP) Program instituted by the California legislature in 1998 appropriated $8 million to support California drug courts. The State Department of Alcohol and Drug Programs and the Administrative Office of the Courts, in a joint partnership, developed an aggregate quarterly reporting system to evaluate the impact of the DCP Program. For seven quarters (January 2000 September 2001), the 33 reporting counties had 7082 new drug court admissions, 2892 graduates, and 3113 participants who did not complete the program. Demographics for new drug court admissions were similar to those of statewide drug treatment population, however, differed from those of statewide drug-related arrests; 62.8% male, 53% white, 26% Hispanic and 15% African-American. New admissions also tended to be methamphetamine users (48%), with long-term drug use (42% used 10 year or more). Comparison of demographic characteristics for new admissions and graduates suggested that some demographic groups were more likely to complete drug court programs. Graduates benefited from the programs in terms of housing, employment, education, and lower average of re-arrest rates 2 years after admission to the program. Aggregate statewide data for participants entering and leaving drug courts in California suggest positive outcomes for program graduates. The data also suggest that drug courts may serve select subgroups of drug-involved offenders whom meet the rigorous inclusion criteria that exist in most drug courts. Further, there may be demographic differences between those entering drug courts and those most likely to graduate from drug court. Additional investigation of these issues can support increased access and effectiveness to drug courts for all participants.

264 RELATIONSHIP OF REGULAR COCAINE, HEROIN AND ALCOHOL USE AND PSYCHOSOCIAL FUNCTIONING IN PREGNANT WOMEN

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Drug use in pregnancy can adversely affect both mother and fetus. Since most drug abusing women report polysubstance use, it is important that we examine diversity in psychosocial functioning and its relationship to regular use of specific substances (i.e. alcohol, heroin, cocaine). The present study compared ASI composite scores and interviewer severity ratings in a sample of 205 treatment seeking pregnant women with and without lifetime histories of regular alcohol, cocaine and heroin use. Demographically, the sample had a mean age of 28.8 years and 81% were African American. There were some demographic differences across the various lifetime regular use patient subgroups. Regular alcohol users were more likely to be Caucasian. Regular heroin users were more likely to be African American and younger on admission, while regular cocaine users were somewhat older on admission. At least 1 year of regular use was reported by over one-fourth (27%) of women for alcohol; nearly three-fourths of women (73%) for heroin, and over two-thirds of women (69%) for cocaine. For alcohol, pregnant women with regular use had higher ASI composite scores for 2 of the 7 domains (alcohol, legal). For heroin, regular users had higher scores on 4 domains (employment, alcohol, drug, legal). A
similar pattern was found for regular cocaine users, with higher scores for the alcohol, drug, family, and psychiatric domains. Similar patterns were observed for interviewer severity ratings, supporting the robustness of study findings. The data confirm different patterns of psychosocial functioning as a function of type of regular drug use. The implications of these data for patient treatment matching will be discussed.

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265 GABA AGONISTS AS PHARMACOTHERAPIES FOR COCAINE ABUSE: A PILOT STUDY

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Compelling results from pre-clinical studies suggest that GABA agonists may attenuate the behavioral effects of cocaine. The aim of this pilot experiment was to determine the combined effects of oral cocaine (0 and 300 mg) and triazolam (0 and 0.5 mg) in cocaine abusers (N = 10). Volunteers received each of the four possible drug combinations in mixed order. Drug effects were assessed before drug administration and every 30 min afterwards for 4 h using a battery of subject-rated drug-effect questionnaires and physiological indices. Cocaine produced classic stimulant-like effects (e.g., increased ratings of High, heart rate, and blood pressure). Triazolam alone produced prototypical sedative-like effects. Combining cocaine and triazolam did not significantly attenuate the subject-rated effects of cocaine. Conversely, cocaine significantly attenuated both the subject-rated and performance-imparing effects of triazolam. Combining cocaine and triazolam produced greater increases in heart rate, but not blood pressure, than observed with cocaine alone. However, the magnitude of the heart-rate effects was not clinically significant (i.e., on average heart rate did not exceed 90 bpm). While the results of this study do not support the utility of GABAA agonists as pharmacotherapies for cocaine abuse, future research should test these compounds using more sophisticated methods (e.g. dose-response curves for the drugs alone and in combination) and behavioral arrangements (e.g. drug self-administration or discrimination). Future studies should also test GABAB agonists (e.g. baclofen).

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266 COCAINE EFFECTS ON THE QT INTERVAL ASSESSED BY DIGITAL AND ANALOG MEOUREMENTS

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Cocaine is associated with ventricular arrhythmias and sudden death. In vitro, cocaine blocks IKr (but not IKs), which may prolong cardiac repolarization. Studies of cocaine and the QT are confounded by heart rate acceleration that tends to shorten the QT. Standard methods of QT 'rate-correction' such as Bazett's (QTc = QT/√RR) function poorly at rates > 80 bpm. Because drugs in development for the treatment of cocaine abuse may affect cardiac repolarization, it is crucial to understand the effects of cocaine alone on the QT interval. We asked whether a digitized, semi-automated method generating a unique linear regression of QT against RR (> 200 points per regression) would be more sensitive and specific than Bazett's formula to assess QT drug effects. The QTc was compared to the digitally determined QT that was predicted by linear regression for a heart rate of 60 (QT60). Cocaine was infused in eight consenting, experienced users in an infusion-sequence double blinded design with placebo and 20 mg cocaine on Day 1 then placebo and 40 mg cocaine on Day 2. Results: QT measurements were compared to predrug measurements taken at identical times during the day. 40 mg cocaine was associated with a significant increase in the QTc 30 min post infusion (432 ± 12 ms on drug vs. 409 ± 7 ms control, P < 0.02) but not the QT60 (391 ± 8 on drug vs. 398 ± 5 ms control). The decrease in RR interval was greatest at this timepoint (P < 0.05), suggesting that the QTc increase was driven by heart rate. Comparison of the QT/RR relation in the digitized ECG data (six of eight subjects with analyzable data) immediately before and during cocaine infusion revealed that while all subjects manifested a shortening in RR interval, this was associated with an appropriate shortening of the QT in two subjects, a greater shortening of QT than expected in two, and a transient prolongation of the observed QT in two. Conclusions: Heart rate acceleration associated with cocaine results in artifactual prolongation of the QTc but not QT60 derived from linear regression. Digitized ECG additionally can capture brief but clinically significant QT prolongation manifested by some individuals in response to cocaine.

267 SEX-SELECTIVE EFFECTS OF STRAIN ON COCAINE SELF-ADMINISTRATION

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Female rats show greater neurobehavioral responses to stimulants than male rats, effects that may relate to activating effects of gonadal steroids, which increase DA levels, or to organizational effects leading to sexual dimorphism of specific brain regions. Data on sex differences in drug self-administration (SA) are conflicting perhaps due to strain differences. Male Lewis (Lew) and Fischer 344 (F344) rats differ in cocaine SA, and in mesolimbic DA and HPA axis functions. Strain differences in these functions for female rats appear to oppose those for males. Thus, we examined IV cocaine SA in female and male, Lew and F344 rats. Rats were trained to self-administer cocaine until response rates were stable. Responding under fixed ratio (FR3; 0.25–1.0 mg/kg per infusion) and progressive ratio (PR; 0; 1 mg/kg per infusion) schedules were examined. Preliminary analysis suggests that male F344 rats have higher response rates under both schedules compared to male Lew rats and these rates are similar to those of female Lew rats. We also find female Lew rats have shorter estrus phase than F344 rats, shown previously to reflect lower estrogen levels. These data suggest that gender interacts with genetic background to affect the behavioral responses to cocaine.

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268 NICOTINE IMMUNOMODULATION OF APOPTOSIS IN HUMAN CORONARY ARTERY ENDOTHELIAL CELLS

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It has been recently reported that nicotine is an important modulator of immune cells at the level of programmed cell death or apoptosis. Apoptosis is a process that helps maintain the homeostasis of the vascular endothelium and smooth muscle cells and alteration of the apoptotic process has been associated with cardiovascular diseases. The present study examined the effects and the mechanisms of action of nicotine on apoptosis in human coronary artery endothelial cells (HCAECs). Cultured HCAECs were treated with nicotine at a concentration that correlates with the tissue level of smokers (1 μg/ml), concurrently with TNF-α (40 ng/ml) and (100 nM) dexamethasone to induce apoptosis. The data showed that nicotine significantly
inhibited apoptosis in HCAECs as verified by the decreased expression level of active caspases compared to cells treated with the apoptosis inducers alone. This decrease was blocked by the addition of t-tubocurarine chloride (d-TC), a general nicotinic receptor antagonist, providing evidence that this action of nicotine was receptor-mediated. The findings were further confirmed by TUNEL assay for DNA fragmentation, characteristic of apoptosis. This action of nicotine on apoptosis in coronary endothelial cells suggests that it may have an impact on cardiovascular pathology and atherogenesis.

AHA FL. 0051206B

269 SUBSTANCE-ABUSING REPEAT OFFENDERS: THE LINK BETWEEN MENTAL DISORDERS AND LONG-TERM OUTCOMES

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The link between mental disorders and crime has been the focus of extensive research. Recent longitudinal research suggests that persons with co-occurring substance abuse and other mental disorders are at greater risk for criminal behavior than the general population. Other researchers have found a link between childhood conduct disorders and adult criminality and/or mental disorders (most of which were substance abuse). This study examines links among substance abuse, criminality, mental disorders, and substance abuse treatment using data from a longitudinal study of male prison inmates with a history of substance abuse who received therapeutic community treatment for substance abuse and a non-treatment comparison group (Total N = 715) at 5 years post release. Measures included the DISIII-R, the Hopkins Symptom Checklist (SCL90), the Beck Depression Inventory, and the Taylor Manifest Anxiety Scale (Shortened). Preliminary results show that 33.1% of subjects met DSMIII-R criteria for a single psychiatric disorder (excluding substance dependence) and an additional 27.6% met criteria for co-occurring disorders (excluding substance dependence). A large proportion of the sample (51.5%) were diagnosed with anti-social personality disorder. Subjects with a DSMIII-R diagnosis were more likely to have engaged in criminal activity and to have taken medication for a psychiatric problem post release than those without a diagnosis, however, they were not more likely to have used drugs in the post-release period or to have accessed substance abuse or psychiatric/psychological treatment. Additional analyses will be presented.

270 TREATING RX OPIOID ABUSE: PRELIMINARY FINDINGS FROM PROJECT PAIN

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As many as 19% of chronic pain patients abuse prescription (Rx) opioids. In response, providers often refuse to prescribe or under-prescribe pain medicine, resulting in increased drug-seeking behavior. The goals of PROJECT PAIN, a Stage I project, are: (1) decreased opioid adherence; and (2) decreased opioid/ QOL. To date, 9 pilot subjects (67% male; 78% white; M age 42.4 years, S.D. = 11.25) have been treated with ‘Motivational Adherence Therapy’ and methadone (10–75 mg q6 maintenance and 5–25 mg q4–6 breakthrough). Eight met criteria for opioid dependence and one for abuse; all had other Axis I diagnoses. Duration of pain was 8.1 years (S.D. = 4.13) years. On the Multidimensional Pain Inventory (MPI), 22% were ‘functional’, 44% ‘emotionally distressed’, and 44% ‘adaptive copers’ (not mutually exclusive). On the Millon Behavioral Medicine Diagnostic (MBMD), they generated clinically significant scores (>74) on depression (79); illness apprehension (82), functional deficits (90), pain sensitivity (97), future pessimism (80), medication abuse (75), and adjustment difficulties (90). Data from the NEO-FFI yielded the following personality information: neuroticism (t = 60), extraversion (t = 38), openness (t = 44), agreeableness (t = 48), and conscientiousness (t = 41). Subjects identified M = 10.7 medication-related problems each (e.g. altering prescriptions, multiple providers, abuse of the ER). In terms of Stage of Change, two subjects were in Contemplation, 6 in Preparation, and 1 in Action. To date, six have completed the eight-session protocol. During the Tx phase, Rx and/or recreational drug use (mostly oxycotnin or cannabis) was detected in six/nine subjects. However, no dirty urines were obtained after session five. At discharge, pain ratings had decreased an average of 2.4 points (highest), 8 (lowest), and 1.9 (typical) on 10-point VAS. At the same time, ‘functioning’ increased for general activity level (3.8), work (3.0), walking (4.0), social relationships (2.8), sleep (5.8), appetite (4.8), mood (3.3), and ability to concentrate (3.8). These promising pilot data suggest that pain and Rx opioid abuse can be reduced and QOL improved using a combined behavioral and pharmacological approach.

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271 EVALUATION OF ANTINOCEPSIVE EFFECTS OF CANNABINOID- AND VANILLOID-LIKE COMPOUNDS IN THE PPO WITHRITHING TEST

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The analgesic and anti-hyperalgesic effects of cannabinoids- and vanilloid-like compounds were evaluated with the PPO pain model, using different routes of administration and potential antagonists. With a few exceptions, all the compounds tested produced analgesic effects. D9-THC and (R)-methanandamide were active by the three routes of administration tested (i.p., s.c. and p.o.), with similar potencies. Arvanil was active by only two routes, producing EDS0s of 4.7 mg/kg (3.0–7.4) s.c. and 0.06 mg/kg (0.02–0.2) i.p. The ED50 for capsaicin was 1.6 mg/kg (0.8–2.8) via s.c. administration. PEA was active i.p., resulting in a ED50 of 3.7 mg/kg (3.2–4.2). Capsazepine, a potential antagonist, was found to be active for antinociception when administered i.p. (ED50 = 9.2 mg/kg (8.3–10.2)) at the 8 min time point; its effects diminished over time. None of the antagonists tested blocked the compounds evaluated with two exceptions: D9-THC was blocked by SR141716A and capsazepine was blocked by nalozone. Western immunosassays performed using three opioid receptor antibodies, a CB1 receptor antibody and a VR1 receptor antibody, yielded no change in receptor protein levels. These data suggest that these compounds produce analgesia via non-CB1, non-VR1 pain pathway not yet identified.

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272 NEUROPSYCHOLOGICAL EFFECTS OF LONG-TERM HALLUCINOGEN USE VERSUS ALCOHOLISM IN NATIVE AMERICANS: CULTURAL LIMITATIONS OF TESTS

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The long-term neuropsychological effects of hallucinogen use are poorly understood. We studied Navajo members of the Native American Church, who regularly use the mescaline-containing cactus, peyote, as a religious sacrament. These individuals have ingested peyote hundreds of times, while using virtually no other drugs. We administered a battery of neuropsychological tests to 51 Navajos who had taken peyote at least 100 times (‘P’ group); 35 Navajos with past
alcohol dependence, but currently sober at least 3 months (‘A’); and 63 comparison Navajos with minimal exposure to peyote, alcohol, or other drugs (‘C’). We found no significant differences among the 3 groups on verbal IQ, reading level, and years of education. On Buschke’s Selective Reminding Test, both A and P subjects performed more poorly than controls, but these differences vanished when we substituted a version of the Buschke with words more familiar to Navajos. This finding illustrates the hazards of using standard versions of verbal English-language tests to evaluate Native Americans. Looking at tests that did not use English words, the A group performed significantly more poorly than the C or P group on the Rey Osterreith Complex Figure Test and on two performance sub-tests of the Wechsler Adult Intelligence Scale. All three groups performed equally on Raven’s Progressive Matrices, the Stroop test, and several tests of immediate and delayed memory. These preliminary results suggest that long-term peyote use does not produce detectable residual neuropsychological impairment in Native Americans, whereas alcohol dependence may cause persistent deficits.

273 LIVER ENZYME ABNORMALITIES DURING BUPRENORPHINE VERSUS METHADONE MAINTENANCE

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Introduction: Recent case reports and in vitro investigations suggest that buprenorphine may be associated with hepatotoxicity, possibly through dose-dependent impairment of liver mitochondrial functioning. Methods: We compared the incidence of liver dysfunction in subjects treated with buprenorphine (4 mg or 12 mg SL daily) or methadone (20 mg or 65 mg PO daily) in a recently completed RCT. Subjects were included in the analysis if baseline alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were within normal limits (wnl: ALT < 60 U/L and AST < 50 U/L) and at least one scheduled monthly follow-up liver enzyme test had been obtained. Of the 116 subjects enrolled in the RCT, 72 had at least one follow-up liver enzyme test, and 68 had baseline tests wnl (30 treated with methadone and 38 with buprenorphine) and were included in the analysis. Liver dysfunction was defined as AST or ALT above normal limit. Results: The incidence of liver dysfunction was 2/30 (6.7; 95% CI: 1.8–21%) in methadone treated subjects and 6/38 (15.8; 95% CI: 7.4–30%) in buprenorphine treated subjects (ns). In these subjects with new onset liver dysfunction, mean follow-up ALT was 120 (range 61–331) in buprenorphine treated subjects and 99 (range 76–123) in methadone treated subjects. Two methadone maintained and 2 buprenorphine maintained subjects with baseline elevations of ALT experienced comparable additional increases from baseline to follow-up (149% methadone vs. 24% buprenorphine). Conclusions: Findings with a small sample size of a non-significant increased incidence of liver dysfunction in buprenorphine compared to methadone maintained subjects warrant further investigation with larger sample sizes with adequate power to detect significant differences of the magnitude observed in this study—a sample size of 400 would provide a power 0.80 to detect the observed differences with a P < 0.05.

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274 BASAL SEX DIFFERENCES IN CIRCULATING LEVELS OF ADRENOCORTICOTROPIC HORMONE (ACTH), CORTISOL, AND PROLACTIN IN NORMAL AND DRUG-DEPENDENT VOLUNTEERS

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Women have been shown to differ from men in their neuroendocrine profile at baseline and in response to hypothalamic pituitary adrenal (HPA) axis probes, such as dynorphin (Kreek et al. J Pharmacol Exp Ther, 1999). It has been reported that basal ACTH secretion is lower and the ratio of cortisol to ACTH higher in normal females than in males (Roelfsema et al. J Clin Endocrinol Metab, 1993), and that stress-induced prolactin release is greater in women than in men (Jezova et al. Acta Physiol Scand, 1994). We examined placebo data from ongoing studies of human neuroendocrine function for gender effects in normal, methadone-maintained (MM), and cocaine-dependent (CD) volunteers. Blood was sampled prior to I.V. administration of saline placebo and at 10, 20, 30, 40, 50, 60, 75, and 90 min timepoints thereafter. Circulating ACTH, cortisol, and prolactin concentrations were determined by RIA. Examination of area under the curve revealed that normal women had significantly lower plasma levels of ACTH (P < 0.002) and higher cortisol levels (P < 0.005) than normal men whereas there was no ACTH or cortisol sex difference in the MM and CD groups. Serum prolactin concentrations in females were two-fold higher than those of males in the normal (P <0.0005), and also in the MM (P < 0.05), and CD (P < 0.05) groups. Elucidating sex differences in basal neuroendocrine function will be important in understanding the role of the HPA axis in addiction and stress responsivity.

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275 FAMILY ENVIRONMENTAL PATTERNS IN CHILDREN OF DRUG-DEPENDENT FATHERS AND CONTROLS

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Risks for substance use abuse and dependence are mediated by both environmental and genetic factors. The influence of the intra-family environment has been shown to contribute to the elevation of risk in the children of drug-dependent fathers. The Family Environment Scale (Moos and Moos, 1986) is a popular measure of family environment. In order to characterize the environments of high-risk families, we performed a K-means cluster analysis on its scales. We found that a two-cluster solution best described the patterns apparent using this instrument. Cluster #1 had higher loadings with scales measuring family Cohesion, Expression, Achievement Orientation, Activity And Recreation, and Moral Empathy. Cluster #2 had only high loadings for Independence. When a $\chi^2$ analysis was performed, we found a significant over-representation of Cluster #2 scale patterns among families with drug-dependent fathers, while control families were best described by Cluster #1. Family processes of control, organization and conflict did not differ between the clusters. The study provides information to assist clinicians, prevention programs, and researchers in characterizing families in which offspring are at heightened risk for substance abuse.

276 TREATMENT PROVIDERS’ PERCEPTIONS OF THE STANDARDIZED INTAKE PROCEDURES REQUIRED BY AN OUTCOME MONITORING SYSTEM

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Substance abuse treatment providers’ perceptions of and experiences with a pilot automated outcome monitoring system (OMS), which included standardized client assessments and procedures and a client follow-up study, were examined in order to inform midstream changes
and future statewide OMS efforts. Focus groups were conducted with treatment provider staff (N = 230) from all 43 sites involved in testing the feasibility of the OMS. Analyses of the context and content of focus group discussions revealed that many participants valued the standardized intake because it offered more in-depth, uniform information about clients early in the recovery process. However, many participants also identified certain aspects of the intake as undermining their client-centered ethos, including the inability to: (1) adjust the length and depth of the intake according to the individual and immediate needs of the client; (2) use discretion when administering the ASI Lite (Addiction Severity Index, Lite version); (3) vary the timing of assessment administration for different client bases (e.g., methadone maintenance; court-mandated); (4) modify the content and presentation of the informed consent form and the locator form when enrolling clients in the follow-up study; (5) allow clients to opt out of the OMS; and (6) completely allay client and staff concerns about confidentiality. Focus group participants suggested that they want an OMS that is flexible enough to accommodate their facilities’ modality and organizational structure, client bases, unique approaches and programs, and client-centered ethos. Hence, the successful integration of research and practice, vital to an effective OMS, may depend upon resolving the conflict between researchers’ need for standardized data and practitioners’ need for individualized intake and assessment strategies.

277 **OUT-PATIENT DETOXIFICATION USING BUPRENORPHINE (SUB-UTEN)**

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Opiate detoxification is a primary treatment goal for some opiate-dependent patients. Current treatment includes the use of alpha-adrenergic blockade with or without benzodiazepines or naltrexone. These treatments may diminish unpleasant withdrawal symptomatology, but they do not reduce craving associated with opiate withdrawal. Buprenorphine is a partial opioid agonist pending FDA approval as a pharmacotherapy for opioid dependence. The pharmacologic properties of buprenorphine suggest that it may be particularly useful for opioid detoxification. In the context of a larger study where subjects were required to be free of illicit opiates, we have provided buprenorphine to a small group (26) opiate-dependent individuals. About 22 subjects reached a target dose of medication (8–16 mg) that relieved both physical withdrawal symptoms plus craving for illicit opioids. All but two subjects reached their target dose within 3 days of initiating treatment at 8 mg. The majority of subjects received 12 or 16 mg. Subjects continued to receive this established dose for the 4–8 weeks of the study. In addition to receiving buprenorphine, subjects were given the opportunity to receive weekly-manualized drug treatment counseling by a masters level counselor. Following the detoxification phase of the study, 18 subjects were slowly tapered off the medication in an individualized manner to minimize withdrawal. Nine subjects completed taper to a mean final dose of 3 mg in an average of 4 weeks. Although these findings may not generalize to a standard community treatment program, the results suggest that low doses of buprenorphine are effective for opiate detoxification.

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278 **COST-EFFECTIVENESS OF BUPRENORPHINE MAINTENANCE TREATMENT, A RANDOMIZED COMPARISON WITH METHADONE MAINTENANCE**

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This study reports the results of a randomised open-label prospective study of the costs and outcomes associated with providing buprenorphine, compared to methadone maintenance for heroin users and existing methadone maintenance patients. A total of 139 participants were recruited to the study (57 methadone maintenance patients and 82 heroin users), half of which were randomised to buprenorphine, the other half to methadone maintenance. The economic evaluation assessed the impact of buprenorphine maintenance on health outcomes (including heroin use), medical costs, health care costs and costs associated with criminal behaviour over the course of 12 months. The primary outcome was incremental cost per heroin free day. The results indicated that neither the costs nor the outcomes associated with those randomised to buprenorphine appeared to differ significantly from those assigned to methadone treatment. This economic evaluation of buprenorphine compared to methadone suggests that offering buprenorphine as an alternative to methadone does not result in decreased cost, nor reduced heroin use.

279 **EFFECT OF CONTINUOUS-RELEASE LOBELINE ON METHAMPHETAMINE-INDUCED HYPERACTIVITY AND METHAMPHETAMINE SELF-ADMINISTRATION IN RATS**

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Lobeline (LOB) decreases methamphetamine (METH) self-administration and inhibits amphetamine-evoked dopamine (DA) release from striatum in vitro, possibly by reducing cytoplasmic pools of DA available for METH-induced reverse transport of the DA transporter (Harrod et al., 2001; Miller et al., 2001). To determine if LOB, which has a relatively short t1/2 of 60 min, decreases the reinforcing effect of METH, the present experiments determined if continuous release of LOB (s.c., osmotic mini-pump) would attenuate METH-induced hyperactivity and METH self-administration using a progressive ratio (PR) reinforcement schedule. Rats were implanted with pumps (LOB, 30 mg/kg per day, 1 μl/h) or were given sham surgery, and 24 h later, either METH (1 mg/kg) or saline was injected (s.c., once daily for 7 days), and activity determined during 50-min daily sessions. METH-induced hyperactivity was attenuated by LOB, however, only on the first day of testing; whereas tolerance developed to the effect of intermittent LOB injection after 2 days. In the self-administration study, rats were implanted with jugular catheters, trained to lever press on a PR schedule for intravenous METH, and implanted with a pump (LOB, 30 mg/kg per day, 1 μl/h) or were given sham surgery. Response rates were recorded on 7 daily 10-h sessions. Continuous-release LOB attenuated METH self-administration, however, only during the first session; whereas we previously found that LOB decreased METH self-administration across seven intermittent injections using a fixed ratio five schedule. These results demonstrate that LOB reduced the reinforcing effect of METH, however, the effect of LOB was transient, which may be due to the development of tolerance or instability of LOB in this continuous release preparation.

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Performance on a computerized gambling task, which measures the ability to balance immediate gains against long-term negative consequences, has been reported to be poorer in abstinent marijuana users compared to controls. The effects of acute marijuana use on gambling task performance have yet to be examined under controlled conditions. In the present study, a within-participant double-blind design was employed to evaluate the effects of acute marijuana smoking on gambling task performance in experienced marijuana smokers. Eighteen marijuana abusers, who reported smoking 24 marijuana cigarettes per week, completed this three-session outpatient study; sessions were separated by at least 72-h. Participants completed the gambling task before and after smoking a single marijuana cigarette (0, 1.8, or 3.9% D9-THC w/w). Marijuana cigarettes were administered in a double-blind fashion and the sequence of D9-THC concentration order was balanced across participants. Marijuana dose-dependently increased the time participants required to complete the task, but performance, as measured by net earnings and advantageous card selections, was significantly improved when participants smoked the 1.8% D9-THC cigarette, relative to the placebo condition. Additionally, heart rate and several subjective-effect ratings (e.g. 'Good Drug Effect,' 'High,' 'Mellow') were significantly increased in a D9-THC concentration-dependent manner. These data suggest that a moderate D9-THC concentration cigarette improves gambling task performance of regular marijuana smokers.

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The emergence of illicit use of tryptamine, piperazine, and phenethylamine derivatives

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There are increasing evidence that several classes substances are emerging as new popular drugs of abuse in the United States. In response to this apparent problem, DEA is presently gathering information regarding the scope, pattern of abuse, and the public health risk that these substances pose to determine the appropriate control status of these substances under the CSA. Examples of these new emerging abused substances are summarized below. Benzylpiperazine (BZP) and 1,3-trifluoromethylpiperazine (TFMPP) are N-monosubstituted piperazine derivatives that are not approved for medical use in the US. Abuse of these piperazines is increasing in the US as evidence by increasing encounters by law enforcement and discussions on websites popular with recreational drug users. BZP are showing up in the similar venues as MDMA (ecstasy) and are being promoted as a legal alternative to MDMA. BZP and TFMPP are mainly co-abused in order to obtain a fuller MDMA-like effect that includes euphoria, sense of well-being, and mild changes in body perception (i.e. slight visual, and auditory alterations). 2,5-Dimethoxy-4-(-a)-propylthiophenethylamine (2CT-7) is a phenethylamine hallucinogen that is structurally related to mescaline and 4-bromo-2,5-dimethoxynethylamine (2CB, Nexus). 2CT-7 effects are as being similar to those of 2CB and unlike LSD. Effects include psychedelic ideation. 5-Methoxy-N,N-disopropyltryptamine (5-MeO-DIPT). 5-MeO-DIPT is a psychoactive tryptamine analog that was developed in the 1980’s. It is easily synthesized clandestinely. 5-MeO-DIPT is a relatively potent, fast acting, and short-lived tryptamine with effects similar to those of 2C-B and LSD. It is also one of the few tryptamines that is orally active. It is structurally similar to N, N-dimethyltryptamine (DMT) and N, N-diethyltryptamine (DET). The first indication of its abuse became evident in 1999 with discussions on Internet websites popular with recreational drug users. 5-MeO-DIPT’s effects were characterized as being similar to those of MDMA at low doses (8–10 mg). More hallucinogenic properties dominate at higher doses.

Further observations on the role of CRA in the CRA + vouchers treatment for cocaine dependence


We have been researching the efficacy of an outpatient treatment for cocaine dependence, known as the Community Reinforcement Plus Vouchers Approach (CRA + vouchers). CRA is an intensive behavioral intervention originally shown to be efficacious for treatment of alcohol dependence. The majority of cocaine-dependent outpatients in our clinic are also alcohol dependent. CRA focuses on facilitating healthy lifestyle changes in substance use, social/recreational practices, family relations, and vocation. The vouchers component is a contingency-management intervention wherein vouchers exchangeable for retail items are earned through biochemically verified cocaine abstinence. CRA + vouchers as a combined intervention has been demonstrated to be efficacious in reducing cocaine use during treatment and follow-up. In dismantling studies, the vouchers component has been shown to increase retention and reduce cocaine use during treatment and follow-up. We have now completed a randomized clinical trial in which 100 cocaine-dependent outpatients were randomized to CRA + vouchers or vouchers only. As reported at last year’s CPDD meeting, adding CRA to vouchers significantly increased retention in treatment and cocaine abstinence during the 24-week treatment period. Preliminary results from 6 months of post-treatment follow-up suggest no significant effects of CRA on cocaine use during follow-up above those from vouchers only, but significant reductions in frequency of alcohol use, days of drinking to intoxication, frequency and severity of depressive and other psychiatric symptomatology, and increases in days employed and related vocational outcome measures. These results demonstrate that CRA is an active component of the CRA + vouchers treatment that improves outcomes during treatment and follow-up.

Heterogeneity of personality among adolescent males with substance abuse and conduct disorder

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Cloninger suggests two distinct pathways to substance abuse. Type I is characterized by high reward dependence, high harm avoidance, and low novelty seeking which leads to such problem behavior as loss of control, difficulty terminating binges, guilt feelings, and later onset. In contrast, Type II is characterized by high novelty seeking, low harm avoidance, and low reward dependence, which lead to such behaviors as antisocial personality, persistent seeking of substances for their euphoric effects, and early onset of inability to abstain entirely. The purpose of this study was the application of Cloninger’s model to a sample of 200 male adolescent probands (ages 13–19) in treatment for substance abuse and conduct disorder. Due to the nature of this sample-males with early onset drug abuse and conduct disorder diagnosis—we hypothesize that the majority of them would fit Cloninger’s type II pattern. A k-means cluster analysis was used. Our results suggest more heterogeneity than is implied by Cloninger’s theory. Type II described only a minority of the treatment probands (N = 29). High novelty seeking and low reward dependence tended to cluster together regardless of harm avoidance in a series of clustering classifications, while high harm avoidance appeared to consistently form a cluster of its own regardless of novelty seeking and reward dependence. In examining the discriminative validity of the clusters, we found no substantial mean differences for variables not included in the cluster analysis such as exact age of onset, externalizing and internalizing behaviors. These results suggest a complex relationship between personality and drug use behavior in adolescent males. This research was funded in part by NIDA grants DA-01531, DA-11015, and DA-12845.

Intensity-related effects of imagery scripts on tobacco craving

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We have developed the Tobacco Craving Questionnaire (TCQ) to assess current craving for cigarettes. When the TCQ was administered to 213 smokers and factor analyzed, it yielded four constructs characterizing craving: emotionality, expectancy, compulsivity, and purposefulness. The purpose of this study was to manipulate craving using active imagery to examine further the reliability and validity of the TCQ. Current smokers not trying to quit (n = 25 to date) participated in a single test session in which they listened to three 50-s audiotaaped scripts that presented situations that contained either no mention of smoking (no-urge condition), minimal mention of desire to smoke (low urge), or extensive descriptors of desire to smoke (high urge). Subjects were instructed to imagine themselves in the scene. At the start of the session (baseline) and after each script, subjects completed the 47-item TCQ, a mood form, and several visual analog
scales (VAS). Self-reported tobacco craving significantly increased as a function of script-urge intensity for all four TCQ factors. VAS ratings of 'urge for a cigarette' and 'crave a cigarette' were also increased in an intensity-related manner. These data suggest that the TCQ is a valid, multi-factorial measure of tobacco craving and that drug craving is not an all-or-none phenomenon. This laboratory procedure will provide a means for the experimental analysis of tobacco craving.

288 REINFORCEMENT OF DIAZEPAM UNDER ANXIOLYTIC AND NEUTRAL CONDITIONS

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The present study evaluated the relationship between therapeutic efficacy and diazepam (DZ) reinforcement by comparing the reinforcing properties of DZ under anxiogenic (Anx-C) and neutral (ntrl-C) conditions. Individuals with social anxiety (S.A.; n = 11) and healthy controls (H.C.; n = 10) were participants. Current substance use and Axis I diagnoses (except S.A.) and alcohol consumption > 11 drinks per week were exclusionary criteria. There were two five-session conditions. In the Anx-C, participants gave a brief speech to an audience. In the Ntrl-C participants completed a computer task. Each phase employed a standard choice procedure (two sample, three choice sessions) comparing 10 mg DZ and placebo (Pbl). During Anx-C, DZ preference was greater among S.A. than H.C. (82 vs. 40% P < .05).

Group differences in preference did not exist under the Ntrl-C (55 vs. 50%). To evaluate the relationship between reinforcement and anxiety ratings, data for each phase were separately analyzed with repeated measures ANOVA. In Ntrl-C, time was the only significant effect (P = .05). In Anx-C, there was a drug x time x group interaction (P < .05). Post-hoc analyses revealed that DZ, in comparison to Pbl significantly reduced anxiety scores for S.A. but not H.C. S.A. participants (after both 10 DZ and Pbl) reported greater anxiety ratings than H.C.s. These results demonstrate that in participants with S.A., DZ reinforcement occurs under conditions of both increased anxiety and therapeutic efficacy.

289 PSYCHIATRIC CARE OF OPIOID-DEPENDENT PATIENTS: PHYSICIAN KNOWLEDGE, ACCEPTANCE AND WILLINGNESS TO PROVIDE CARE

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The Drug Abuse Treatment Act (DATA) of 2000 provides an opportunity for office based opiate treatment (OBOT). This study examines current patterns of psychiatric care for patients with opiate abuse/dependence (OAD), psychiatrist awareness of DATA, and comfort levels in providing OBOT. These data provide a point of comparison from which to assess changes in rates of psychiatrists' treatment of OAD associated with DATA 2000 and pending FDA approval of buprenorphine. Detailed patient data will be collected in 2003; observed increases in the proportion of patients with OAD treated by psychiatrists would be expected to be associated with more successful DATA implementation. The current study assessed sociodemographic, clinical and treatment characteristics associated with provision of care to OAD patients. Frequency distributions and bivariate analyses by SAS/SUDAAN compared OAD patients to patients with other substance use disorders (SUD) and patients without SUD, using clinically detailed data from the 1997 and 1999 PRN Study of Psychiatric Patients and Treatments (n = 2678). Psychiatrists reported 11% (n = 286) of their adult patients had illicit SUD; of these patients, 15% (n = 43) had an OAD diagnosis. OAD patients were more likely to be young, white and had more years of education than patients with other SUD; 54% of OAD patients were treated in solo office settings compared to 44% of non-SUD and 25% of other SUD patients (P < .001). A higher rate of OAD patients (26%) had problems accessing health care services compared to 15% of other SUD patients and 8% of non-SUD patients (P < .01). Psychiatrists who treated OAD patients were significantly older, more likely to be white/non-Hispanic, and reimbursed by discounted fee for service than those treating non-SUD or other SUD patients. Data from the 2002 National Survey of Psychiatric Practice (currently underway) will also be presented, characterizing the extent to which psychiatrists are aware of current DATA status and legislation as well as their level of comfort in providing OBOT.

290 ESTABLISHMENT OF A CONDITIONED PLACE PREFERENCE TO (+)-, 4-METHYLENEDIOXYMETHAMPHETAMINE [(+)-MDMA]: ECSTASY

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MDMA is a substituted amphetamine that increases locomotor activity and has conditioned stimulus properties, as shown by the conditioned place preference (CPP) paradigm. In previous studies, (+)-MDMA has been shown to dose-dependently produce a CPP, although the ability of (+)-MDMA to establish a CPP has not been examined. Therefore, we tested the hypothesis that (+)-MDMA produces a CPP, as previously demonstrated with (+)-MDMA. The study consisted of three stages: (1) Preconditioning: Male Sprague–Dawley rats (n = 8) were allowed to freely roam the CPP apparatus for 60 min to ensure that the animals had no natural preference for either conditioning chamber. (2) Conditioning: During each of eight conditioning sessions, animals received an injection of saline or (+)-MDMA (4 mg/kg, SC) and were immediately confined to one side of the CPP apparatus for 45 min. Control animals were paired with saline in both conditioning chambers, while (+)-MDMA-treated animals received four pairings with (+)-MDMA in one chamber and four pairings with saline in the other environment. (3) Testing: 24 h following the last conditioning trial, the animals were tested for expression of a CPP in a drug-free state. They were allowed to freely roam the apparatus for 15 min and the total locomotor activity, number of entrances, and time spent in each chamber were recorded. Compared to control animals, (+)-MDMA-treated animals developed a CPP (P < .05), as shown by a greater time spent in the chamber formerly paired with drug. However, drug treatment did not alter the number of entrances into each chamber. Animals treated with (+)-MDMA exhibited increased locomotor activity in the drug-paired chamber, although this effect did not reach statistical significance. This study demonstrates that (+)-MDMA produces a CPP, as previously shown with (+)-MDMA. Future studies will investigate the dose-dependent nature of a CPP to (+)-MDMA.

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291 USE OF BIOLOGIC MARKERS TO DISTINGUISH LEGITIMATE PAIN PATIENTS FROM DRUG SEEKERS

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There is a need to objectively distinguish persons with legitimate pain from those who are drug seekers. About 50% adult ambulatory patients with severe, intractable pain and who described their pain as constant, excruciating, and produced a bed or house-bound state were screened by a panel of biologic markers. Patients were treated with a long-acting opioid preparation consisting of methadone, oxycodone, or fentanyl in addition to short-acting opioid for breakthrough pain.
The biologic markers screened before treatment and after 3 months of opioid treatment were: (1) blood pressure; (2) pulse rate; (3) morning cortisol and pregnenolone serum concentrations; and (4) erythrocyte sedimentation rate (ESR). The percentage of patients with physiologic abnormalities before and after 3 months of treatment were as follows: (1) hypertension above 140/90 mmHg; 28 (56.0%) vs 14 (28.0%); (2) tachycardia above 84 per min; 21 (42.0%) vs 9 (18.0%); (3) elevated serum cortisol concentration; 12 (24.0%) vs 2 (4.0%); (4) low serum cortisol serum concentration; 7 (14.0%) vs 1 (2.0%); (5) low pregnenolone serum concentration; 18 (36.0%) vs 3 (6.0%); and (6) elevated ESR; 10 (20.0%) vs 3 (6.0%) (P < 0.05). Mean blood pressure, pulse rate, ESR, and serum concentrations of cortisol and pregnenolone in patients who demonstrated a physiologic abnormality all positively and significantly (P < 0.05) altered these markers toward normal. This study indicates that some physiologic abnormalities, particularly those related to pituitary-adrenal over-stimulation with excess output of catecholamines and glucocorticoids, may serve as biologic markers which can help to distinguish legitimate pain patients from drug seekers.

292 PROGRESSION OF DRUG AND ALCOHOL DEPENDENCE AMONG WOMEN ENTERING SUBSTANCE ABUSE TREATMENT: EVIDENCE FOR TELESCOPING

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Objective: To evaluate the effect of gender on the progression, severity and frequency of current DSM-III-R drug and alcohol dependence and related behaviors in a sample of 271 patients (mean age: 32.6 ± 7.7 years; 156 women) entering treatment. Method: Multivariate and univariate ANOVAs were used to compare age at onset of regular use of cocaine, heroin, cannabis and alcohol. Time elapsed between initiation of regular use of each substance and entry into an index treatment and impairment scores on the Addiction Severity Index (ASI) were also examined. Results: There was no effect of gender on age at onset of regular use of cocaine, cannabis, or heroin among drug-dependent patients. However, alcohol-dependent women were older than their men counterpart at onset of regular alcohol drinking (F = 7.53, df = 1100, P = 0.01). There were no gender differences in rates of current cocaine, heroin, cannabis or alcohol dependence. However, drug-dependent women reported fewer pretreatment years of regular use of heroin (F = 4.21, df = 196, P = 0.04), cannabis (F = 5.01, df = 1,38, P = 0.03) and alcohol (F = 7.71, df = 1,100, P = 0.01). Across diagnostic groups, women experienced similar severity of drug and alcohol dependence and more severe medical, psychiatric, and employment problems than men (range of F values = 7.21–13.4, df = 1,271, P’s < 0.05). Conclusions: Although age at onset of regular use of drugs was comparable between men and women, and despite the fact that women were older at onset of regular drinking, women had briefer drug and alcohol use careers at treatment entry than men. Nonetheless, women experienced more medical and psychosocial problems related to alcohol and drug use. These findings support the notion of an accelerated or telescoped progression of heroin, cannabis and alcohol dependence among women. Replication of these findings in relation to drug dependence is warranted and an effort should be made to identify the specific mechanisms responsible for this apparent effect.

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293 DIPYRONE POTENTIATES MORPHINE-INDUCED ANTINOCICEPTION AND MASKS THE DEVELOPMENT OF ANTINOCICEPTIVE TOLERANCE AFTER REPEATED ADMINISTRATION

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The combination of morphine (M) with dipyrone (D) might result in acute analgesic potentiation, but there is no evidence whether this potentiation persists after chronic treatment. This work analyzes the effects of repeated administrations of M and D using the tail-flick test. Male Wistar rats (180–220 g), cannulated in the jugular vein, were treated with either M (3.1 mg/kg), D (600 mg/kg) or the combination M + D twice a day for 5 days. Dipyrone produced a mild analgesic effect that did not change throughout the study. Morphine was initially more effective than D, but developed a progressive tolerance that was complete after the fifth administration. The combination of M + D resulted in a significant potentiation and a maximal antinociceptive effect that decreased after the sixth injection, but never reached basal values. In a different series of experiments, drug treatment was switched at the sixth administration. In rats treated initially with M (that developed tolerance at the fifth administration), the administration of M + D resulted in an initial recovery of the antinociceptive effect followed by a gradual decrease. Animals treated with M + D for five sessions and then switched to M developed complete tolerance after the ninth administration. These data suggest that dipyrone potentiates morphine-induced antinociception to such a degree that the development of antinociceptive tolerance can be masked during the initial phases of the treatment. Supported by grants 30571 M (S.L.C.) and 125264 (G.P.H.) from Conacyt.

294 A LABORATORY EVALUATION OF BINGE COCAINE DOSING AND ABSTINENCE ON THE EEG OF COCAINE ABUSERS

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Few studies have examined the neurophysiological effects of chronic cocaine exposure under controlled conditions. This study employed double-blind, multi-day, repeated cocaine administration using a within-subject design. Cocaine dependent volunteers (n = 9) resided as inpatients for 6 weeks and were studied during 4-day bouts of cocaine exposure (175 mg, p.o. given five times at 1-hr intervals) and during 28 days of withdrawal. Six EEGs were recorded at the following times: after 4 days of abstinence, on Days 1 and 4 of cocaine dosing, and on Days 1, 10, and 28 of withdrawal. EEG data were recorded during a 3-min, eyes-closed, resting session from 16 electrodes and transformed by an FFT. Absolute delta and theta power were significantly (P < 0.01) increased at frontal sites during cocaine exposure. Absolute alpha1 power was significantly (P < 0.05) reduced at posterior sites on the days when oral cocaine was administered and on the first day of abstinence. Reductions in delta and theta power have been reported previously during cocaine abstinence; these effects were reversed in the present study by repeated cocaine dosing. These data suggest that the EEG deficits observed in abstinent cocaine abusers may be directly related to prolonged use of cocaine.

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295 PERFORMANCE IN A LABORATORY CHOICE PROCEDURE PREDICTS DRUG USE HISTORY

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We tested whether individual differences in performance in a laboratory choice procedure were correlated with individual differ-
Maternal smoking is the most important preventable cause of poor pregnancy outcomes in the US, and a leading cause of pediatric morbidity and mortality. Effective interventions have been developed for promoting smoking cessation during pregnancy, but cessation rates are low (<20%), especially among less educated and highly nicotine-dependent women. We are investigating the efficacy of a voucher-based incentive program for promoting smoking cessation in this population. The voucher program is based on one demonstrated previously to be efficacious for promoting cocaine abstinence in dependent outpatients. As part of a pilot study on this topic, we have recruited 34 pregnant women from local obstetrical care clinics who were still smoking at their first prenatal care visit. On average, the women were 22.5 ± 5.1 years old, completed 11.6 ± 2.1 years of education, and reported smoking 23.1 ± 11.5 cigarette per day prior to learning of their current pregnancy. The first 25 consecutive admissions were assigned to a contingent-vouchers condition wherein vouchers are earned via biochemically-verified smoking abstinence and the next nine to a noncontingent-control condition where vouchers are delivered independent of smoking status. Subject characteristics are comparable across the two conditions. The number of women enrolled in the noncontingent condition will be increased to 25 by the June meeting. A maximum of $786 in vouchers can be earned during the prenatal period, and $360 during 3-months of postpartum monitoring. 12 of the 25 (48%) women in the contingent condition are currently abstinent, defined as self-reported no smoking for at least 7 days verified by saliva cotinine analysis, versus only 1/9 (11%) of women in the non-contingent condition. 3 of the 12 abstinent women in the contingent condition have delivered. All are in still in the first 3 months of the postpartum period where vouchers remain available and have sustained abstinence; none of the women in the noncontingent condition have delivered. Overall, these preliminary results support the potential efficacy of contingent-vouchers for promoting and sustaining relatively high levels of smoking cessation among pregnant and recently postpartum women.

Hypothesis: Oxycontin use in rural areas has received intense media attention during the last year, but relatively little work has been done to examine who uses it, how it is used, and how widespread is its use. The current study, therefore, examines oxycontin use and its correlates in a sample from rural Eastern Kentucky. Procedures: An in-depth structured interview, based on the Addiction Severity Index (ASI), was conducted with 125 felony probationers (72%-male, 28% female). Drug use characteristics, including use of oxycontin, were assessed including age at first use, and frequency of use in the preceding 3 months and 30 days. Analyses: Because this is a pilot study, descriptive analytic techniques and correlations were the primary methods of data analysis. Results: One-third (34%) of the sample reported prior illegal use of oxycontin (average age at first use was 28). The primary routes of administration were snorting (49%), oral ingestion (32%), and injection (15%). Men and women showed similar rates of oxycontin use. Use of other diverted prescription drugs (sedative, other types of prescription opioids) was strongly correlated with use of oxycontin, as was cocaine, marijuana, and amphetamine use. Implications of Study: Oxycontin, as an emerging drug, warrants additional study, especially in rural areas where its abuse was first noticed.
In order to better understand the relative reinforcement value of nicotine and alcohol (individually and in combination), a multiple-choice questionnaire was administered to 78 individuals seeking outpatient treatment for both substances. Participants were asked to choose between pairs of substances and then between each substance and a series of monetary values. In substance comparisons, results demonstrated that the combination (one drink and one cigarette) was preferred over each individual substance. When using monetary values as the standard point of reference, the average cross-over point was higher for the combination ($13.75) than for the drink only ($10.90) or the cigarette only ($8.20). These findings suggest that the combination of substances is more highly valued and more reinforcing than the individual substances. Such information can be useful for understanding variable treatment response in nicotine-alcohol dependent populations and may point to potential patient-treatment matching strategies to meet the needs of such a diverse patient population.

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300 EDUCATIONAL AND EMPLOYMENT OUTCOMES FOR YOUTH WITH DISABILITIES WHO USE ALCOHOL AND DRUGS: ANALYSIS OF NELS:88 LONGITUDINAL DATA

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Adolescents with disabilities, who represent about thirteen percent of school-age children, report using alcohol and other drugs (AOD) at the same or higher levels as their peers, based upon several studies. To test this hypothesis and related hypotheses, longitudinal student data from the National Education Longitudinal Study of 1988 were analyzed, including data from three follow-up collections in 1990–1994. In a sample of n = 16,489 students from the second follow-up study (longitudinal weighted population = 2,970,835), students with disabilities exhibited slightly higher alcohol and cocaine use rates than their non-disabled peers and comparable marijuana use rates by the twelfth grade. Students with disabilities exhibited significantly higher cigarette use and drop-out rates than their non-disabled peers throughout high school. In a sample of n = 13,120 youth surveyed in 1994 (longitudinal weighted population = 2,968,426), high school cigarette and marijuana use were significantly associated with dropping out and no college attendance for adolescents with and without disabilities.

301 FAMILY TRANSMISSION OF MARIJUANA USE, ABUSE, AND DEPENDENCE

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Hypothesis: Marijuana Abuse or Dependence will display greater familial aggregation than marijuana use. Species: Human. Number of Subjects: 2375. Procedures: Adolescents recruited from residential and day treatment program for youth with conduct and substance problems, matched controls, and all available family member were interviewed with the CIDI-SAM. Marijuana Use, Abuse, or Dependence was coded for each subject. Statistical Analyses: Relative risks to relatives were calculated based upon whether they had marijuana use, abuse, or dependence. Results: Base rates for relatives of controls without marijuana use were: Marijuana Use: Fathers 37%, Mothers 23%, Brothers 21%, Sisters 12%. Abuse: Fathers 15%, Mothers 7%, Brothers: 12%, Sisters: 5%. Dependence: Fathers: 6%, Mothers: 3%, Brothers: 5%, Sisters: 3%. Relative Risk for Use, Abuse, and Dependence to relatives if marijuana use was present in adolescent proband (in controls): Father: 1.9*, 2.5*, 2.2, Mother: 2.1*, 1.3, 1. Brother: 2.2*, 2.8*, 3.5. Sister: 2, 2.8, 3.3. If marijuana abuse was present in adolescent proband (in treatment families): Father: 2*, 2.7*, 2.7*, Mother: 2.5*, 3.3*, 2.7* Brother: 2.7*, 3.3*, 4*. Sister: 4.2*, 5*, 3.7*. For marijuana dependence (in treatment families): Father: 1.9*, 2.7*, 2.3*, Mother: 2.3*, 3*, 2.7*. Brother: 2.7*, 3.3*, 4*. Sister: 4.4*, 5*, 4.3*. * indicates a significant P < 0.05. Significance of findings: Familial aggregation of Marijuana Use, Abuse, and Dependence is substantial for all three measures, and is present in controls as well as treatment families. There was somewhat greater familial aggregation of abuse or dependence compared to use.

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302 GENDER-DIFFERENTIAL PATHWAYS TO SUBSTANCE USE AND ABUSE

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Despite continued efforts to reduce and/or prevent alcohol and drug use among children and adolescents through media and school prevention efforts, and despite an apparent declining trend during the 1980s in the USA, the last few years have witnessed an increase in the prevalence of drug use, particularly the illicit ones. These data suggest that prevention and/or intervention strategies may have to be examined from a different conceptual framework than has been done for traditional programs. One possibility is that the focus for prevention or intervention activities should be on distal events prior to the acquisition of drug use behaviors and established drug use patterns. Moreover, there is evidence that acquisition patterns differ by gender and by age. As part of a longitudinal study beginning in elementary school several hundred children were followed-up in high school. Early assessments were based on school-related variables including social and academic behaviors. High school assessments included parent and adolescent questionnaires and interviews of drug use and a variety of psychosocial variables. The results showed differential predictors by gender over a 5-year period. Predictors for girls were more heavily weighted by academics whereas boys predictors were more likely to be in the social arena. These results by gender have significant implications for prevention and intervention efforts.

303 RELATIONSHIP OF EXECUTIVE FUNCTIONS TO LEGAL AND EMPLOYMENT PROBLEMS IN COCAINES-DEPENDENT PATIENTS

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Although the neurocognitive sequelae of cocaine dependence have become an active area of investigation, the functional correlates of cognitive deficits in cocaine-dependent patients have rarely been explored. Some preliminary findings have suggested a relationship between executive functions (e.g. problem solving, cognitive flexibility) and social/occupational functioning in these patients. The present study examined the relationship between executive functions and social/occupational variables in 59 cocaine-dependent outpatients (49 male, 10 female) entering treatment, after approximately 10 days of abstinence. All were between the ages of 21 and 50; exclusion criteria included other substance dependence (except nicotine), other major psychiatric disorders, neurological disorders, history of significant brain trauma, and use of psychoactive medication. Patients were administered the Trail Making Test (a sensitive, relatively nonspecific measure requiring cognitive flexibility and maintenance of a complex response set) and the Wisconsin Card Sorting Test (a problem-solving task requiring cognitive flexibility) as part of a larger neuropsychological assessment.
Derived indices on the Trail Making test (TMT), a test often used for screening for cognitive impairment, are examined in a sample of hallucinogen abusers in drug abuse treatment programs. The Trail Making Test (TMT) is a brief, portable and an inexpensive test battery. They were also administered the Addiction Severity Index (ASI), a structured interview assessing various domains including social, occupational, and legal functioning. Pearson correlations were performed between neuropsychological test scores and ASI occupational and legal indices. After Bonferroni correction, poorer performance on Part B of the Trail Making Test was significantly associated with longer total lifetime incarceration \( r = 0.40, P = 0.001 \). Trail Making and Wisconsin Card Sorting Test scores were not significantly correlated with lifetime number of convictions or major driving violations, length of longest full-time job, or summary indices of legal and employment problem severity. These results suggest a relationship between executive functions and legal problems in cocaine-dependent patients.

### 304 Derived Trail-Making Test Indices in a Sample of Hallucinogen Abusers: Demographic Effects

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Derived indices on the Trail Making test (TMT), a test often used for screening for cognitive impairment, are examined in a sample of hallucinogen abusers in drug abuse treatment programs. The Trail Making Test (TMT) is a brief, portable and an inexpensive neuropsychological test that has been used to assess cognitive dysfunctions for over a half century. A mixed race sample \( N = 128 \) of subjects with a primary problem of hallucinogen abuse was drawn from electronic files of data from the Drug Abuse Treatment outcome Study (DATOS). The DATOS was a naturalistic, prospective cohort study that collected data from 1991–1993 in 96 programs in 11 cities in the United States. Data were analyzed to determine the effects of demographic variables on derived indices created by adding, subtracting, multiplying and dividing parts A and B of the TMT in this large treatment sample of substance abusers. The variables of gender and age were not statistically significant for derived indices of the TMT. The variable of ethnicity was significant for the all derived indices except the ratio score (divide part B by part A) and the variable of education was significant for the interaction score (multiply part A by part B and divide by 100).

### 305 The Early Caregiving of Heavy Cocaine-Using Mothers

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The purpose of this study was to study the caregiving of heavy cocaine-using mothers during the first 18 months of their offspring’s lives. Prior research has shown that the caregiving of substance abusing women is compromised early on. 71 women and their offspring participated in this study that lasted from pregnancy until the infants were 18 months of age. Maternal prenatal drug use was assessed through the ASI and urine toxicology screens at delivery. Prenatal maternal psychopathology was assessed using the MCMI-I. Maternal sensitive caregiving was assessed at 1-, 6-, and 18-month post-delivery. Maternal sensitivity remained low for the great majority of the sample over the 18 months of the study. No relationships were found between maternal sensitivity at any age and the measures of prenatal drug use. However, prenatal maternal psychopathology was consistently related to poor caregiving at all ages. These findings suggest that maternal caregiving is more influenced by psychopathology and treatment programs should include psychiatric evaluations and ongoing psychological support.

### 306 Patient-Therapist Relationships, Patients’ Treatment Motivation, and Post-Treatment Outcomes

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This paper examines the associations among patient-therapist relationships, patients’ motivation for treatment, and post-treatment outcomes. Our sample is comprised of patients \( N = 511 \) recruited from 19 treatment programs randomly selected to represent four major modalities ( outpatient drug-free, inpatient, residential, methadone maintenance) in Los Angeles County. Patients’ drug use and related behaviors were assessed at baseline and at the one-year follow-up. At baseline, patients were interviewed about their relationships with their primary counselors as well as their motivation for treatment. Preliminary analyses showed that both the therapeutic relationship (empathy, openness, acceptance) and treatment motivation (problem recognition, desire for help, readiness for treatment) were significant predictors of abstinence at follow-up. Patients’ perceptions of their counselors were also significantly associated with motivation for treatment. Further analysis will be conducted using a path model to assess the associations among the patient-therapist relationship, treatment motivation, and outcomes (e.g., drug use or criminality at the one-year follow-up). The findings from this study may help inform the development of more effective drug abuse treatment processes.

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### 307 Center for Substance Abuse Treatment: An Examination of How Best to Meet Primary Healthcare Professionals Needs

S. Hubbard, K. Mulvey, and S. Hayashi, Center for Substance Abuse Treatment, Johnson, Bassin, and Shaw

To provide substance abuse (SA) treatment guidelines to professionals outside of SA treatment programs, the Center for Substance Abuse Treatment (CSAT) disseminates the Treatment Improvement Protocols (TIPs) to the medical community and beyond. TIPs are best practice SA treatment guidelines. To examine how effectively the TIPs are meeting target audience needs, CSAT has undertaken a 4-year evaluation of the TIPs. This presentation highlights one study, the TIP#24 Study. The target audience for TIP#24, A Guide to Substance Abuse Services for Primary Care Physicians, and its related documents (a concise desk reference and a pamphlet) is the medical community. The TIP#24 Study used diffusion of innovations theory (Rogers, 1995) and evaluated the utility of TIP#24 materials for primary care clinicians. Study objectives were to determine healthcare professionals’ awareness and attitudes towards TIPs and the TIP#24 materials; the appropriateness of the TIP#24 content and the use of the TIP#24 materials in clinical practice. Results from the 137 healthcare professionals indicated awareness of the TIPs and the TIP#24 materials. Attitudes were generally positive towards the TIP#24 materials. Participants used the information and encouraged others to use it. Results also revealed useful information for information dissemination strategies to the medical/healthcare community.

### 308 Brief versus Extended Smoking Treatment

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Cigarette smoking is widely recognized as an addiction. Treatment for most addictions include treatment of extended duration, follow-up support, and, when feasible, easy reentry into treatment. However, the standard treatment for nicotine dependence uses a brief model of
309 CONTINUOUS NALTREXONE ATTENUATES COCAINE-INDUCED BEHAVIORAL SENSITIZATION IN C57BL/6J MICE

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In spite of much intense research, the mechanisms by which chronic cocaine exposure produces the phenomenon of sensitization in rodents remains only partially understood. Several neurotransmitter systems have been implicated in cocaine-induced changes in behavior. Specifically, this study examined the role of opioidergic influence in this regard. Male C57BL/6J mice were either subjected to sham surgery or implanted with naltrexone Alzet mini-osmotic pumps subcutaneously. The pumps were primed to deliver naltrexone continuously at an average rate of 10 mg/kg per day for 21 days. One day following surgery, baseline locomotor activity was assessed for all mice. About 2 days later, mice began receiving daily injections of either saline or cocaine (15 mg/kg IP) for 10 days. Seven days following the last saline or cocaine injection, all mice received a single cocaine challenge (15 mg/kg IP). Locomotor activity was recorded on days 1, 7, 10, and 17 of the study. On days 1, 7, and 10 both sham and naltrexone exposed mice injected daily with cocaine displayed enhanced locomotor activity compared to saline injected controls. The locomotor-activating effects from daily cocaine, however, were attenuated in the naltrexone exposed mice compared to sham controls. Daily cocaine administration clearly sensitized sham mice to the locomotor-activating effects of a cocaine challenge on day 17. Sensitization on day 17 was not apparent in the naltrexone exposed mice. Furthermore, compared to sham animals, these mice too demonstrated an attenuated locomotor response to cocaine challenge. Collectively, these data support a role for opioidergic involvement in the modulation of cocaine manifested behavior. The specific nature of this involvement, however, is still uncertain. Current studies are being conducted in our laboratory to delineate receptor selectivity for the aforementioned observations, as well as to further understand the precise nature of opioidergic influence in this cocaine-induced phenomenon.

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310 POTENTIAL IRREVERSIBLE KAPPA ANTAGONISTS BASED ON GNTI

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Kappa agonists are dysphoric in animals, including humans, yet little is known about the level of kappa efficacy needed to produce dysphoria. Irreversible antagonists could be utilised in the determination of relative efficacy for series of kappa agonists as achieved for mu-agonists with C-CAM and beta-FNA. Although DIPPA is an irreversible antagonist at the kappa receptor it also has short-lived agonist activity at this receptor. We have prepared a series of substituted GNTI analogues having the guanidine moiety substituted with simple alkyl or benzylic groups. In binding assays analogues having the substituted guanidine moiety directly attached to the naltirindole core have higher selectivity than congeners having an ethylene spacer. This is particularly true for kappa over delta selectivity. Preliminary in vitro data for the p-chlorobenzyl analogue (BU20023) suggests that it is an irreversible kappa antagonist, having no initial agonist activity. As irreversibility in this instance cannot be due to covalent bond formation, BU20023 must be binding sufficiently tightly to impart pseudo-irreversibility, in a manner similar to C-CAM at the mu-opioid receptor. Molecular modelling studies indicate that the lipophilic group of the guanidine side chain could be interacting with a lipophilic pocket in the kappa receptor.

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311 OPIOID IMMUNOMODULATION IS NOT RELATED TO MU RECEPTOR BINDING AFFINITY

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Morphine alters immune system function indirectly via the CNS and directly via naloxone-sensitive and-insensitive peripheral cell surface receptors. The aim of the current study was to compare the effect of morphine-6-glucuronide (M6G), oxycodone and buprenorphine with morphine, on immunocompetent cells using a mitogenesis assay and the opioid receptor antagonist naloxone. Splenocytes were incubated in 96 multiwell plates with Concanaavalin A (10 mg/ml) and opioid agonist (10−4 – 102 mM) with or without the antagonist naloxone (102, 100, 10−2, 10−4 mM) for 24 h, alamarBlue™ added (3 h) and fluorescence was quantified. Data were fitted to either a negative Hill equation or the sum of a negative and positive Hill equation. Biphasic inhibitory responses (U shaped responses) were observed over the concentration range used for M6G and oxycodone, whilst buprenorphine only displayed a negative slope. Morphine displayed a biphasic response, however it caused induction of the response at higher concentrations. The rank order for the nadir of inhibition was buprenorphine > oxycodone > M6G = morphine. However, the rank order of the concentrations at which maximum reduction in the response was observed was oxycodone < M6G < morphine < buprenorphine. Naloxone antagonised the inhibition of all four opioids but did not alter the induction by morphine. The use of a short incubation time, and a non-toxic proliferation detection method allowed the evaluation of both a decrease and an increase in the opioid proliferative response and responses which were naloxone-sensitive and -insensitive. The presence of naloxone-sensitive and -insensitive effects were observed.
responses and the rank order of immune effect of these opioids, which is different to their mu receptor binding affinity rank order, indicates the non-classical opioid nature of the immune system’s response to the presence of opioids. Hence, each opioid needs to be evaluated for its immune effect, as it is not possible to predict their immunomodulatory response using previously obtained CNS data.

312 Bad behaviors or bad personality: what leads to nonadherence in HIV?

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Nonadherence to medications has been called ‘our other drug problem’ and in HIV, nonadherence leads to drug resistance. The purpose of this study was to compare bad behavior (smoking, drug and alcohol use) to bad personality (extremes of the Big-5 personality factors and indicators of personality disorder) in their contribution to predicting medication adherence. Subjects were 120 HIV+ patients (46 women, 74 men, 83% African–American, 15% Caucasian) in a Mid-Atlantic infectious disease clinic who volunteered for the cross-sectional study, gave informed consent, and completed interview and questionnaires. Measures included Demographic questions, the NEO-Five Factor Inventory, the AUDIT, the CIDI-Short Form, the Iowa Personality Disorder Screen, and electronic medical records. Analyses included descriptive statistics and four logistic regression equations modelling prediction of different forms of nonadherence: running out of medication, failing to take medication as directed, taking below 95% of prescribed medication, and having notations of noncompliance in the medical record. Results: 79% were cigarette smokers, 20% had shared needles, and 41% had taken and discontinued a protease inhibitor. 37% failed to take medication as directed, 44% had ever run out of medication, and this was more common among smokers ($x^2 = 7.69, P < 0.01$). 28% took an ineffective proportion of medication, and 32% had notations of noncompliance in medical records. Smoking (OR 4.5) having a ‘primary drug’ (OR 3.6) and Neuroticism (OR 1.1) contributed to the prediction of ever running out of medication (Model $R^2 = 0.20$). Smoking, and recent illicit drug use were protective factors while Extraversion and Openness were risk factors for failure to take medication as directed. Agreeableness was a protective and primary drug a risk factor for notations of non-compliance, while recent illicit drug use and drug or alcohol dependence on the CIDI were risks for low proportion of medication taken. Conclusions: Both bad behavior and bad personality contribute to non-adherence, with important clinical and research implications to be discussed.

313 Intervention study on increasing awareness of adolescents’ illegal drug use for parents and youth using sharing experience with ex-users and their parents

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Increasing use of illegal drugs such as amphetamine (ecstasy), methamphetamine (shabu), heroin (putaw) is apparent in Indonesia, indicated by arrest reports, treatment centers and hospitals. However, there is still limited service facility compared with the needs of the middle lower class, despite high proportion of illegal drug use among youth from the class. While primary health center (PHC), which provide health service for the community still prioritize the infectious disease, and mother child health. The available treatment center for drug-abused patients cannot be reached by most who need it because of the price. Apart from seminars that were often conducted, still lack of knowledge on the right information on use of illegal drug among public. Also traditional belief that is impossible for families with proper manner and good religiousness have member who use illegal drugs. As consequence, families with illegal drug use member tend to hide or try to handle themselves because of shame. In the long term this attitude could lead to family disruption mostly confused and depressed mother. To help community obtain right information, handle the problem and get appropriate treatment, an intervention study using previous drug users who already treated with no relapse for at least 2 years and their parents to share experience with the community was conducted in Cilandak, South Jakarta. At the same time, joined with PHC, low price service for those needed help on drug abused was set up. Indicator of intervention is the number of people attend the PHC either for consulting, urine analysis or get treatment for drug abuse. The results revealed that to maximize the benefit of community education on illegal drug use program, an integration with the service provider will increase the willingness of society to get more information as well as searching for treatment.

314 Providing mobile opioid treatment


A mobile outpatient opioid treatment program was undertaken in the fall of 1998 in response to a record number of opiate-related deaths in King County, Washington and limited access to methadone treatment programs exemplified by long treatment waiting lists at fixed site clinics and needle exchange programs. The goals of the program were to: Establish a mobile opioid treatment program in two areas of King County as a collaboration between established public health clinics and a community-based methadone treatment provider. Increase the number of funded treatment slots in the local area Streamline access to opiate substitution treatment through the County Health Department’s Needle Exchange and HIV/AIDS outreach programs though the use of treatment vouchers Evaluate the efficacy, efficiency, and acceptability of mobile treatment services. This presentation will describe the van and mobile treatment program design and the regulatory and community implementation strategies employed. We will provide a comparison of the demographic characteristics, 6-month treatment retention (66% for mobile vs. 77% for fixed site) and six-month treatment outcomes of those served in the mobile service and those served in the fixed-site.

315 A pilot study on the consistency of self-reported drug use and urinalysis results

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This study examined the consistency between retrospective self-reported drug use and urinalysis results among 285 male opioid dependent subjects seeking treatment at an outpatient clinic of Drug Dependence Treatment Centre from January 2001 to December 2001 at All India institute of Medical Sciences, New Delhi, India. Subjects provided information about the recent drug use, frequency and typical dose of their drug use in the preceding 7 days. Urine samples were collected and analyzed for opioids (morphine, codeine, buprenorphine), benzodiazepines (diazepam, nitrazepam), cannabis and pheniramine. Preliminary analysis indicated that there was moderate to high concordance between the two measures among different drug types. On an average 69% of urine test results matched with self report. Recent drug use was the best predictor of urine test results. Implications of the results will be discussed.
This study was supported by Drug Dependence Treatment Centre, AHMS, New Delhi, India.

316 TRAUMA AND SUBSTANCE ABUSE: IMPLICATIONS FOR TREATMENT PROVIDERS

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The events of September 11th have sensitized substance abuse treatment providers to the important relationship between trauma and substance abuse. There is a substantial body of research that suggests that a significant proportion of patients in treatment settings have comorbid substance use disorders and post-traumatic stress disorder (PTSD). Additionally, many studies point to high rates of PTSD among ‘hard’ drug use, such as those individuals using cocaine and opiates. The literature also suggests that individuals with substance abuse and PTSD are more likely to relapse if trauma issues are not addressed (appropriately in a comprehensive fashion). The issue of trauma is of particular importance to women with substance abuse problems, since they are known to develop PTSD at a higher rate than men, despite evidence indicating that substance-abusing men have more exposure to traumatic events. The clinical presentation of PTSD and a substance use disorder can be quite complex, and is often accompanied by serious consequences such as psychosocial impairment.

Current research focused on the substance abuse clinical workforce indicates that there is a substantial need for improvement in the training of professional and paraprofessional treatment providers in properly treating individuals with a substance use disorder and PTSD. The reviewers aim to discuss implications for workforce development, with special attention on projected clinical needs after the September 11th Terrorist Attacks.

317 THE IMPACT OF MANAGED CARE ON TREATMENT FOR DRUG-DEPENDENT WOMEN AND THEIR CHILDREN: 1-YEAR FOLLOW-UP

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Managed health care has imposed restrictions on the quantity and frequency of services for many high-risk patient subgroups including pregnant drug dependent women and their offspring. Jansson and colleagues (2001) previously reported higher rates of adverse outcomes and complications for pregnant opiate dependent women treated under managed care (MC) as compared to fee-for-service (FS) reimbursement plans. The FS model of care offered integrated substance abuse, OB/Gyn and pediatric health care; the MC model reduced service integration, with greater reliance upon community referral for pediatric and maternal health care. There was a seven-fold increase in in-utero deaths and a three-fold increase in infant deaths for the MC as compared to FS groups. Immunization rates at 4 months were significantly lower for the MC infants (P < 0.001). The present study followed MC and FS mothers and infants through 12 months of age. Outcomes for the two groups were compared using chi-square and t-test analyses. In addition to immunization and medical records, Child Protective Service (CPS) involvement and foster care placement were also examined. Participants were 132 women who delivered an infant in 1993 under FS reimbursement and 108 women who delivered an infant in 2000 under MC reimbursement. The women were predominantly African American (85% FS, 96% MC) with a mean age of (29.0 FS, 31.3 MC) years. Patient demographics and drug use severity were comparable for the two groups. In our preliminary analysis, MC infants were nearly twice as likely to have CPS involvement (25%) as FS infants (13%) (P < 0.025). The clinical and economic implications of such findings will be discussed. Immunization status at 6 months and one year will be reported. Additional analyses will examine maternal as well as staff perceptions of FS and MC models of care and the relationship of such perceptions to program management as well as maternal and infant functioning.

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318 INTERACTIONS BETWEEN THE CB1 RECEPTOR AGONIST DELTA-9-THC AND THE CB1 RECEPTOR ANTAGONIST SR-141716 IN RATS: OPEN-FIELD REVISITED

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This study examined the interaction between the CB1 antagonist SR-141716 and the CB1 agonist delta9-THC on open-field (O-F) behaviors in male Sprague-Dawley rats. Animals were examined after administration of δ9-THC alone (dose range 0.3 – 5.6 mg/kg), SR-141716 alone (dose range 1 – 5.6 mg/kg), and the two drugs combined; injections were given i.p. 30 min. pre-session. There was a dose related suppression of ambulation (vertical activity) and rearing (horizontal activity) after δ9-THC administration. Co-administration of SR-141716 counteracted this suppression. However, normalization was only partial with regard to rearing. Interestingly 1 mg/kg SR-141716 was as effective as were 3 and 5.6 mg/kg SR-141716. No dose of δ9-THC increased ambulation or rearing. Increasing doses of δ9-THC produced an increase in latency (the time in sec. to leave the starting area, the circle in the center of the field) as well as an increase in circling (the number of times the animals turned around its vertical axis, 0.5 point given for each 180 degrees turn). Those effects were completely blocked by SR-141716. There was an increase in grooming and scratching with increasing doses of SR-141716. The latter SR-141716 induced effects seemed to be only partially blocked by co-administration of δ9-THC (3 and 5.6 mg/kg). When given alone, only the highest dose of SR-141716 (5.6 mg/kg) examined slightly depressed ambulation; rearing and latency were not significantly changed and circling was absent. The categories vocalization, urination and defecation did not differentiate among the groups. Data may be interpreted as SR-141716 is acting as (i) an inverse agonist and/or (ii) that the endogenous cannabinoid system could be tonically active under certain conditions.

319 EVALUATION OF THE ABUSE POTENTIAL OF THE METHYLPHENIDATE TRANSDERMAL SYSTEM

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Oral preparations of methylphenidate (MP) have high abuse potential and are abused by the oral and intranasal routes and after aqueous extraction by the iv route. MTS may reduce abuse since aqueous extration is unlikely from a patch. The potential for abuse by the transdermal route is not known. A double-blind crossover study was conducted in 18 males and females with histories of stimulant abuse to learn if MTS can be abused by the transdermal route. A 48 h intervals, each subject was given a placebo (P), MP 25 and 50 mg SC, Phentermine 30 mg po (PH), and 3 and 6 MTS (placed for 24 h). Treatments were given according to 3 balanced Latin squares. Each dose day, subjects received an injection, oral capsules and six patches. Active treatments were accompanied by placebo injections, capsules, or patches (triple dummy). Subjective effects and euphoria were measured with standard instruments for amphetamine-like drugs. Behavioral effects, blood pressure and pulse effects, and plasma levels
of each drug were also assessed. MP sc produced expected dose related subjective effects, euphoria, behavioral effects and cardiovascular effects with onset within 1/2 h and peak in 1–2 h after administration and dissapating by 6–8 h. PH had a similar time course. MTS and PH produced less intense effects than MP. The onset of subjective effects and euphoria fro MTS were not seen until 1–4 h after placement of the patches and reach peak intensity at 4–12 h after placement. The intensity of the subjective effects and euphoria with MTS was no greater than that produced by the PH and was significantly less than that produced by MP. Accompanying the euphoric effects produced by MTS were dysphoric effects that increased in intensity throughout the 24 h period of placement and were greater than that produced by PH or MP. MTS is a preparation that has low abuse potential in coparison to the oral preparations of MP and PH. Use of MTS in ADHD should reduce the public health and social problems that attend the abuse of oral preparations of MP.

320 Health and mental health service needs of adolescents in treatment

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Adolescent substance abusers present to drug treatment with poor physical health, emotional problems, and behavioral problems. Less well known is whether youths in treatment receive services addressing these problems, and whether these services suffice to meet their needs. This study examines treatment needs and services received in a national sample of adolescents participating in the Persistent Effects of Treatment Study (PETS-A; N = 1206). Treatment needs and recent services received were assessed at treatment admission and 3 and 6 months later. At admission, 45% report clinically significant psychological distress, and 34% report significant health problems. Over time, problem rates decline for mental health (32 and 29% at 3 and 6 months), but increase for physical health (40 and 43%). Whereas a small percentage of youths report receiving mental health services at each time point (15, 24, 18%), physical health services are more common (47, 46, 43%). Unaddressed need for mental health services (i.e., need with no services reported as received at current or last assessment) dropped from 34% at baseline, to 13 and 13% at 3 and 6 months. Physical health needs went unaddressed at lower rates for each timepoint (12, 6 and, 9%). These results suggest adolescents in drug treatment have considerable unmet needs for mental health services. Planned analyses examine if services provided adequately meet youths’ treatment needs.

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321 c-fos and AP-1 activation by cocaine in fischer rats. Roles of gender and NMDA

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Previous studies have shown that the immediate early gene c-fos and the AP-1 transcription factors increase after cocaine administration in male rats. In this study we used quantitative solution hybridization and electrophoretic mobility shift assays to measure the c-fos mRNA and AP-1 DNA binding in caudate/putamen, frontal cortex, amygdala and hypothalamus of male and female Fischer rats after one single injection of cocaine (15 mg/kg). A single cocaine administration increased c-fos mRNA levels after 30 min and AP-1 DNA binding after 3 h of treatments in the caudate/putamen and the frontal cortex but not in the hypothalamus or the amygdala of both male and female rats. Furthermore, the NMDA antagonist, MK801, blocked this cocaine-induced upregulation of c-fos mRNA levels in the caudate/putamen and the frontal cortex. The induction of these molecular markers may be used as a tool to study neuronal activation that lead to addiction in different sexes after cocaine.

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322 Opiate dependency: a barrier to substance abuse treatment among pregnant women

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The use of heroin and other opiates during pregnancy can lead to serious multiple consequences for the woman, fetus and newborn infant. Treatment entry is therefore critical early in pregnancy in order to prevent significant maternal and infant morbidity and to improve health and social outcomes. The objective of this qualitative study was to examine extrinsic barriers to substance abuse treatment among 36 pregnant and parenting women enrolled in residential perinatal treatment programs in northern California. Results indicate that among a subset of women (n = 5), the status of opiate dependency in particular acted as a barrier that delayed and deterred women from treatment entry. Requirements of child welfare agencies and substance abuse treatment programs, health care providers' mismanagement of opiate dependence, and unfavorable methadone maintenance treatment financing policies served as extrinsic barriers to substance abuse treatment. The findings suggest the need for education and training initiatives for substance abuse treatment personnel, child welfare staff and health care providers. Policy implications for child welfare agencies and substance abuse treatment programs and systems will be discussed.

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323 Subacute dosing with isradipine blocks cocaine euphoria and craving in phase II lab trials for medications to treat cocaine dependence

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Twelve male cocaine-dependent research volunteers, aged 21–46 years, who were not seeking treatment participated in a study examining the ability of repeated doses of isradipine or placebo to antagonize i.v. cocaine-induced euphoria. Cocaine challenges included an ascending series of cocaine doses (placebo, 0.325, 0.6 mg/kg, i.v.) administered across three successive days. Isradipine effects were examined as a double-blind crossover in two 8-day phases with at least one week between each phase. Each phase began (Day-1) with an initial exposure to 0.325 mg/kg cocaine, i.v. to insure clinical tolerance followed by nightly (qHS) dosing with 30 mg oral isradipine sustained release or placebo. On Days 5–7, an immediate release formulation of isradipine (15 mg) or placebo was administered prior each of the i.v. dose challenges. At repeated time-points before and after the i.v. injection, subjects reported cocaine effects on Visual Analog adjective rating scales of stimulant euphoria, side effects, and craving. Compared to placebo pre-treatments, isradipine dose significantly (P < 0.05) decreased cocaine-related stimulant euphoria on ‘high’, ‘like’, ‘good’,
‘rush’, and ‘stimulated’. Reductions in craving ratings of ‘crave’, ‘urge’, and ‘want’ were also seen with isradipine. These results replicate earlier findings of isradipine-induced changes in stimulant effects, but also represent a maximal dose loading procedure of the L-type calcium channel blocker. Future studies may wish to examine combinations of isradipine with other medications acting by different mechanisms to enhance the effectiveness of those medications.

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324 MANAGING NEGATIVE AFFECT INTERVENTION IN A RESIDENTIAL SUBSTANCE ABUSE TREATMENT FACILITY

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There is little evidence to support the introduction of other treatments into therapeutic communities. Because of this, we tested the feasibility of initiating a clinical service comprised of 8 weeks of Cognitive-Behavioral group therapy aimed at managing negative affect in residents at TROSA, a private, non-profit, residential substance abuse facility. The hypothesis was that group members would report less depressive symptoms and mood states following the intervention. The first group (n = 8) consisted of two Caucasian males, two Caucasian females, and 4 AA females, representing a variety of ages, psychiatric comorbidities, substances abused, and time in residence (up to 15 months). The manualized intervention (to be presented) occurred for 6 consecutive weeks (1-h sessions). The group focused on identifying mood states; identifying, challenging, and replacing irrational thoughts; stress-reduction; anger management; and relaxation techniques. Baseline and Week 6 BDI scores were M = 25 and M = 9, respectively. Baseline and Week 6 POMS scores were M = 126 and M = 93, respectively. Three month follow-up data will be presented. These preliminary findings indicate that addressing negative mood states associated with psychiatric comorbidity and recovery in a residential treatment community shows promise as an adjunctive treatment strategy. Future clinical trials to test efficacy are planned.

325 DELAY DISCOUNTING IN ECSTASY USERS

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The rate at which a $1000 reward was delay discounted was compared between a group of volunteers who reported using ecstasy (3,4-methylenedioxymethamphetamine or MDMA) ten or more times and a group of non-drug using matched controls. Consistent with the results of previous studies on drug dependent populations (i.e., heroin dependents, cigarette smokers, and alcoholics), the recreational ecstasy users showed a higher rate of delay discounting for the $1000 reward compared to matched controls. Both groups also participated in a similar task measuring the delay discounting rate for a duration of improved health judged equivalent in value to $1000 by each subject. Ecstasy users also performed a task measuring the delay discounting rate for an amount of ecstasy judged equivalent in value by each subject to $1000. Consistent with previous studies showing increased delay discounting of drugs relative to money, ecstasy users discounted ecstasy more than money, and money more than health. No group differences in health discounting were observed. These results suggest that the same pattern of increased discounting observed in drug dependent populations is also exhibited in recreational ecstasy users.

326 HIV-RISK, VIOLENCE, AND DEPRESSION AMONG AFRICAN AMERICAN FEMALE DRUG USERS

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African American women are disproportionately burdened with HIV infection; thus, the need for increased understanding of the contributing factors is critical. This paper examines drug use, violence, and depression to determine if the presence of these factors conjointly are associated with an increased risk for HIV among African American women and thus warrant specific consideration in designing interventions. The analyses use data collected from the NIDA-funded ‘EachOneTeachOne’ project (Dr. L. Cottler, PI). Data were collected on 420 African American women who were current injection drug users, heroin smokers, or crack cocaine users and at least 18 years of age. A mutually exclusive tripartite classification system was developed and the women were stratified across the tripartite based on whether they were drug users only (n = 253), drug users with a violence exposure (n = 65), drug users with depression (n = 62) or drug users with both violence and depression (n = 40). Logistic regression analyses were conducted at each level to determine which risk factors were predictive of having one, two, or all three of the tripartite factors when confounding variables were considered in the model. Both violence (25%) and depression (24%) were highly prevalent within the sample. Having a reported history of a sexually transmitted disease was significant at each of the tripartite levels. In addition, women who had two or more sexual partners in the last 30 days (OR = 2.89) and women who had an early onset of alcohol use (OR = 2.71) were at an increased risk for having the full tripartite, while never having married was a protective factor. These results indicate that perhaps some sexual risk factors and early onset alcohol use can be utilized as a screening mechanism for potential violence and depression in drug using African American women who present for treatment. The presence of psychopathology in the lives of these women increases the risk trajectory for HIV infection and thus should be considered in HIV intervention efforts.

327 TRAJECTORIES OF MARIJUANA USE: RESULTS FROM A 20-YEAR LONGITUDINAL STUDY

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In this study, we are interested in the variety of marijuana use trajectories and adult outcomes among subjects who were studied over a 20-year span. Data concerning the use of marijuana among adolescents who were 12 years of age at the time of first interview were obtained from a sample of community-based subjects participating in a longitudinal study who were followed from 1980 to 2000. At all five test times, behavioral, psychosocial, and drug consumption measures were gathered. Results of analysis found five longitudinal trajectory groupings: (1) no marijuana use (31%), (2) onset of use after age 18 with cessation in late 20's (24%), (3) onset of use prior to age 18 with cessation in early 20's (18%), (4) use onset prior to age 18 with continued use throughout adulthood (20%) and (5) use onset after age 18 with continued use throughout adulthood (8%). Early onset users were more likely to have alcoholic or depressed parents. Subjects who reported an onset of marijuana use prior to age 18 were less likely to attend college, and subjects who reported use at time five, regardless of age onset, were more likely to have never married. Subjects who had never used marijuana or who had stopped their use, reported higher levels of T3 satisfactions with relationships, inner spirituality, finances and environment. Subjects who reported an onset of marijuana use prior to age 18 reported higher levels of alcohol use and related problems at age 15 and 18 than the other user groups, but by age 25, there were no differences in these measures in any of the four marijuana using groups. Delinquency by user group differences were
only apparent when subjects were 15 years of age. Users of marijuana who put off onset of use until after age 18 fared as well as non-using subjects in terms of educational achievement, however nonusers and those who ceased use reported more subjective satisfactions in life by Time 5. We conclude that there are identifiable risk and protective factors associated with age of marijuana use onset and this age is a critical determinant of adult outcomes.

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328 **Does time spent with smoking friends influence the number of quit attempts among teen smokers?**

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The influence of peers on adolescent smoking is well recognized. Both pharmacological effects and social interactions reinforce smoking behavior. Findings indicate that smoking identity defined by social interactions has an inverse relationship with cessation efforts. Among teens requesting cessation assistance, we hypothesized that time spent with smoking friends would be inversely related to previous quit attempts at baseline. Data was gathered from 71 (68% female, 32% Male; 72% Caucasian, 20% African American, 5% American Indian, 3% Hispanic) teen smokers enrolled in an accruing smoking cessation program. Linear regression analysis examined the relationship between the amount of time an adolescent smoker spent with smoking friends and number of quit attempts, controlling for number of years smoked. Selected findings indicate that among smokers who had at least one quit attempt, number of years smoking and time spent with smoking friends were significant predictors of number of quit attempts ($r = 0.36; F = 4.7 P = 0.01$); time spent with smoking friends was marginally associated with number of quit attempts ($t = -1.927 P = 0.058$). Future analysis will examine the relationship between change in time spent with smoking friends and tobacco smoking after three months of treatment. These preliminary findings suggest that time spent with smoking friends, which may be driven by strength of smoking identity, may be correlated with the number of quit attempts.

329 **Life trajectories of adolescents with conduct and substance problems versus control adolescents**

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Substance problems are commonly thought to begin in late childhood or early adolescence. Thus, prevention efforts may be directed towards children slightly prior to this time. But, are experiences of some of these youths different even before that age? Hypothesis: Experiences of patient adolescents differ significantly from those of control adolescents from an early age. Methods: 98 adolescents in treatment for substance use and delinquency problems and 102 community controls (both groups ~40% female) along with their parents completed an extensive battery of assessments. Results: Significant differences include: Biological parents treated for alcohol/drug problems (patients 40% vs. controls 15%), Biological parent treated for emotional problems (44% vs. 16%), Biological parent convicted of illegal acts (45% vs. 12%), Biological mother smoked during pregnancy (45% vs. 23%), and child born prematurely (17% vs. 7%). Conclusions: Patient and control adolescents have differing life experiences beginning as early as in utero.

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330 **Preventing opiate-dependent individuals from illicit drug relapse using reinforcement-based therapy**

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Introduction: Preventing relapse following inpatient opioid detoxification is a clinical challenge. The novel drug free treatment, reinforcement based therapy (RBT) applies principles of community reinforcement approach and contingency management in the form of rent payments for structured drug-free housing in a group outpatient setting. The effectiveness of RBT for preventing illicit drug relapse of opioid dependent participants was examined in comparison to standard aftercare referral. Methods: Participants were randomly assigned to RBT ($N = 72$) or standard aftercare (SA; $N = 128$) and compared at 1 and 3 months on self-reported and positive urine toxicology positive for opiate and cocaine use. Results: Participants did not differ on intake drug use or demographics. Participants had mean of 36 years of age, 11 years of education, 87% unemployment, 69% African-American and 59% used heroin intravenously. Compared to SA at one month, RBT participants had significantly fewer urine samples positive for opiates (79 vs. 48%; $P < 0.05$), cocaine (57 vs. 37%; $P < 0.05$) and fewer reported days of opiate (13 vs. 7; $P < 0.05$) but not cocaine use (6 vs. 4; $P = 0.20$). At 3 months, relative to SA, RBT had fewer opiate (70 vs 50%; $P < 0.05$) and cocaine (57 vs. 37%; $P < 0.05$) positive specimens and fewer reported days of opiate (15 vs. 10; $P < 0.05$) but not cocaine use (7 vs. 5; $P = 0.23$). Conclusions: Results suggest that RBT is an effective method for preventing illicit drug use relapse in detoxified opioid dependent individuals.

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331 **Can smoking relapse be prevented after a lapse? Testing a novel lapse-responsive intervention strategy**

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New approaches are needed to enhance quit rates in smoking cessation. While there have been important advances in pharmacotherapy for smokers, there has been little movement in development of new behavior therapies to address the needs of smokers who have difficulty quitting. A single smoking episode after quitting is one of the strongest predictors of full relapse, and upwards of 90% of individuals who lapse after quitting return to regular smoking. A novel concept tested in this project is a lapse-responsive intervention. Participants in this trial were heavy smokers with a history of failed quit attempts. Baseline treatment consisted of 9 weeks of Zyban and a single individual counseling session. Once a post-quit smoking lapse was identified (through daily telephone contacts), participants were randomly assigned to receive 3 post-lapse intervention sessions or to no treatment control condition. Each post-lapse treatment session consisted of two rapid smoking trials and a counseling session. Rapid smoking was similar to the procedure originally developed by Lichtenstein and colleagues (Lichtenstein et al., 1973), and involved taking a puff on a cigarette every 6 s until nausea developed. This aversive counter conditioning procedure is meant to alter the valence of smoking stimuli from positive to negative. The counseling component addressed cognitive and behavioral reactions to the lapse, and attempted to reinstate commitment to smoking abstinence. Individuals in the control condition participated in follow-up assessments, but received no additional treatment after a lapse episode was identified. Preliminary data addressing the utility of the intensive post-lapse
intervention will be presented. Results support the need for further development of novel behavioral treatments for tobacco dependence. Targeting smoking lapse as a point of intervention may hold promise for increasing overall smoking cessation rates.

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332 THE LONG-ACTING COCAINE ANALOG HD-23 INCREASES COCAINE INTAKE USING A DISCRETE-TRIALS PROCEDURE

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Methadone maintenance therapy is predicated on the idea that a long acting opiate compound will decrease the motivation to seek heroin or morphine. Parallel attempts are being made to find a long-acting cocaine analog that could be used in the treatment of cocaine abuse. HD-23 is one such compound that displays a neurochemical profile similar to cocaine except that it has a very long duration of action. The effect of HD-23 on cocaine self-administration was evaluated using a discrete trials procedure. Male Sprague-Dawley rats were implanted with a chronically indwelling intravenous cannulae and trained to self-administer cocaine (1.5 mg/kg per infusion) on an FR schedule of reinforcement. After a stable baseline was established, animals were given the opportunity to self-administer cocaine during 10 min discrete trials. A trial was initiated every 20 min throughout the day/night cycle. The introduction of a lever into the cage signaled the start of the trial. The trial was terminated if a response was made (and an injection delivered) or after 10 min, whichever occurred first. This procedure engendered a circadian pattern of drug intake; trials in the last 6 h of the dark cycle show the highest probability of terminating in a cocaine injection. Pretreatment with HD-23 (1.0 mg/kg; IP) significantly increased cocaine intake. Animals pretreated with HD-23 showed a high probability to self-administer for about 9 h. These data offer no support for the hypothesis that HD-23, a long acting cocaine analogue, decreases the motivation of animals to self-administer cocaine.

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333 OUTCOMES FOR CO-MORBID PARTICIPANTS IN AN INTEGRATED TREATMENT PROGRAM

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This effectiveness study tests a model of integrated care for substance abusers with chronic, severe infectious disease (HIV, HCV, TB). The present report compares program participants who complete with those who do not finish the prescribed course of treatment at Detroit LIGHT House Plus, a 90-day domiciliary, medical case-management/ IOP for people with drug dependence and communicable diseases. The study population is 75% male, averaging 46 years of age (range 35–64) and 12 years of education (range 6–16). The most commonly used drugs are crack > alcohol > heroin > marijuana. Approximately 40% have had and continue to receive therapy for depression or bi-polar disorder. All participants are assessed using the Addiction Severity Index, Quality of Life Inventory, SF-36 Health Survey, the Working Alliance Inventory and a global wellness scale at intake (baseline), completion and 6-month follow-up. Those who complete the program are distinguishable from non-completers at baseline on theASI and other measures. Graduates report significantly lower levels of alcohol and other drug use than non-graduates at program intake and completion. Completers are twice as likely to be abstainers. Overall, they report a 50% reduction in severity on the ASI drug subscale; mean scores dropped from 0.28 to 0.14 (t = 2.96, P < 0.02). Similar, but less dramatic improvements occur for other ASI subscale composite scores. Perhaps more noteworthy, graduates fare better than non-graduates on other health and social outcomes, with 20–30% greater gains in mental health, vitality and overall well-being. Initial data from 6-month follow-ups indicate that gains are sustained in mental health, vitality and physical functioning.

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335 ASSESSMENT OF THE UTILITY OF HARM REDUCTION DATA IN RUSSIA FOR EVALUATION NEEDS

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The Former Soviet Union states are experiencing the world’s steepest HIV infection curve–most of the new cases resulting from injection drug use (IDU). Appropriate public health policies and timely interventions, such as Harm Reduction (HR) programs (e.g., methadone maintenance, needle-exchange) can help prevent, stabilize and even reverse HIV epidemics among drug users. In 1996–1997, Medicine Sans Frontieres-Holland (MSF-H), together with other NGOs, initiated the Russian AIDS Prevention Initiative-Drugs (RAPID). Through this initiative, some 200 participants from over
336  CORRELATION BETWEEN ANCILLARY COMMUNITY SERVICES WITH ADOLESCENT SUBSTANCE USE DISORDERS TREATMENT OUTCOME

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Little is known empirically about the efficacy of treatment methods for adolescent Substance Use Disorders (SUD). The literature on efficacy is characterized by methodological limitations, one of these being the lack of control in measuring ancillary community services during treatment and follow-up. Objective: The purpose of this study was to assess whether the Teen Treatment Services Review (T-TSR; Kaminer et al., 1998) summary of ancillary therapeutic service contact days would predict objective and subjective outcomes of adolescents with SUD among youth treated either in Cognitive Behavioral (CBT) or Psycho-Education (PET) group setting. Method: Eighty-eight consenting adolescents, 13–18 years of age, were recruited for this study at an outpatient clinic and were administered the T-TSR each week for 8 weeks during treatment, and again at 3- and 9-M post-treatment follow-up. Outcome variables included measures at three time points: During Treatment (DT), 3-, and 9-M, and were: Urinalysis, as well as the T-ASI (Kaminer et al., 1991) Alcohol, Substance, and Psychological subscales. The predictor variable was the number of reported Out-of-Program (OoP) service contact days. Results: High DT OoP days correlated with negative DT urinalysis, but neither 3- nor 9-M OoP correlated with 3- nor 9-M Urinalysis, respectively. High 3-M OoP days correlated with poor outcomes on 3-M T-ASI Alcohol, Substance, and Psychological subscales. High 9-M OoP services correlated with poor outcome only on 9-M T-ASI Psychological subscale. Conclusion: The more outside therapeutic services received, the poorer the outcome. Implications for future outcome studies will be discussed.

337  COCAINE WITHDRAWAL SYMPTOMS AND SUBTYPES OF COCAINE-DEPENDENT PATIENTS

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Background: Patients with more severe cocaine withdrawal symptoms at treatment entry, measured by high scores on the Cocaine Selective Severity Assessment (CSSA), have been shown to be more likely to drop out of treatment and less likely to attain abstinence from cocaine in standard outpatient treatment programs. This project attempted to identify other patient characteristics that were associated with more severe cocaine withdrawal symptoms and poor treatment outcome. Methods: Data were obtained from 240 cocaine dependent subjects who participated in 8-week outpatient medication trials for the treatment of cocaine dependence. Measures included, the Structured Clinical Interview for DSM-IV (SCID), the Addiction Severity Index (ASI) obtained at baseline, the CSSA obtained at baseline and urine toxicology screens obtained three times weekly over the course of 8 weeks. Results: High CSSA scores were associated with poor treatment outcome regardless of the medication being evaluated, measured by percent cocaine-negative urine toxicology screens submitted. High scores on the CSSA were associated with more severe cocaine dependence measured by higher ASI composite drug scores, higher ASI interviewer severity ratings for drug problems, more days of cocaine use in the preceding 30 days, and more money spent for drugs in the preceding 30 days. High scores on the CSSA were also associated with more severe psychiatric symptomatology including higher ASI composite psychiatric scores and a greater probability of a lifetime history of major depression. Subjects with high CSSA scores were more likely to have antisocial personality disorder and have a history of violent behavior. Finally, subjects with high CSSA scores were more likely to have a family history of drug dependence.

Discussion: The results of this trial suggest the existence of a subgroup of cocaine dependent patients with characteristics analogous to those of Baber’s Type B alcoholics-more severe cocaine use problems, more psychopathology, a higher incidence of ASPD, more violent behavior, and a higher likelihood of a family history of drug problems. The identification of such a subgroup may have implications for both pharmacotherapy and psychosocial treatment research for cocaine dependence.

338  MARRIED DRUG-ABUSING MEN: AN EXAMINATION OF HIV HIGH RISK BEHAVIORS AND FACTORS ASSOCIATED WITH UNPROTECTED SEX WITH THEIR WIVES

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Married men entering outpatient treatment for substance abuse (N = 329) and their wives were interviewed at admission about behaviors in which they had engaged that placed them at high risk for HIV transmission. One hundred forty five husbands (44%) reported that they (a) had engaged in unprotected sexual intercourse with their wives at least once in the last 3 months, (b) had also engaged in unprotected sex with other partners or shared needles with other IV drug users during the last 3 months, and (c) were unaware of their present HIV seropositive status. One hundred of the wives (69%) of this subset of husbands reported that they were unaware that their husbands had engaged in these high risk behaviors during the last 3 months. The remaining 45 wives (31%) were aware of these behaviors but chose to engage nonetheless in unprotected sexual intercourse with their husbands. Logistic regression revealed the following factors were associated with couples engaging in unprotected sexual intercourse: (a) higher reported relationship satisfaction, (b) husbands meeting criteria for antisocial personality disorder, (c) wives meeting current abuse or dependence criteria for one or more psychoactive substances, and (d) longer marital relationships. Clinical and ethical implications of these findings will be explored.
339 Impact of role induction on treatment retention among clients who did or did not require on-site detoxification

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Retention in outpatient drug-free treatment is poor. Strategies that improve retention in this modality are needed. This ongoing study examined the impact on early retention of a role induction session on the day of intake. Because 52% of the sample reported daily heroin use at intake, we also examined the impact of role induction on retention for clients who did or did not require a 3-day Buprenorphine detoxification (part of routine services offered at the Harambee Treatment Center). Participants (N = 224; 59% male; 35% attended detox) were randomly assigned to Role Induction (RI; N = 150), a 30–45 min individual session that focused on helping the person adopt the role of a drug treatment client, or to a standard clinic orientation session (ST, N = 74), which involved a brief description by a counselor of clinical services and rules in a group setting. Participants exposed to the buprenorphine detox were retained for fewer days (M = 25; S.D. = 52) than clients who did not medically qualify for the detox (M = 59; S.D. = 68); F(1,220) = 9.0, P = 0.003. RI clients who did not require a medication detox were retained for more days (M = 69; S.D. = 73) than ST clients who did not require a detox (M = 37; S.D. = 50), and than participants in either condition who did not need medical detoxification (RI: M = 24; S.D. = 63; ST: M = 26; S.D. = 29), F(1,220) = 3.37, P = 0.068. A single Role Induction session was associated with improved retention (of at least a month) for clients who did not require medical detoxification. More research is needed to develop and evaluate strategies that improve retention and engagement into drug-free treatment of clients with opioid physical dependence that require brief medical detoxification.

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340 Decreased frontal lobe phosphocreatine levels during treatment for cocaine dependence are associated with treatment failure


Phosphocreatine (PCr) and creatine (Cr) are important molecules in cerebral bioenergetics. Since PCr serves as a high energy buffer to maintain brain adenosine triphosphate (ATP) levels, PCr levels are inversely related to cerebral metabolic rates. Although PCr levels are most commonly measured using phosphorus-31 magnetic resonance spectroscopy (MRS), we have recently reported that proton MRS may be used to estimate ratios of PCr/(PCr + Cr) with a substantial increase in sensitivity. These methods were successfully applied to a cohort of 25 cocaine dependent subjects who were enrolled in a three arm, 8 week, NIDA-funded treatment trial for cocaine dependence. Comparison data were obtained from 17 healthy comparison subjects. At baseline, left frontal lobe ratios of PCr/(PCr + Cr) were 0.43 in the cocaine dependent subjects and 0.45 in the comparison subjects. At the end of eight weeks, these ratios decreased by 7% in those 19 cocaine dependent subjects who completed treatment (P = 0.08) and increased by 2% in the comparison group (P = 0.60). However, when the cocaine dependent subjects were considered in terms of their treatment response, nonresponders significantly decreased the PCr/(PCr + Cr) ratios by 17% (P = 0.005) while responders (25% decrease in cocaine use) did not decrease their PCr/(PCr + Cr) ratios (P > 0.99). These results suggest that an increase in cerebral metabolism during treatment for cocaine dependence, measured as a decrease in PCr, is associated with treatment failure and treatments that increase mitochondrial function may be of therapeutic value.

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341 Studies on substance P as a neuromodulator for pain and itch

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We are studying the pharmacological overlap between itch and pain. It is well known that opioid receptors are involved in the inhibition of noxious pain sensations. We have recently demonstrated that opioids can inhibit compound 48/80-induced scratching in mice. The present study was carried out to establish whether pain and itch conduct nociceptive information in the CNS via a common neurotransmitter or neuromodulator, namely substance P (SP). Intracerebral microdialysis was used to measure changes in the extracellular level of SP released from the periaqueductal gray (PAG) of freely moving, male Sprague-Dawley rats (250–280 g; n = 6) after noxious cold (tails submerged into –3 °C cold water) or pruritic stimulation (injection of 25 mg/kg compound 48/80, s.c. into the back of the neck). Artificial cerebrospinal fluid was perfused into the dialysis probe in the PAG and samples were collected every 30 min for 4 h. SP-like immunoreactivity in the samples was measured by ELISA. The baseline SP level measured was 0.63 ng/ml. Noxious cold stimulation induced a 5.6 fold increase in SP levels. Pruritic stimulation caused no significant change in measured SP levels. The peripherally selective kappa agonist, ICI 204448 (10 mg/kg, s.c.), injected 30 min before noxious cold stimulation, inhibited cold-evoked SP release. Pretreatment with ICI 204448 had no significant effect on SP levels evoked by pruritic stimulation. This work has shown that noxious cold-induced increases in extracellular SP levels can be attenuated through peripheral kappa receptors. Compound 48/80 as a pruritogen in rats was shown to have no effect on extracellular SP levels. These data support the contention that itch is a separate sensory modality and not merely a form of pain.

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342 Behavioral effects of amphetamine and diazepam in high- and low-sensation seekers


This ongoing study explores the acute behavioral effects of oral d-amphetamine and diazepam in young adults who were consistently in the highest or lowest third of their age-based cohort on a modified Zuckerman Sensation-Seeking Scale that was completed annually between their sixth and tenth grade years. Healthy 18–21-year-old subjects (N = 14), participated three days per week for 16 days. Sessions consisting of Repeated Acquisition, Digit-Symbol Substitution, and Math Tasks, Visual-Analog Scale (VAS) ratings of drug effect, and the ARCI and POMS were completed 0, 50, 110, 170, 230
and 290 min after drug administration. Placebo and each of the 3 active doses of both drugs (2.5, 5.0 and 10.0 mg/70 kg) were administered under double-blind conditions on 2 days according to a randomized-block design. Typical stimulant and sedative effects were obtained with amphetamine and diazepam, respectively. The magnitude of drug effect on cardiovascular and task performance measures was higher in high sensation seekers. Subjective effects (VAS ‘Liking’ and ‘A’, ‘PCAG’ and ‘LSD’ scales of the ARCI) were consistent with greater reinforcing effects in high sensation seekers. These data suggest that the abuse liability of drugs may be greater in high sensation seekers who are also more likely to initiate drug use.

Supported by DA-05312.

343 EFFECTS OF ESTROGEN AND PROGESTERONE ON NOCICEPTIVE RESPONSES AND MORPHINE-INDUCED ANTILOCITION IN OVARIOMIZED RATS


Menstrual/estrous cycle and gonadal hormones modulate pain sensitivity in females. No complete systematic study to deduce the effects of estrogen and progesterone on acute and tonic pain states has been reported. By delivering graded subcutaneous doses of beta-estradiol (estrogen) and progesterone to ovariectomized (OVX) animals, this study was able to assess any dose dependent effects on baseline nociceptive thresholds and morphine cumulative dose response curve values using the antinociceptive tail-flick test (acute thermal). OVX rates received estrogen (5, 10, 15 or 20%) or progesterone (100%: 1, 1.5, 3, 9 cm) or cholesterol; (placebo) via subcutaneous SILASTIC capsules. Compared to placebo, these doses of estrogen or progesterone did not alter baseline tail-flick threshold values (at 48, 52.5 or 55 °C) or the ED50 values of morphine. It is possible that estrogen and progesterone modulate other nociceptive behaviors such as hyperalgesia. Concurrent studies in our group are addressing this possibility.

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344 GONADAL STEROIDS’ EFFECTS ON SYNERGISTIC NEUROTOXICITY OF COCAINE WITH HIV-PROTEINS

S.L. Kendall, C. Anderson, A. Nath, C.F. Mactutus, R.M. Booze, University of Kentucky, Lexington, KY, HIV-Associated Dementia (HAD) is more prevalent among HIV infected IV drug users than non-users. The HIV infection rate is growing faster among women than it does to men. We have developed an in vitro model of human neurotoxicity to investigate cellular mechanisms that may contribute to HAD. Our previous work has shown that the HIV-proteins, Tat and gp 120, are dose-dependently neurotoxic and that physiological levels of cocaine (Coc) (1.6 uM), in conjunction with subtoxic levels of gp 120 and Tat, produces synergistic neurotoxicity. The goal of this work was to determine whether Coc or its longer-lived metabolite, benzoylecgonine (BE), promotes toxicity and to identify gonadal steroids’ effects in this model. After 15-h drug treatment cell death was assayed by trypan blue exclusion. We found that BE is not neurotoxic, and unlike Coc, does not synergize with HIV-proteins. This is true even at the supraphysiological levels that may accumulate with repeated Coc use (100 uM). Additionally, Coc and HIV-protein synergistic neurotoxicity is reversible by both 17β-estradiol (10 nM) and 5α-testosterone (10 nM). The dose response is described from no protection to full reversal of toxicity (1pM–10uM). Neither the non-aromatizable testosterone analogue, dihydrotestosterone (DHT) (1–100 nM), nor progesterone (1–100 nM) reverse this synergistic toxicity. However, the anti-oxidant, vitamin E (1–100 nM), is potently neuroprotective. In sum: (1) Neurotoxicity is not due to the Coc metabolite, BE; (2) Coc, not BE, synergizes with HIV-proteins to produce neurotoxicity; (3) Estradiol, testosterone and vitamin E have neuroprotective effects, but DHT and progesterone do not. This is evidence for a direct interaction of Coc with HIV-protein mediated neurotoxicity. Furthermore, while an estrogen receptor-mediated neuroprotective mechanism is not proven, the current data strongly support such a process. Importantly, our results suggest that investigation of receptor-mediated, steroid-specific treatment of HAD is warranted.

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345 COUNSELORS’ PERCEPTIONS OF CHANGES IN THE SUBSTANCE ABUSE TREATMENT POPULATION FOLLOWING THE SEPTEMBER 11TH ATTACKS

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The impact of the September 11th attacks continues to be reported in the media. There is speculation that in the substance using population the attacks may have resulted in changes in drug use patterns, early treatment terminations, or relapses. We collected data from counselors and patients in substance abuse treatment programs in four cities, including New York City. This report presents data collected on counselors’ perceptions of changes in patients and staff after the attacks. Eighty-six counselors at 25 programs completed the 10-question surveys between November 28, 2001 and January 4, 2002. All programs are participants in the Drug Evaluation Network System (DENS). The counselors voluntarily completed the five-minute surveys. All of the 44 female and 42 male counselors were compensated for their participation with a $20 gift card. About 64% (n = 55) of the staff reported receiving changes in fellow staff members and 56% (n = 48) of staff surveyed perceived changes in their patients. Perceptions of staff included more concern about and compassion toward other employees and patients, more anxiety and stress, and fear of layoffs. Perceived changes in patients included reports of changes in the demand for services, such as the number of outside referrals to treatment, patient attendance rates, and premature treatment termination. Eight of the 11 counselors working in Veterans Affairs Medical Centers (73%) saw a change in the frequency of PTSD symptoms as compared to 35% (n = 26) of the non-Veterans Affairs counselors. The current survey results suggest that the attacks may have had minimal impact on the substance using population, this in contrast with speculation from the media.

346 PERINATAL OPIATE DEPENDENCE: METHADONE AND BIRTH OUTCOMES

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The use of methadone for treatment of perinatal opiate addiction remains clinically controversial, particularly among abstinence-oriented drug treatment clinicians. The majority of data supporting administration of methadone during pregnancy originate from clinical studies of perinatal addiction. The purpose of the current study is to compare pregnant opiate dependent pregnant women receiving methadone maintenance (N = 137) with opiate dependent pregnant women electing abstinence-based treatment (N = 80). Participants were pregnant opiate dependent women admitted to a comprehensive treatment program for perinatal drug dependence. Most were never married (75%), African–American (80%) with a mean age of 29 years. Half had completed high school. Infants born to methadone maintained mothers differed from infants born to nonmethadone maintained mothers differed only on birthweight, with methadone-exposed infants weighing significantly less at delivery than those infants not exposed to methadone in-utero. A similar pattern was seen for infant birth length, with methadone maintained infants having shorter birth lengths than nonmethadone infants. Interestingly, however, when measures of opiate use severity (e.g., quantity and frequency of opiate use in month prior to treatment admission, route of administration, years of regular opiate use) were included in the data analysis, infants of methadone maintained mothers no longer differed from infants of nonmethadone maintained mothers for birthweight or birth length. Study findings suggest that difference in birth weight and length were due primarily to greater opiate use severity among methadone maintained pregnant women. After controlling for opiate use severity, study data suggest no additional, independent teratogenic impact specific to methadone administration during pregnancy.

347 DETECTION OF ANTIBODIES TO OPIATE AND GLUTAMATE RECEPTORS BY METHODS OF REACTION LATEX AGGLUTINATION (RLA) AND ELISA

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Adsorption ability of few kinds of latex covered by synthetic peptide fragments of mu and delta opiate receptors (OR) and GluR1 subunit of AMPA glutamate receptors is investigated. The levels of aAbs to glutamate and opiate receptors fragments in the blood serum of patients with drug abuse and epilepsy are detected by reaction latex agglutination (RLA) and ELISA. The patients with drug abuse demonstrated positive RLA for serum dilutions from 1:16 and higher in 71% of cases. The levels of aAbs OR in the blood of patients with drug abuse was 1.4 times higher than in the blood of epileptic patients and 2.8 times higher then the control data. The correlation between levels of aAbs to opiate receptors obtained by methods of RLA and ELISA is revealed. Epileptic patients had increased levels of aAbs to GluR1 subunits of glutamate receptors. The obtained data confirm our hypothesis concerning existence of specific changes in the immune system linked with some CNS disorders like drug abuse and epilepsy. Thus, the level of aAbs to specific receptors could be used as the new criterion for diagnostics of drug abuse and epilepsy.

348 CURRENT PSYCHIATRIC DISORDER IS ASSOCIATED WITH HIGHER RATES OF DRUG USE AND RISK BEHAVIOR IN NEEDLE-EXCHANGE CLIENTS

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The present study evaluates if the presence of a current nonsubstance use psychiatric disorder is related to drug use and HIV risk behavior in new Baltimore Needle Exchange Program (NEP) participants. To date, 279 new registrants to the NEP have been administered the Structured Clinical Interview for the DSM-IV, the Addiction Severity Index (ASI), and the Risk Assessment Battery (RAB). Participants were categorized into one of four mutually exclusive groups: (1) Antisocial Personality Disorder (APD) only (n = 66); (2) APD plus current Axis I disorder (n = 33); (3) Current Axis I disorder only (n = 34); or (4) No Axis I disorder or APD (n = 146). Study participants reported a M age = 38 years; 11 years of education; 68% were male; 80% were Black; 11% were homeless; and 89% were unemployed. The results show that participants with a current psychiatric disorder (i.e., Groups 1–3, above) exhibited higher rates of sedative use disorder (42% vs. 17%) than those with no history of a psychiatric disorder (P < 0.01). Participants with any Axis I disorder (with and without APD) evidenced elevated medical and drug use composite scores, and exhibited higher rates of HIV high-risk behavior (P < 0.01) compared to other study participants. These results suggest that a substantial subgroup of NEP participants exhibit an untreated current nonsubstance use psychiatric disorder (48% overall; 24% with current Axis I disorder), and that these individuals are at higher risk for drug use, medical problems, and HIV transmission.

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350 SYNTHESIS AND EVALUATION OF 2,5-CIS-DIMETHYLPIPERAZINE-N-YL-[3-METHOXYPHENYL]-METHYL-N-ETHYL-N-PHENYLBENZAMIDES AS POTENTIAL, SELECTIVE, MU OPIOID RECEPTOR ANTAGONISTS

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Potent and selective mu or delta opioid antagonists have been discovered in almost every type of opioid, in, for example, the phenylpiperidine, 5-phenylmorphinan, 4,5-epoxymorphinan, and, 6,7- benzoazomorphan series. However, mu opioid antagonists have not, insofar as we are aware, ever been found in the piperazine series of the SNC 80-type of molecule, 4-[(4-allyl-2,5-trans-dimethyl)piperazin-4-yl)-[3-methoxyphenyl]-methyl-N,N-dietethylbenzamide (compound 1). Both delta opioid agonists and antagonists are claimed in that series. We noticed that, in a related series, N-phenyl analogues appeared to have increased affinity for mu opioid receptors, and have also noted from other work that some cis dimethylpiperazines appeared to have opioid antagonist actions. From these data, we theorized that if a few changes could be made to compound 1, to obtain, for example, a derivative of 4-[2,5-cis-dimethyl-piperazin-4-yl]-[3-methoxyphenyl][methyl]-N-ethyl-N-phenylbenzamide (compound 2), we might be able to find a new type of mu antagonist. We have now synthesized the N-allyl derivative of compound 2 (i.e., compound 4, below), and we have separated the diastereomers based on the benzylic carbon atom. The key intermediate, 4-[chloro-(2,5-cis-dimethyl-piperazin-4-yl)][3-methoxyphenyl][methyl]-N-ethyl-N-phenylbenzamide (compound 3) was obtained in 67% overall yield in 3 steps. Compound 3 was reacted with 2,5-cis-dimethylpiperazine to give 4-[2,5-cis-dimethyl-piperazin-4-yl)-[3-methoxyphenyl]-methyl]-N-ethyl-N-phenylbenzamide (compound 2), which provided 4-[4-allyl-2,5-cis- dimethylpiperazinyl)-(3-methoxyphenyl)-methyl]-N-ethyl-N'-phennylbenzamide (compound 4). We separated the diastereomers of compound 4 based on the benzylic carbon atom via flash column chromatography. The compounds examined, thus far, however, appear to be considerably more selective for delta receptors than mu or kappa opioid receptors.

351 IMAGING HUMAN ALPHA4BETA2 NICOTINIC ACETYLCHOLINE RECEPTORS


Knowledge about mechanisms by which nicotine, the primary addictive ingredient in tobacco smoke, causes dependence could lead to treatment strategies that promote smoking cessation. Nicotine acts at the α4β2 subtype of nicotinic receptors (nAChRs) and its administration causes increases in the densities of these receptors. Research in this field would be facilitated by the ability to image these receptors in vivo, but until very recently, suitable ligands for imaging nAChRs in humans were lacking. A promising candidate for this purpose is 2-[F-18]fluoro-3-[(S)-2-azetidinyl-methoxy]pyridine (2-[F-18]FA). In rodent and non-human primate studies, 2-[F-18]FA exhibits low toxicity along with promising kinetics and dosimetry estimates for human studies. Therefore, the focus of the current study is to determine if 2-[F-18]FA could be used to image nAChRs in human brain with positron emission tomography (PET) within radiation dosimetry limits. We administered a sterile, apyrogenic solution of 2-[F-18]FA in saline (0.043 mCi/kg; i.v.; sp. act. 5000–20000 Ci/mmol at injection time; <10 pmol/kg, radiochemical purity >98%) to healthy non-smokers and acquired PET scans over the next 7 h. Our results demonstrate that 2-[F-18]FA is suitable for imaging nAChRs in the human brain with PET. The total radioactivity accumulated in human brain was ca. 2.5% of injected dose, sufficient for visualizing nAChRs up to 5 h after injection. Consistent with the distribution pattern of nAChRs in human brain, accumulated radioactivity was greatest in the thalamus, superior colliculus and pons; intermediate in the cerebellum and cortex; and least in white matter. We found that more than 90% of radioactivity after 2-[F-18]FA administration was excreted in the urine (effective half-life ca. 4 h). Therefore, the bladder received the greatest radiation dose. These data yielded an estimate of the effective equivalent dose to the urinary bladder wall, with a 2.4-h void interval, of ca. 0.7 rem/mCi. In conclusion, 2-[F-18]FA is a new tool for studying cerebral nAChRs in smokers and during smoking cessation in vivo.

352 A CONTROLLED TRIAL OF METHADONE MEDICAL MAINTENANCE: 12-MONTH RESULTS

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The most effective therapy for chronic heroin dependence is methadone maintenance (MM). Unfortunately, MM is not available to many individuals who might benefit from it. One way to enhance availability of MM is through implementation of methadone medical maintenance for stabilized, well-functioning patients. Medical maintenance reduces the reporting schedule to once per month with counseling done by medical staff. Care is provided in traditional clinics or by physicians in private medical practices. We report on the 12-month treatment outcome of 92 highly stable MM patients from 2 MM clinics randomly assigned to one of three conditions: routine care, medical maintenance at the MM program, and medical maintenance at a private doctor’s office. A Step Care system of treatment intensification was used for patients who failed recall or had drug positive urine specimens. Medical maintenance patients received a 28-day supply of methadone dispersible diskettes. All patients performed a medication recall once per month and gave two urine samples each month (one on a random basis). About 77 patients completed 12 months. Drop out was due primarily to problems with handling methadone (n = 6) and disliking the recall frequency (n = 6). Only 1% of urine specimens were positive for illicit drugs, though patients self-reported occasional alcohol and marijuana use. Only 4% of medication recalls were failed, with very low rates of medication misuse. Treatment satisfaction was high in all groups, but the medical maintenance patients initiated more new employment or family/social activities than routine care patients. The Step Care treatment approach was well tolerated and helped match patients to an appropriate intensity of service within a continuum of substance abuse care.

353 THE ITEM RESPONSE THEORY MODELING OF TEN DRUG CATEGORIES

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This study examined the psychometric characteristics of an index of substance use involvement based on item response theory (IRT). The index estimates a unidimensional latent trait indicated by 10 categories of psychoactive drugs as binary items (use/non-use). The sample was composed of 292 adult men and 140 women who qualified for a DSM-III-R substance use disorder (SUD) diagnosis and 293 men and 445 women who did not qualify for SUD. Consumption data were employed to derive an index of substance use involvement. The results indicated that men had a higher probability of endorsing substance consumption levels of trait severity compared to women. The index of
substance use involvement significantly predicted health, psychiatric and psychosocial disturbances as well as level of substance use behavior and severity of substance use disorder at 2-year follow-up in both men and women. In addition, this latent trait score accounted for 35% and 31% of the total variance on drugs and females on the Drug Use Screening Inventory (DUSI-R) in males and females. The results of this study indicate that the IRT-derived index of substance use involvement, encompassing all compounds ever used, is a reliable and useful prognostic indicator of the risk for substance use disorder and the medical and psychosocial sequelae of drug consumption.

354 Effects of opioid receptor agonists on the hypothalamic-pituitary-adrenal axis in rhesus monkeys


Opioids can modulate several neuroendocrine systems; however, the roles of opioid receptor types in the hypothalamic-pituitary-adrenal (HPA) axis of primates are unknown. The aim of this study was to characterize the effects of opioid receptor agonists on plasma ACTH and cortisol levels in rhesus monkeys. The blood-collection procedure was used in home-caged and unanesthetized monkeys (n = 7–8) that had indwelling i.v. catheters. Low and stable ACTH and cortisol levels were observed. Three non-peptidic opioid agonists, fentanyl, U50488, and SNC80, were used; they are highly selective for mu, kappa, and delta opioid receptors, respectively. Plasma samples were collected for 3 h after i.v. administration of each compound and plasma ACTH and cortisol levels were quantified using commercial radio-immunoassay kits. Fentanyl (0.00032–0.032 mg/kg) did not change either ACTH or cortisol basal levels. U50488 (0.01–1 mg/kg) profoundly increased both ACTH and cortisol levels in a dose-dependent manner and the increased ACTH by U50488 was attenuated by pretreatment with a selective kappa receptor antagonist, nor-binaltorphimine (3.2 mg/kg). In addition, SNC80 (0.032–0.32 mg/kg) did not change either ACTH or cortisol basal levels. The doses of fentanyl and SNC80 used herein are active behaviorally in monkeys; thus, only the behavioral actions of U50488 are accompanied by strong changes in the HPA axis. These results may indicate that kappa opioid receptors play a prominent role in modulating the HPA axis in non-human primates. (Supported by USPHS Grants DA00254 (J.H.W.) and DA13685 (M.C.K.).)

355 Gender differences in alcohol and polydrug abuse among young adults

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Differences in drinking, smoking, and polydrug abuse between male and female undergraduate students were investigated. Questionnaires containing items assessing demographic characteristics, alcohol frequencies and severities, and polydrug use patterns were administered to 61 undergraduate students as part of a class assignment. A One-Way ANOVA was conducted to test the hypothesis that there are differences in alcohol use between males and females. The results support the hypothesis that males drink more heavily in a 14-day and a 30-day period than females. T-tests demonstrated significant differences in polydrug use between males and females. This finding further supports that males are more likely to use illicit drugs. A gender-specific model may be effective in preventing and treating substance abuse disorders among young adults.

356 Flipping biased coins: statistical analyses of drug discrimination data

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Results of drug discrimination tests are often classified as ‘full substitution’, ‘no substitution’, or ‘intermediate responding’, but different criteria are used, and formal rules are lacking. To classify test results objectively, it may help to examine whether they are significantly different from the results obtained under training conditions. For quantal test data, this means comparing the proportion of subjects selecting the drug-appropriate response (DR) during a test with those during training, and assessing the statistical significance of differences among these proportions. Conventional statistical tests of such differences, however, make restrictive assumptions and lack sensitivity. Sensitive statistical tests can be developed, however, by taking the performance of the discrimination, once acquired, into account. From this performance, the probabilities of DR selection after saline and after the training dose are estimated for each subject. Based on these probabilities, the statistical significance of differences between test results and training performance can be assessed by combining different Bernoulli distributions, and also by Monte Carlo simulations. Unlike conventional statistics, such simulations do not restrict the design of drug discrimination tests, and allow one to examine statistically not only the effects of individual doses, but also other aspects of drug discrimination results. For example, they can examine the shape of the dose-response curve (e.g., monotonic, biphasic), without requiring equally spaced doses and equal sample sizes. And they can estimate 95% confidence limits of ED50 values, without the assumptions of the Litchfield and Wilcoxon method. It is hoped that these procedures, which can be carried out with Microsoft Excel, will help to analyze and classify drug discrimination data.

357 Transdermal nicotine alters marijuana's subjective effects in human volunteers

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Nicotine and marijuana are often consumed together and tobacco smokers are more likely to use marijuana than non-smokers. However, few studies have examined the effects of this drug combination in humans. The present study investigated whether nicotine pretreatment via a transdermal patch (placebo and 21 mg) alters the subjective and cardiovascular effects of smoked marijuana (1.94% and 3.59% Δ9THC). Following a 4-h nicotine pretreatment phase, subjects smoked a marijuana cigarette under controlled conditions. Findings from 8 subjects indicate that post-marijuana ratings of intoxication, high, anxiety, feeling bad, slurred speech, sleepiness, and floating were lower during the active nicotine condition compared to placebo. These effects were most pronounced during the low dose marijuana condition and occurred in the absence of any pre-marijuana differences in subjective ratings. Also, post-marijuana MBG scores from the ARCI were lower during the nicotine condition. There was no significant nicotine-marijuana interaction on cardiovascular responses. Nicotine increased heart rate an average of 10 bpm before marijuana, but marijuana-induced increases in heart rate were not altered by nicotine. Subjects experienced average increases of 35 bpm after the low dose of marijuana and 45 bpm after the high dose of marijuana regardless of the nicotine dose. Our findings may have important implications for individuals who smoke marijuana while on the nicotine patch. If individuals compensate for the decreased marijuana effects during nicotine patch exposure by increasing their marijuana intake, they may develop increased tolerance and be at higher risk for developing cannabis dependence.

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Drug use behaviors that receive repeated practice may become routine, automatic, and effortless, carried out quickly with little or no awareness of the steps involved. This shift in performance with practice has been described as the development of ‘automaticity.’ Automatic processes in drug dependence may contribute significantly to the high rates of relapse. However, little research has been conducted on the features underlying automatic processes in substance abuse, and no self-report instruments have been developed to assess automaticity in this population. To facilitate research in this area, an instrument development project was initiated. The Impulsive Relapse Questionnaire (IRQ), a new measure of impulsive drug use, was subjected to tests of internal consistency, reliability, and validity. The goal was to design a self-administered questionnaire that would distinguish between individuals prone to impulsive versus non-impulsive relapse with a high degree of sensitivity and specificity. The psychometric properties of the 33-item IRQ were evaluated in a sample of 212 adults with primary substance use disorders receiving treatment at a VA hospital. Factor analysis revealed five interpretable dimensions for the scale: automaticity, control deficits, denial, capacity for delay, and speed. Internal consistency of the measure was established (coefficient α = 0.76). Convergent validity of the IRQ factor scores was supported by significant correlations with subscales of the Barratt Impulsivity Scale-11 (BIS-11) and the Impulsiveness scale on both the NEO PI-R and TCI. The IRQ holds promise as a useful self-report measure encompassing several relevant dimensions of impulsive or ‘automatic’ relapse for use with a substance abuse treatment population.

The endogenous opioid system is central in mediating neurophysiological responses to drugs of abuse and alcohol. The mu opioid receptor (MOR) is one of the major targets for the analgesic and rewarding properties of the synthetic mu opioids in the naltrexone group was significantly higher than the placebo group beginning at the end of the first month. At the end of 6 months, 12 naltrexone patients (44.4%) were abstinent and 15 (55.6%) had dropped out; in the control group, 4 patients (16%) were abstinent and 21 (84%) had dropped out (P < 0.05). Compliance with naltrexone and placebo was 85–95% among non-dropouts. Naltrexone reduced craving for heroin more than placebo within the first two months, but it did not influence anxiety, depression or anhedonia. These data show that naltrexone is likely to be an effective medication for prevention of relapse to heroin dependence in Russia, and that it can play an important role in HIV prevention if made more available to treatment programs.

**361 Adolescent THC exposure affects adult behavior in rats**

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Marijuana dependence is the most commonly cited drug dependence issue in adolescent populations. However, little experimental evidence about the consequences of adolescent cannabinoid exposure for adult behavior exists. The purpose of this study was to test the hypothesis that adolescent exposure of rats to THC during adolescence would influence adult behavior to test this hypothesis, male rats were treated [hMOR (A118G); one-way ANOVA]. Although all expressed receptors significantly reduced maximal forskolin-induced cAMP-levels, inhibition of cAMP-accumulation was less prominent in hMOR (A118G) (~58%) compared to hMOR (wt) and hMOR (C17T) (~72%, 73%) indicating that this receptor mutant could alter DAMGO-induced intrinsic efficiency.

with emulsor vehicle or THC 5 mg/kg once daily from days 25–50. Behavioral testing began on day 90. Learning was assessed in the Morris Water Maze and performance in a light/dark box and social interaction tasks were used to evaluate anxiety-related behaviors. The effects of acute THC intoxication on learning was determined in a separate cohort of rats in the Morris Water Maze with training started on day 30 or day 60. Acute THC treatment during Morris Water Maze learning impaired learning similarly in adolescents and adults. However, when animals exposed to THC during adolescence were tested as adults, their Water Maze performance was significantly different from vehicle-treated controls. THC-treated adolescents showed fewer transitions across sides in a light-dark box and less interaction with an unfamiliar rat in the social interaction task. These findings suggest that adolescent THC exposure permanently changes subtle aspects of adult behavior long after exposure has stopped. These findings are concordant with recent studies showing subtle cognitive defects on adults who used THC heavily during adolescents, even if they abstain in adulthood.

362 Molecular modeling, design and synthesis of novel N-substituted benzotropine analogs as probes for the dopamine transporter


Understanding the molecular interactions with the dopamine transporter, (DAT) of structurally divergent ligands, may be essential to developing effective medications for cocaine abuse. The development of structure-activity relationships (SAR) with divergent classes of dopamine uptake inhibitors and comparing their behaviors in animal models of cocaine abuse has provided insight into the complex relationship between structure, binding profile and behavioral activity. A 3D-QSAR molecular modeling study was performed on 76 benzotropine analogs previously generated. This model was then used to design a series of novel N-substituted benzotropine analogs, which contained optimal structural components for high affinity and selective DAT binding. Furthermore, an appreciation of the roles that pharmacokinetics play in the potential effectiveness of a pharmacotherapeutic was incorporated into the drug design. Thus, the N-substituents were chosen to enable varied physicochemical properties, including lipophilicity. A comparison of SAR at the monoamine transporters and muscarinic receptors will enable the identification of highly selective and potent dopamine uptake inhibitors with appropriate physicochemical properties for behavioral evaluation. These studies will further improve our understanding of the role played by physical properties in the behavioral actions of these molecules. This information is essential for devising an efficacious medication strategy for cocaine addiction. This work was supported by the NIDA-IRP.

363 Diaphin (diacetylmorphine)-A new legal drug in Switzerland: Subjective side effects and risk for osteoporosis

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The Psychiatric University Clinic of Basel provides methadone maintenance treatment (MMT) for 170 persons and heroin-assisted treatment (HAT) for 150 persons. MMT and HAT are separate treatment settings within the outpatient opioid treatment clinic. Since December 2001, Diaphin® (diacetylmorphine) is approved by Swiss legal authorities as a drug in opioid dependence treatment. We used a structured interview and self-report checklists to identify side effects of Diaphin® and methadone (N = 80 each). In addition, subjects were screened for clinical signs of weakening of the bones (e.g. increased incidence of fractures, dysmenorrhea) and underwent an osteodensitometry examination afterwards (N = 10 each). The results of both groups (MMT and HAT) were analyzed with respect to gender and age differences, infectious diseases (AIDS, hepatitis), socioeconomic aspects, and individual history of drug abuse. Both treatment settings were compared to each other and to all Swiss HAT centers. Our results provide for the first time important information about side effects of Diaphin® and methadone with special reference to osteoporosis in a large clinical sample of severely addicted comorbid subjects.

364 Are physicians worried about dependence on benzodiazepines?

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It was evaluated if physicians properly orientated the patients about benzodiazepine (BZD) dependence risk. From a random stratified sample (n = 120) formed by patients who searched the pharmacist to buy the prescribed BZD, only 26% reported they had received orientation about dependence risk. About 61% of the patients were using BZD for more than one year, 71% were using ceaselessly, 61% had been prescribed 60 tablets in only one consultation and 78% reported that the physician had not guided them for how long the BZD would be used. Contrary to our expectancy, psychiatrists (P) gave the worst orientation about dependence when it was compared to the clinicians (C) and neurologists (N): 12% of the psychiatrists’ patients, 39% of the clinicians’ patients and 27% of the neurologists’ patients were oriented about dependence risk (z2 = 5.42; P < 0.02). No significant difference (P > 0.05) was observed among the three specialists (P × N × C) concerning the duration of BZD use by their patients being the majority of them using BZD for more than one year (C: 68%; N: 45% and P: 67%). The data suggest that the patients may depend on BZD and physicians were not worried about this.

365 High buprenorphine dosage in pregnancy: first data of a prospective study


In order to investigate the effects of buprenorphine exposure during pregnancy, a multicentric prospective study comparing 100 buprenorphine- and 100 methadone-exposed pregnant women is now in progress in opiate maintenance therapy centres, maternitys, general practitioner networks and centres of drug information in pregnancy in Toulouse and Paris. All pregnant women who are treated with buprenorphine or methadone are included before the end of the eighth month of pregnancy. For each woman, the following data were collected: sociodemographic data, medical past history, duration of addiction, substance use, prescribed and self-medicated drugs and obstetrical events. For offspring, birth weight, characteristics and severity of withdrawal syndrome, malformations, neonatal diseases and neonatal mortality were recorded. We report the first data about 34 pregnancy outcomes in buprenorphine-exposed women. 31 of them ended in birth, one infant was stillborn, one ended in spontaneous abortion and one was voluntary terminated. A neonatal withdrawal was observed in 13 cases (41.9%) and eight babies required an opiate treatment. Neonatal abstinence signs occurred between 1 and 8 days (mean of 3 days). Two neonates had a malformation: a tragus appendice in a newborn also exposed to sulfamethoxazole, trimethoprime, lamivudine and zidovudine in utero and a premature ductus.
Pathological gambling and drug dependence have many similar features. Cognitive behavioral therapy has been shown to be effective in treatment drug dependence but little is known regarding its efficacy in the treatment of pathological gambling. This study evaluated the efficacy of a group cognitive treatment for pathological gambling. Gamblers, meeting DSM-IV criteria for pathological gambling, were randomly assigned to treatment (N = 34) or wait-list control (N = 24) conditions. Cognitive correction techniques were used first to target gambler’s erroneous perceptions about randomness, and then to address issues of relapse prevention. The dependent measures used were the DSM-IV criteria for pathological gambling, gamblers’ perception of control, frequency of gambling, perceived self-efficacy, and desire to gamble. Post treatment results indicated that 88% of the treated gamblers no longer met the DSM-IV criteria for pathological gambling compared to only 20% in the control group. Similar changes were observed on all outcome measures. Analysis of data from 6, 12 and 24 month follow-ups revealed maintenance of therapeutic gains. Recommendations for group interventions are discussed, focusing on the cognitive correction of erroneous perceptions toward the notion of randomness. The findings have implications for treatment not only of pathological gambling, but also addictive disorders in general.

367 Effects of CP55940 on rates of local cerebral glucose utilization

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Previous studies in this laboratory with the low-efficacy CB1 agonist delta-9 THC have shown significant decreases in brain functional activity at a wide range of doses. There have been recent reports, however, of increased cerebral metabolism following administration of high-efficacy cannabinoid receptor agonists, WIN55212-2. Although high and low efficacy cannabinoids produce largely similar effects, their behavioral profiles are not completely concordant. The purpose of the present study was to determine if intrinsic efficacy affects the cerebral metabolic effects of cannabinoid receptor activation. High efficacy CB1 agonist CP55940 have been characterized using the [14C]-2-deoxyglucose (2-DG) method and compared to low efficacy agonist delta-9 THC. Adult male Sprague-Dawley rats were treated with either vehicle or CP 55 940 (0.03 or 0.3 mg/kg, i.p.) and the 2-DG procedure was initiated 30 min following treatment. Administration of the higher dose produced significant decreases globally both in anatomical extent and magnitude. In contrast, administration of 0.03 mg/kg CP55940 produced marked increases predominantly in limbic and motor regions. The biphasic effects observed with this high efficacy cannabinoid agonist differ significantly from those found with delta-9 THC, which produced only decreases. These data suggest, therefore, that efficacy plays an important role in determining cerebral metabolic effects of cannabinoid receptor activation. DA6634

368 Chronic Fra induction following intermittent morphine and heroin administration in rats

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To examine long-lasting biochemical changes following repeated drug administration, novel transcription factors, such as deltaFosB have been examined. That is, upon repeated drug exposure, the 33 kDa protein deltaFosB induces more stable proteins in specific brain regions termed Fos-related antigens (chronic Fras). Previous studies have reported chronic Fra induction following repeated treatment with some drugs of abuse, including cocaine (Nye et al., 1995) and morphine (Nye and Nestler, 1996). While the dose and time course of chronic Fra induction following cocaine treatment has been well-established, morphine-induced chronic Fra induction has been reported only for a single intermittent dosing paradigm. Therefore, the present study examined: (1) chronic Fra induction following three escalating dosing schedules of morphine (low, medium and high) for 6 or 10 days and (2) whether the findings with morphine extend to another opiate drug of abuse, heroin. Male Sprague–Dawley rats received subcutaneous injections of morphine, heroin or saline twice daily. Chronic Fra immunoreactivity was then analyzed in the caudate putamen (Cpu) by immunolabeling using a FosB antibody. Following 6 days of morphine administration, there were increases in chronic Fra levels in both the low (161% of control) and medium (152% of control) dose morphine groups and a slight increase in the high (125% of control) dose morphine group in the Cpu. Following 10 days of morphine administration, chronic Fra levels were increased in the low (147% of control) and significantly increased in the medium (176% of control) dose morphine groups. Like morphine, chronic heroin administration significantly induced chronic Fra levels in the Cpu (159%). Taken together, it is likely that morphine-induced chronic Fra induction is dependent both on dose and the duration of treatment. Changes in chronic Fra levels following both morphine and heroin administration in the NAc as well as other brain regions are currently being tested.

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errors than the marijuana-smoking adolescents. On the sensitivity to consequences task, control adolescents’ response distributions tracked the changes in reinforcement frequency. This process was disrupted in the marijuana-smoking adolescents, who allocated more responses to the decreasing option and subsequently earned significantly fewer reinforcers. These data are consistent with prior results showing that THC may disrupt adaptive behavior change and/or cognitive processing. This study extends the literature by demonstrating residual effects in adolescent marijuana smokers.

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370 Functional magnetic resonance imaging (fMRI) of regional cerebral blood flow during heroin-related cues in opiate-dependent subjects

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Methadone maintenance (MM) is effective in preventing opiate withdrawal symptoms, however some patients continue experiencing drug craving. Data indicates that such craving may be a response to conditioned drug-related stimuli. Functional Magnetic Resonance Imaging (fMRI) has practical advantages over Positron Emission Tomography for the in-vivo study of the brain substrates of higher cognitive functions, however Blood Oxygenation Level Dependent fMRI is prone to motion artifact when used to image prolonged states, such as drug craving. We used an alternative, perfusion-weighted pulse sequence to study the regional cerebral blood flow (rCBF) response to heroin cues in MM patients. In an ongoing study, MM subjects viewed non-drug and heroin-related videos (10 min each) while undergoing Pulsed Arterial Spin Labeling fMRI (PASL fMRI). Statistical parametric mapping (SPM99) was used to compare rCBF during heroin cues with baseline and correlate rCBF with subjective and physiological measurements of desire to use opiates. Preliminary analysis showed significant reductions in IL-1 beta, TNF-alpha, and iNOS expression in heroin-treated animals relative to saline-treated animals, that was independent of the method of drug delivery. Furthermore, we established a time course of cytokine and iNOS expression that was altered by heroin treatment. In particular, heroin-treated animals show reduced TNF-alpha levels at 3 h, with no difference seen at 1 or 6 h, and reduced IL-1beta and iNOS levels at 3 and 6 h. The results provide evidence that heroin-induced a pronounced alteration in the expression of important cytokines such as IL-1beta, TNF-alpha, and the enzyme iNOS, which may play a role in the higher incidence of infectious diseases observed in heroin users.

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372 A 24-week follow-up study of methadone and buprenorphine new users using data of a French prescription database


Objective: Using data collected by the French Health Insurance System, the aim of this study was to assess the percentage of patients under opiate maintenance at 24 weeks and the patterns of drug use in the context of ambulatory care of opiate addicts. Design and method: This study was performed among a sample of patients identified from the ‘Haute-Garonne’ prescription database. Patients were defined as new methadone or buprenorphine users since they were not treated during a 2-month period before inclusion in March-July 2000. Data were collected during 24 weeks after inclusion. Results: All new users of buprenorphine (n = 282) or methadone (n = 10) were included. They were men (74%), mean age 32.4 ± 6.1 years. Prescribers were mainly general (93%) and hospital practitioners (6%). The 24-week treatment retention rate was 70% for methadone and 37% for buprenorphine users. Using ATC classification, 82% of patients used psychotropic or ‘Nervous System’ drugs (mainly anxieties 43% or hypnotics 40%). Flunitrazepam (21% of patients), bromazepam (20%) and clorazepate (19%) were the most frequently associated drugs, whatever the treatment group. Conclusion: These data in real life conditions suggest a rational opiate maintenance therapy use for almost patients at least in the Haute-Garonne area.

373 Integrated family and cognitive-behavioral therapy for adolescent drug abusers: 1-month and 6-month post-treatment outcomes

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The primary aim of the present Stage I study was to develop and evaluate the efficacy of an adolescent drug abuse treatment that integrates cognitive-behavioral and family therapy components. The treatment, designated Integrated Family and Cognitive-Behavioral Therapy (IFCBT), was developed in response to NIDA’s Behavioral
Therapies Development Program (DA10777). The present study included 43 adolescents assigned at random to either Integrated Family and Cognitive-Behavioral Therapy (IFCBT; \(N = 21\)) or Psychoeducation (PE; \(N = 22\)) conditions. At one month-follow-up, youth receiving PE were approximately six times more likely to use alcohol when compared to youth receiving IFCBT, while controlling for several potential confounds (e.g., age, gender) (OR = 6.45, \(P < 0.05\)). Similarly, drug abusing youth receiving PE were nearly seven times more likely to use marijuana during the first posttreatment month when compared to youth receiving IFCBT (OR = 6.94, \(P < 0.05\)). Findings on drug use and psychosocial outcomes at six-month follow-up will also be available for presentation. The initial findings suggest that IFCBT is a promising approach to the treatment of drug abuse/dependence among adolescents.

374 Perceived reasons for substance abuse among dually diagnosed persons

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About one-half of substance users have a comorbid psychiatric disorder, which is associated with greater impairment and poorer prognosis. Dually-diagnosed (DD) persons in recovery report significantly more difficulty with substance use than with mental disorders. Most theories of the causes of substance abuse among DD have received little empirical support; few have explored individuals’ stated reasons for substance use. Such individual perceptions, whether accurate or not, may themselves drive substance use and thus merit further inquiry. This study examines DD persons’ reasons for substance use and its relation to mental health. Ss were 310 members of a dual-focus self-help recovery group, mostly members of underserved minority groups with long histories of substance abuse and mental disorders. Primacy of onset: mental health symptoms before substance use (35%), substance use first (54%), both at same age (11%). Ss initiated substance use at 17 years (mean age) chiefly in response to peer pressure (58%), emotional issues (12%) or because caretakers were users (12%); 31% also used drugs to cope with first mental health symptoms. Alcohol (87%) and marijuana (61%) were most often used as first substances. Treatment was not sought or received until age 27 (mean); 50% went back to drug use after treatment. Major triggers to drug use: negative emotional states (e.g., lonely, bored, angry: 54%), stress (40%) and temptations to use (33%). Mean length of use = 19 years with two abstinent periods lasting 26 months (mean). Main reasons for stopping drug use: wanting a better life (54%) and negative consequences of drug use (12%). Ss (69%) reported that symptoms get worse with substance use, and 44% feel like using ‘very much’ when experiencing symptoms. Findings suggest a complex association between substance use and mental disorders among dually-diagnosed individuals. Clinical implications are discussed.

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375 BD RCT of Suboxone (Buprenorphine/Naloxone) vs Methadone/Lofexidine for stabilization and withdrawal of low dose outpatient opiate addicts

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Background: This study is the first RCT to compare stabilization on Suboxone (Sx) nad methadone (M), and also the first to compare gradual Sx withdrawal and lofexidine (L) assisted methadone withdrawal. Sx is a buprenorphine/naloxone combination in a 4:1 ratio designed to reduce misuse potential if diverted. L is an alpha-2-adrenergic agonist which causes less sedation and hypotension than clonidine. Method: 80 low dose heroin (half gm. chased or quarter gm. injected) or M (30 mg or less) users were randomized to 4 mg Sx or 30 mg M for 2–6 weeks. Patients qualified for progression to the withdrawal phase when they provided 3 consecutively opiate clean urines (taken 3x per week). Sx was reduced over 10 days (1 mg every 3–4 days) and M was reduced over 3 days with L provided for 16 days. Hypotheses: No differences during the stabilization phase were expected. During the withdrawal phase, withdrawal symptoms for L/M are expected to peak following termination of M, and for Sx to peak following termination of Sx. Withdrawals were therefore expected to be greater on days 4 – 10 for L/M, and greater on days 11 – 17 for Sx. Opiate positive urines and dropouts were expected to be greater in the L/M group. Results: L/M patients had higher withdrawal scores (\(P < 0.05\), 1 tailed t-test) during days 4–10, and were more likely to drop out of the study during the withdrawal phase (\(P = 0.003\), \(\chi^2\)). During stabilization no significant differences were detected, and contrary to expectation there were also no differences in withdrawal scores on days 11–17, and no differences in urine TES scores during withdrawal. When the stabilization and withdrawal phases were combined, all significant differences disappeared. Conclusions: Suboxone is a potential new treatment for opiate addicts with results as good as methadone in stabilization, and better that lofexidine for withdrawal.

376 Search for new, selective opioid antagonists in the 5-phenylmorphin series, using uncommon \(N\)-substituents

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Racemic \(N\)-phenylethyl-9b-methyl-5-(3-hydroxyphenyl)morphinan (3- (2-phenethyl-2-aza-bicyclo[3.3.1]non-5-yl)-phenol) was reported by Thomas et al., to have high affinity for the mu-opioid receptor, to be fairly mu selective and, most unusual, to be an opioid antagonist. We have formerly noted that an \(N\)-phenethyl-substituted phenylmorphinan enantiomer without the 9b-methyl substituent was a selective mu opioid antagonist, as determined using the same \([35S]GTP\) gammaS assay as Thomas et al. The antagonist activity apparently caused by the \(N\)-phenethyl substituent in the 5-phenylmorphinan molecule is very different from the potent agonist activity that it is known to induce in the 6,7-benzomorphan and morphinan opioids. We have now extended our work in this area in order to see whether we could find new and more potent opioid antagonists in the 5-phenylmorphinan series using more unusual \(N\)-substituents. We have synthesized about 15 enantiomeric compounds, at least nine of them having high affinity for the mu-receptor, to be mostly mu receptor mediated, opioid antagonists (e.g., \((-)-3\)-[2-[2-(3-chloro-phenyl)-ethyl]-2-aza-bicyclo[3.3.1]non-5-yl] -phenol, \((-)-3\)-[2-[2-(3-chloro-phenyl)-ethyl]-2-aza-bicyclo[3.3.1]non-5-yl] -phenol, \((-)-3\)-[2-[3-nitro-phenyl]-ethyl]-2-aza-bicyclo[3.3.1]non-5-yl]-phenol, and \((-)-3\)-[2-(o-tolyl)-ethyl]-2-aza- bicyclo[3.3.1]non-5-yl]-phenol). This corroborates and extends our initial finding (Hashimoto, et al.) that pure antagonists can be prepared in the 5-phenylmorphinan series where the 5-phenyl moiety is conformationally unrestricted. There is no alkyl group present in the molecule that might act as a barrier to its rotation in three-dimensional space. Thus, it is apparently unnecessary to fix the spatial position of the 5-phenyl ring in the 5-phenylmorphinans to obtain opioid antagonists. Qualitative change to potent and selective antagonists, rather than quantitative modification of the pharmacological profile of the 5-phenylmorphin compounds from opioid agonists to antagonists, are possibly related to the spatial position of that 5-phenyl ring, although this must be further evaluated.
Current motivation assessment instruments (e.g., URICA, SO-CRATES) evaluate clients' cognitive attributions about their readiness for change. These instruments have helped to establish that motivation for change is a predictor of treatment response. However, they do not indicate why clients are motivated or assist clinicians in retaining unmotivated clients in treatment. We interviewed over 1000 clients in a wide range of programs about their reasons for entering treatment, scored their responses according to standardized criteria, demonstrated high inter-rater reliability (> 85%) using these scoring criteria, and established the concurrent and predictive utility of the data. We then used interview responses from a random sub-set of respondents (N = 115) to generate the items and content domain for a structured interview, the STEP-UP. Protocol analysis of the STEP-UP (N = 60) confirmed that clients understood the items and instructions. Administration of the STEP-UP to clients in a wide range of programs (N = 54 at present) revealed adequate internal consistency for the 12 scales of the instrument (mean Cronbach's α = 0.70, S.D. = 0.12) and test/retest reliability (4+day interval) for the items (mean ICC = 0.67, S.D. = 0.12). Future analyses will evaluate item endorsement rates, item difficulty, factor structure, and external validity of the STEP-UP in an even larger and more diverse sample of respondents.

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378 Comparison of 2 behavioral risk tasks across multiple administrations for the assessment of risky behavior

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Behavioral tasks of risk taking have shown poor convergent validity with self-report measures of risk-related constructs and little relation to the occurrence of real-world risk behaviors. One exception is the Bechara Gambling Task (BGT; Bechara, Damasio, Damasio, and Anderson, 1994) on which riskiness is correlated with the self-reported occurrence of real-world risk behaviors including risky substance use. A potential limitation of the BGT, however, is that learning may occur over repeated administrations of the task. Learning is especially problematic when examining the influence of external variables that require repeated administrations (e.g., drugs, stress). To address such issues, we have developed the Balloon Analogue Risk Task (BART; Lejuez et al., in press) on which subjects make an increasing amount of money if balloons explode before subjects stop pumping them up. As such, the task may be less resistant to learning because it rewards risky behavior up to a certain level, at which point further riskiness is punished. In an initial study, the BART evidenced sound experimental properties, and riskiness on the task was correlated with scores on measures of sensation seeking, impulsivity, and deficiencies in behavioral constraint. Additionally, riskiness on the BART was correlated with the self-reported occurrence of addictive, health, and safety risk behaviors, with the task accounting for variance in these behaviors beyond that accounted for by demographics and self-report measures of risk-related constructs. In the current study, we compared the sensitivity of the BART and BGT tasks over three repeated administrations. The results (n = 60) indicated that learning occurred on the BGT but not the BART. Furthermore, only performance on the BART was related to a variety of real-world risk behaviors including cigarette smoking, unsafe sex, and drug/alcohol use at each of the three administrations.

379 Family transmission of alcohol use, abuse, and dependence in the CADD sample

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Familial aggregation of alcohol use and abuse has long been noted in the drug abuse literature. Using data collected by the Center for the Genetics and Treatment of Antisocial Drug Dependence (CADD) different models of family transmission of alcohol use and dependence can be tested. The CADD dataset includes a proband group, selected on the basis of entry into a drug treatment facility, a demographically matched control group, and members of each groups’ families. A structured face-to-face psychiatric interview (CIDI-SAM) that assessed DSM-IV symptoms was used to classify individuals into five groups: no alcohol use, alcohol use with no diagnosis, alcohol abuse, alcohol dependence, and dependence with withdrawal symptoms. The influence of both vertical (parent to child transmission), and horizontal (assortative mating in parents, and sibling effects in children) influences on alcohol use and abuse can be compared in these two groups, allowing for the testing of multiple hypotheses related to the family transmission of alcohol related behavior. The control group subjects had a moderate tetrachoric correlation for alcohol abuse with their parents, and a substantial correlation with their siblings. The spousal correlation in the parental generation was also substantial. This suggests that vertical familial transmission, horizontal cohort effects, and assortative mating all play a role in the familial aggregation of alcohol related behavior.

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the case in this study. Implications suggest that community follow-up and close aftercare could be important to sustain reductions in drug abuse and violence for drug users.

381 TREATMENT OF ADULT ADHD IN METHADONE MAINTENANCE PATIENTS: PRELIMINARY FINDINGS FROM A DOUBLE-BLIND, THREE-ARMED, PLACEBO-CONTROLLED TRIAL


Open trials suggest that pharmacotherapies targeting ADHD symptoms in substance abusers with ADHD may reduce both ADHD symptoms and substance abuse. This study is designed to compare the efficacy of two medications, sustained-release methylphenidate and sustained-release bupropion, to a placebo control group, using a randomized, three-armed design. All patients entering this study meet DSM-IV criteria for adult ADHD and are currently being maintained on methadone. At present, 105 patients have been entered into this 12-week study and 92 have been randomized into one of the three treatment groups. The randomized sample has been 57% male, 41% Caucasian, 37% Hispanic, and 22% African–American. About 67% of the randomized sample completed the 12-week study. Comorbidity has been common, with 16% having a current affective disorder and 20% having a current anxiety disorder. The average methadone dose for the entire randomized sample has been 85 mg/day. The medications have been well-tolerated in that most patients received the highest maximum doses allowed based on the study protocol (sustained-release methylphenidate = 80 mg/day and sustained-release bupropion = 400 mg/day). Initial power analyses require 75 completers. To date 63 individuals have completed the 12-week trial. Although the percentage of individuals who completed the entire study was slightly higher for the placebo group compared to the bupropion or methylphenidate groups (73 vs. 67 and 63%, respectively) this difference was not significant (t = 0.52, P = 0.77). Findings from this study may suggest whether pharmacologic treatments of adult ADHD have clinical utility in this specific substance-abusing population and whether one medication is clinically more advantageous than the other in treating this dually-disordered population.

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382 THE REVERSAL OF OPIOID-INDUCED RESPIRATORY DEPRESSION IN RODENTS USING THE PERIPHERALLY ACTING OPIOID ANTAGONIST, NALOXONE METHIODIDE

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Deaths due to illicit opioid overdose are a problem in Australia and throughout the world. Suggestions have also been made that in an attempt to reduce side effects, the doses of opioids administered therapeutically may be lower than that required for adequate pain control. Opioid induced respiratory depression is a major factor in these deaths and we hypothesise that peripheral mechanisms may play a role. To test this we are investigating the effects of naloxone methiodide (NAL-M) on respiratory depressed rodents. We have previously reported that high acute doses of morphine (300 mg/kg ip) depressed respiratory rate to 62 ± 1% of baseline (P < 0.0001) in male Swiss−Albino mice (n = 6). Naloxone (NAL)(0.5, 1, 2 and 3 mg/kg ip) and NAL-M (30, 50, 70 & 100 mg/kg ip) dose-dependently reversed this respiratory depression but only NAL-M did so without significant withdrawal (Lewanowitsch et al., 2001). Further investigation has found that 100 mg/kg ip NAL-M is able to reverse the respiratory depression induced by chronic morphine administration (300 mg/kg per day ip for 5 days) without the withdrawal that occurs with 3 mg/kg ip NAL. NAL-M is also effective in increasing respiratory rate with no significant withdrawal in mice administered doses of morphine (8 mg/kg ip), methadone (6.5 mg/kg ip) and heroin (17.5 mg/kg ip) that produce 80% of maximum respiratory depression (n = 4). We have now extended these studies using radiotlemetry to monitor cardio-respiratory parameters in chronically methadone treated male Sprague−Dawley rats (30 mg/kg per day ip for 5 days, n = 4) and have shown that NAL-M is effective in reversing the respiratory depression that occurs in these animals. Therefore it appears that peripheral mechanisms are involved in opioid induced respiratory depression and may be targeted to produce effective treatments for opioid overdoses.


383 THE EFFECTS OF PYRROLE N-SUBSTITUTION IN DERIVATIVES OF TETRAHYDRONALTRINDOLE AND TETRAHYDROXOMORPHINDOLE

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Introduction of substituents (e.g. benzyl) at the pyrrole N-atom of naltrindole and other pyrrolmorphinans results in interesting modification of pharmacological profiles. This study investigated the SAR of such substitution in derivatives of tetrahydro naltrindole and tetrahydrooxomorphindole. The naltrindole derivatives had high binding affinity for delta opioid receptors, but no significant selectivity. In [35S]GTPgammaS assays all compounds had very low delta efficacy and were also mu antagonists; kappa efficacy was more variable ranging nearly from full agonist ([N-cyclohexylmethyl] to antagonist (N-benzyl, N-methyl). The oxomorphindole derivatives also had high delta binding affinity with modest selectivity over mu, but substantial selectivity over kappa. In the functional assays they displayed partial agonist activity with δ = k > μ efficacy and significant selectivity in delta potency. The N-benzyl derivatives of tetrahydro naltrindole and tetrahydrooxomorphindole were studied in the PPO writhing assay in mice. The former showed substantial delta antagonist activity at 1 mg/kg and the latter had antinociceptive ED50 5.1 mg/kg, an effect that was partially reversed by naltrindole. This compound appears to be a selective delta agonist and justifies further study.

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Animal studies suggest that psychostimulant drugs preferentially increase synaptic dopamine (DA) levels in the ventral striatum/nucleus accumbens. Individual variability is substantial, and might be a trait related to both novelty seeking and drug seeking. In the present study, eight healthy men underwent two positron emission tomography (PET) [11C]raclopride scans, once following placebo, once following d-amphetamine (0.30 mg/kg, p.o.). PET data were analyzed using (i) brain parametric maps to statistically generate regions of significant change, and (ii) a priori identified regions of interest (ROI) manually drawn on each individual’s co-registered magnetic resonance (MR)
images. Compared to placebo, d-amphetamine increased extracellular DA levels, as measured by decreased [11C]raclopride binding potential (BP). Significant effects were seen in the ventral but not dorsal striatum. Change in BP in the statistically generated cluster correlated with self-reported drug-induced ‘drug wanting’ (r = 0.83, P = 0.01) and the personality trait of Novelty Seeking-Exploratory Excitability (r = 0.79, P = 0.02). The same associations were seen in the manually drawn ROI in ventral striatum but not in dorsal putamen or caudate. Changes in extracellular DA did not correlate with mood. The results suggest that (i) in humans, d-amphetamine increases DA release preferentially in the ventral striatum/nucleus accumbens, (ii) mesolimbic DA might mediate interest in obtaining reward rather than reward, per se, and (iii) individual differences in amphetamine-induced DA release might be related to predispositions to drug and novelty seeking.

385 A RANDOMIZED CONTROLLED TRIAL OF INTENSIVE OUTPATIENT, FAMILY-BASED THERAPY VS. RESIDENTIAL DRUG TREATMENT FOR CO-MORBID ADOLESCENT SUBSTANCE ABUSERS

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Study tests the effectiveness of an intensive outpatient, family-based treatment, Multidimensional Family Therapy (MDFT), with a Resident Treatment (RT), 80 subjects (Ss) are dually-diagnosed adolescent drug abusers referred for RT. Study is a two treatment (tx) conditions (MDFT, RT) by 6 time periods (intake; 2, 4, 12, and 18 months post-intake, and at termination/discharge) randomized design. Hypothesis includes: (1) The progression of adolescent symptoms over time (drug use and co-morbidity) in the two tx s will reflect differences in the rate of change between the two tx s at 2 months post-intake with Ss participating in RT evidencing more improvement than Ss receiving MDFT. A reversal will begin to occur between 12 and 18 months post-intake with MDFT Ss showing more improvement than Ss receiving RT. (2) Parent involvement with their adolescent measured at 2 months post-intake will predict improvement in (a) parenting behaviors and (b) adolescent life skills at 4 months post-intake. (3) Improvement in parenting and adolescent social skills at 4 months post-intake will predict reduction in adolescent symptoms at termination, and 12–18 months post-intake. (4) Improvement in (a) social skills and (b) adoption of philosophy and behaviors of 12-step model at 4 months post-intake will predict reduction of adolescent symptoms and improved functioning at termination, and 12–18 months post-intake. Intent to treat analyses conducted with HLM methods. Preliminary findings: from intake to discharge, the outpatient family-based tx was equally effective as RT in reducing marijuana use and externalizing symptoms. 12 months after intake, RT Ss report increasing their marijuana use after their discharge front tx; while MDFT Ss continue to show a reduction in their marijuana use, after tx ends. These effects persist at 1 year fu. Study is first randomized study to compare RT versus outpatient tx for ASUD. Findings reveal that an effective family-based outpatient tx alternative can achieve equal or superior outcomes to RT with comorbid adolescents. Policy and referral practices for the residential treatment of comorbid, drug abusing teens can be reexamined in the context of empirical evidence of this kind.

386 SCREENING FOR SEXUALLY TRANSMITTED INFECTIONS IN SUBSTANCE ABUSE TREATMENT PROGRAMS: PREVALENCE AND SCREENING CRITERIA

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Hypothesis: New technology enables the use of urine samples to screen for sexually transmitted infections (STI). We hypothesized that universal STI screening in substance abuse treatment settings would detect Chlamydia or Gonorrhea infections in 5% or more clients, both asymptomatic and in those not meeting recommended CDC guidelines for screening. Number of Subjects: 670 (406 clients of a detoxification program [Detox] and 174 from a methadone maintenance program [MM]). Procedures: All subjects (n = 670) provided urine samples and 80% (533/670) completed an interview including demographics, substance use history, prior STIs, current STI symptoms, and sexual risk behaviors. Statistical Analyses: Descriptive summary statistics. Results: STIs were diagnosed in 0.9% of all subjects (5/670). Subject (n = 533) characteristics were as follows: 67% male; median age 37 years; 33% Black, 26% Hispanic, 36% White and 5% Other. Primary drugs of choice were alcohol (18%), cocaine (11%), and heroin (65%). Prior STIs (including HIV) were reported by 40% (211/533) of all subjects. Of subjects who reported being sexually active within the previous two months, 42% (178/422) reported more than one sexual partner. 74 subjects reported genitourinary symptoms. No subject tested positive for Gonorrhea; five (0.9, 95% CI = 0.1–1.8%) had Chlamydia. No STI was detected in MM subjects, which represented 74% (174/235) of all MM clients. All five Chlamydia positive subjects fell within the CDC guidelines for STI screening (age less than 25 years, inconsistent use of barrier method, new or more than one sex partner in the past three months, current STI). Although 2.7% (274) of subjects with STI symptoms had Chlamydia, three of five Chlamydia positive subjects were asymptomatic. Chlamydia prevalence was 2.2% (5/227) among those who met CDC guidelines. Importance of Findings: Based on prevalence, universal screening for STIs in substance abuse treatments programs is not warranted. Current CDC screening guidelines adequately detect the small percentage of persons with STIs.

387 BACK TO BASICS: WHAT DO THE DIS, CIDI, AND SAM ASSESSMENTS COVER?

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Over the past 15 years, the Epidemiology and Prevention Research Group at WUSM has been developing assessments for diagnosing substance use disorders and presenting these assessments at CPDD. Although only a small proportion of researchers have been assessing substance use disorders, the trend is changing and more investigators are becoming aware of the need to assess these disorders. Our group is a training center for the Diagnostic Interview Schedule-IV (DIS), the Substance Abuse Module (SAM), and the World Health Organization-Composite International Diagnostic Interview (CIDI). This requires us to answer questions on a regular basis about the differences and coverage of the assessments. It occurred to us that we need to return to the basics of similarities and differences between these assessments at this year’s CPDD. The topics covered in this comparison will include: diagnostic systems, socio-demographic factors, risk and protective factors, the course and severity of the disorders, other diagnoses covered, training needed, algorithms for diagnoses, and different ways to administer these assessments. Additionally, the cost and time of administration will be compared. The purpose of these comparisons is to identify the similarities and differences between the interviews, in order to assist investigators in selecting the assessment that will most benefit their research, and which will enhance the growing body of epidemiological prevention and treatment literature.

388 EFFECTS OF MARIJUANA AND PARTIAL SLEEP DEPRIVATION ON MOOD, EQUILIBRIUM, AND SIMULATED DRIVING

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This study tested the hypothesis that impairment by marijuana (MJ) of both standing balance and brake latency in a driving simulator would be greater following partial sleep deprivation (PSD) than after a full night of sleep. Five healthy subjects who regularly used MJ completed six test sessions in a counterbalanced within-subject design. Each session began with an overnight stay in a sleep laboratory. Bed and wake times were calculated based on mean data from individual sleep diaries. Time-in-bed was either regular (mean 8.3±0.5 h) or shortened (35% of regular time-in-bed, with bedtime delayed). At 2 and 4 h after waking, sleepiness was measured with sleep latency tests and self-report questionnaires. Approximately 6.5 h post-waking, subjects smoked a cigarette (0, 2, or 3.5% THC). Test batteries were completed 2, 62, and 122 min after smoking. PSD and MJ had expected subjective effects. Sleepiness was significantly greater following PSD than after regular sleep. Ratings of ‘high’ were unaltered by PSD but increased with both MJ doses (P<0.1). MJ (3.5% THC) increased body sway only after PSD (P<0.1). There were no significant effects of MJ or PSD, alone or in combination, on brake latency. Consistent with our prior marijuana research, the present results suggest that increased body sway from MJ-PSD combinations may not coincide with increased response time while driving.

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389 ATTENUATION OF COCAINE SELF-ADMINISTRATION BY SUBSTITUTED TROPANES: RELATION TO DOPAMINE TRANSPORTER OCCUPANCY DETERMINED BY PET IN RHESUS MONKEYS

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The reinforcing and psychostimulant effects of cocaine are thought to be mediated by the dopamine transporter (DAT). Thus, recent efforts to develop a substitute agonist pharmacotherapy for cocaine addiction have targeted DAT. This study compared the effect of pretreatments with either the selective dopamine uptake inhibitor, RTI-177, or the mixed action dopamine/serotonin uptake inhibitor RTI-112 on cocaine self-administration under a second order, fixed interval 600 s (FR20:S) schedule of cocaine-reinforced responding in rhesus macaques. Daily experimental sessions consisted of five consecutive fixed intervals each followed by a 60 s timeout. Drug pretreatments were administered i.v. 15 min before the cocaine self-administration session. Each pretreatment dose was tested on three consecutive days on two separate occasions. RTI-177 and RTI-112 are both substituted tropanes with similar IC50s for both binding and uptake in rat tissue in vitro. In vivo locomotor data showed similar efficacy and less than a 3-fold difference in potency in stimulating horizontal movement in mice. When tested as pretreatments to cocaine self-administration in rhesus monkeys, however, a much larger difference in potency was observed. In this assay, RTI-177 was more than 6-fold less potent in decreasing cocaine-reinforced responding than was RTI-112. ED50 for attenuation of cocaine reinforced responding was 0.11 mg/kg for RTI-177 and 0.017 mg/kg for RTI-112. Reductions in cocaine reinforced responding with pretreatments of RTI-177 were associated with significant occupancy of the dopamine transporter (>70%) as measured using positron emission tomography (PET) in the same animals. Studies are in progress to assess the level of DAT occupancy associated with behaviorally equipotent doses of RTI-112. These studies will elucidate whether the increased potency of RTI-112 to attenuate cocaine reinforced responding is associated with similar levels of dopamine transporter occupancy as effective doses of RTI-177.

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390 IMPROVED DETECTION OF LIMBIC ACTIVATION IN COCAINE CRAVING BY AN AUTOMATED ROI ANALYSIS WITHOUT A-PRIORI HYPOTHESIS

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Limbic transitions pose unique challenges to functional MRI. Conventional fMRI paradigms detect comparatively rapid transitions between ‘cognitive’ states (e.g. ‘finger tapping’ vs. ‘not tapping’, ‘working memory,’ etc., ~ several seconds). Unfortunately, an existing body of evidence suggests that transitions slower than 60–90 s, such as a ‘craving transient,’ will be obscured by low frequency or ‘pink’ noise, a ubiquitous phenomenon in nature now well established in fMRI. Several neuroimaging groups, including our own, have begun to characterize the brain substrates of cue-induced craving. How rapidly patients ‘transition’ into the craving state may be a sensitive marker of vulnerability to relapse. We compared 13 patients with significant histories of cocaine addiction with 12 normal control subjects using our group’s cocaine craving cue-induction paradigm with fMRI. Preliminary analysis (SPM99) yielded significant activation in the right amygdala only, presumably due to insufficient statistical power in the face of the ‘pink’ noise phenomenon. Using a digital brain atlas registered to Talairach space, the Display function within SPM99 was altered to support an atlas-based automated ROI function without an a–priori hypothesis concerning the location of the region of interest. The following structures were detected: left and right amygdala, right hippocampus, left and right globus pallidus. The automated ROI analysis thus appears to be superior in assigning activation to limbic structures, and as such may represent an approach to compensating for the difficulties associated with ‘pink noise’.

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391 ANTAGONISM OF THE HYPERLOCOMOTIVE AND HYPERTHERMIC EFFECTS OF (+)-3,4-METHYLENE-DIOXYMETHAMPHETAMINE BY THE SELECTIVE 5-HT2A RECEPTOR ANTAGONIST M100907

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The psychostimulant 3,4-methylenedioxymethamphetamine (ecstasy, MDMA) is an abused drug of increasing popularity in young adults. MDMA evokes hyperlocomotion and hyperthermia in rodents and serotonin (5-HT) is thought to mediate these effects. The selective 5-HT2A receptor (5-HT2AR) antagonist M100907 has been shown to attenuate hyperactivity induced by (+)-MDMA, and nonelective 5-HT2R antagonists completely prevented hyperthermia in an animal model of the 5-HT syndrome. In the present experiment, we tested the hypothesis that M100907 would attenuate the hyperlocomotion and hyperthermia induced by the more behaviorally-active enantiomer (+)-MDMA. Male Sprague-Dawley rats (N=8), habituated to the photobeam activity monitors, were pretreated (ip) with 10% beta-cyclodextrin (vehicle) or M100907 (0.5, 1, 2 mg/kg) 45 min before an injection (sc) of saline or (+)-MDMA (3 mg/kg). Locomotor activity was then recorded for 90 min. M100907 alone did not alter basal activity and all doses of M100907 decreased (+)-MDMA-evoked hyperactivity by ~50% (P<0.05). To establish the ability of M100907 to shift the dose-effect curve for (+)-MDMA (0-12 mg/kg), rats (N=12–16) were treated (sc) with saline or (+)-MDMA (2–16 mg/kg) 45 min after pretreatment with vehicle or M100907 (1 mg/kg). Locomotor activity was assessed for 90 min and measurement of rectal temperature was taken as subjects were removed from the activity monitors. The results show that (+)-MDMA (0–12 mg/kg)
dose-dependently increased both locomotion and body temperature. Pretreatment with M100907 (1 mg/kg) down-shifted the dose-effect curve for (+)-MDMA and suppressed the maximal response observed at 12 mg/kg of (+)-MDMA. M100907 also completely prevented hyperthermia induced by (+)-MDMA (P < 0.01). These results suggest that 5-HT2A receptors play an important role in the behavioral and hyperthermic effects of (+)-MDMA and so should be a good target for finding pharmacotherapies of MDMA dependence.

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392 CHARACTERISTICS OF OLDER METHADONE MAINTENANCE (MM) PATIENTS

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Introduction: Little research has examined older MM patients to assess whether they have distinctive characteristics or special needs. Purpose: To characterize the demographic, medical, psychiatric, quality of life, and substance use characteristics of MM patients age 50 years or older.

Methods: 30 current MM patients aged 50–66 years drawn from an outpatient treatment program that uses methadone were assessed on demographics, medical diagnoses, psychiatric diagnoses (DSM IV Axis I), Addiction Severity Index variables, recent substance use, and quality of life (SF36v2). Results: 15 males and 15 females were enrolled. The group had the following means: age 54.3 years (standard deviation 3.96), education 11.2 years, lifetime arrests 8 (males 13, females 3), lifetime months incarcerated 60.5 (males 107.3, females 13.8), monthly earnings $490, and in ongoing treatment currently for 5.3 years. 3 subjects (10%) were currently married, 13 (43.3%) were caucasian, 17 (56.7%) were black. 8 subjects (26.7%) had a current and 16 (53.3%) had a lifetime Axis I diagnosis other than substance abuse/dependence. The most common current and lifetime Axis I diagnoses other than substance abuse/dependence were Major Depression (n = 10, 33.3%) and Bipolar Disorder (n = 3, 10%) respectively. The most common lifetime substance abuse/dependence diagnoses excluding opioid dependence were: 73.3% (n = 22) alcohol and 66.7% (n = 20) cocaine. 11 subjects (36.7%) reported use of alcohol, marijuana, cocaine, heroin, or street bought methadone in the past 30 days, however, only 5 subjects were currently drug dependent: 2 (6.6%) marijuana dependent and 3 (10%) cocaine dependent. Subjects reported 15.7 days of the last 30 with medical problems. 15 (50%) had hypertension, 11 (36.6%) had arthritis, 7 (23.1%) had hepatitis C, 3 (10%) had HIV, 3 (10%) had diabetes mellitus, and 3 (10%) had cirrhosis. All eight scales of the SF-36 showed significantly worse functioning than population norms for same aged individuals. Conclusion: Older MM patients have high rates of psychiatric and medical illness with poor quality of life despite low current rates of substance abuse and dependence.

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393 PERCEIVED MOTIVATIONS FOR TREATMENT ENTRY AND RETENTION IN DEPRESSED, SUBSTANCE-DEPENDENT ADOLESCENTS WITH CONDUCT DISORDER

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Substance-dependent (S.D.) adolescents with conduct disorder (CD) rarely self-refer to substance treatment and are often poorly motivated, requiring court order to enter and remain in treatment. Little is known about such youth’s perceived motivations for treatment entry and retention and whether these factors change if incentives or free treatment is provided. Methods: We report pilot data for 10 depressed adolescents (13–19) with S.D. and CD regarding their perceived motivations for treatment entry and retention in a 16-week controlled trial providing free, non-mandatory treatment for S.D. (cognitive behavioral) with concurrent pharmacotherapy (fluoxetine/placebo) for depression. Subjects were compensated for participation in the medication arm. About 10 of 11 subjects randomized to the trial completed the semi-structured Treatment Exit Interview (TEI) assessing self-reported motivations for treatment entry and retention. Results: Primary reasons for study entry sorted into three categories: (1) court-ordered (50%); (2) expectation of improvement in depression and/or life problems (30%); (3) treatment was ‘free’ and/or monetary incentives were provided (20%). 9/11 subjects completed the 16 week study with 36% self-referred. Primary reasons reported for high treatment retention fell into two categories: (1) Improvement in depression/life problems (60%) and (2) caring relationships with therapists/clinic staff (40%), with most reporting that connection to study personnel was important even if not given as the primary reason for remaining in treatment. Conclusion: Treatment entry among depressed adolescents with S.D. and CD may be improved if incentives or free treatment is provided. Treatment retention in such youth may be enhanced by their experience of connected caring relationships with treatment providers emerging later in the course of treatment.

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394 SUBSTANCE USE TREATMENT EXPERIENCES OF TRANSGENDERED MEN AND WOMEN

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Discrimination against transgendered individuals can make their access to health services highly problematic. More specifically, substance use treatment programs may not be sensitive to transgendered individuals who have drug use problems. Because of this, the needs of transgendered individuals may go unmet. A knowledge base must be built to aid substance use service providers in developing policies to increase their effectiveness when working with transgendered men and women. This study will examine (a) factors that may influence transgendered men and women’s substance use, (b) problems that may hinder their access to substance use treatment, (c) and problems they may face within such programs. Transgendered men and women were given self-administered questionnaires. The chief analytic task was to examine relationships between people’s experiences of discrimination and physical/verbal abuse due to being transgendered, their experience in substance use treatment and other health services, and their substance use history. Bivariate analysis was conducted for this study. Many study participants reported experiencing some form of discrimination within the past year. Over half the sample reported participating within some form of drug or alcohol treatment, while approximately two-thirds reported participating within a self-help group (AA, NA, etc.). Generally, of those in treatment and self-help groups, many reported a lack of support from staff and verbal abuse by other clients. Many programs do not have programs that support transgender men and women. Transgendered/transsexual men and women can vary in many different ways and in ways that may not be readily noticeable by service providers. They will likely face problems that are unique to them, and face problems within treatment and self-help contexts. All these will need to be addressed within their treatment plan.
Religiosity and racial/ethnic identity are often cited as important considerations in treatment-seeking and recovery. But there is little formal research on these two constructs, and their relevance for treatment and recovery is not well understood. We explored relationships between religiosity and aspects of racial/ethnic identity among patients receiving narcotic substitution therapy in a clinical trial comparing the effects of LAAM and methadone maintenance on HIV risk behavior. The analytic sample included 125 African Americans, 114 Latinos, and 59 Whites (non-Hispanic). Religiosity was positively and significantly related to ethnic identification and group affirmation among both African Americans and Latinos; the magnitude of relationships was moderate and very similar between these two groups. A positive relationship between religiosity and other-group orientation appeared among African Americans and Latinos and was particularly strong among African Americans. None of these relationships was evident among Whites. The findings suggest that religiosity may be an important aspect of identity for African Americans and Latinos in treatment. In both communities, the church has traditionally played a prominent role in addressing pressing social and health issues. Treatment professionals can utilize this historical foundation by incorporating and recognizing religiosity when designing treatment interventions for African Americans and Latinos. For example, attention to issues of religiosity and group identity in counseling and community re-entry may be more effective if this relationship is taken into account. In addition, because of the link between religiosity and other-group orientation, treatment climate may be enhanced in programs serving mixed non-White populations if opportunities for voluntary expression of religiosity (e.g., group prayer or Bible study) are provided.

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396 Correlation between hair morphine concentration and self-reported use of heroin

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In treatment evaluation studies of current or former heroin users analysis of urine samples for morphine is widely used as an objective indicator of heroin use. Although attempts have been made to use quantitative data (urine morphine concentration), most studies rely on frequencies of morphine positive results. Urinalysis has disadvantages that include the necessity for frequent collection because of the brief duration over which morphine is detectable following heroin administration, the intrusiveness of the procedure and the difficulty of collection in some community settings. Hair analysis offers a number of advantages over urinalysis, but there has been relatively little validation in the population studied in clinical trials. In the present study results from analysis of the morphine concentration of 1 cm hair samples were correlated with subjects’ self-reported frequency of heroin use in the previous month (n = 301). Morphine concentration was quantified by gas chromatography/mass spectrometry. There was a significant correlation between morphine concentration and self-reported use of heroin in the month preceding the collection of hair sample (Spearman’s ρ = 0.721; P < 0.01). While this correlation was highly significant at morphine concentrations of 0 – 1 ng/mg (ρ = 0.594; P < 0.01), at concentrations higher than 1 ng/mg the relationship between these two variables was not significant (ρ = 0.063; P > 0.05) indicating a plateau of the effect. Fourteen percent of subjects who reported no heroin use, 83% percent of subjects who reported 3 – 5 injections and 94 – 98% of subjects reporting 6 or more injections in the previous month were positive for morphine. Thirty three percent of subjects with zero morphine concentration reported heroin use in the previous month, of these, 24% reported only one or two occasions of use and the remaining 9% used on three or more occasions. These results suggest that the detection of morphine in hair is a sensitive indicator of recent heroin use. Morphine concentrations over the range of 0 – 1 ng/mg reflect the magnitude of heroin use.

397 The drug evaluation network system: expanding into a national random sample

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The Drug Evaluation Network System (DENS) was developed in 1996 to gather clinical information on patients presenting for substance abuse treatment in programs throughout the nation. Pilot data have been collected from Philadelphia, New York, Chicago, San Francisco and Albuquerque since 1996, later from Miami (1999) and Los Angeles (2001). Data on patients’ medical, employment, drug, legal, family/social and psychiatric history and status upon entering treatment is collected by program staff using a computerized version of the Addiction Severity Index (ASI). This system provides the opportunity for nearly ‘real-time’ tracking of trends in different areas of the country over time. Data presented at CPDD will reflect approximately 32,000 records collected up to the week prior to the conference and will provide updated findings on information presented at earlier CPDD conferences. For example, 50% of 16 – 25 year olds presenting for treatment in Philadelphia in 1999 reported injecting heroin. The heroin rates increased to 67% in 2000, and returned to 1999 levels (52%) in 2001. Additionally, in 1999 and 2000, amphetamine rates continued to be near or below 1% for DENS sites in Philadelphia, Chicago, New York, and Miami. In San Francisco, drug courts’ amphetamine use rates have increased from 25% in 2000 to 32% in 2001, while treatment programs’ rates have decreased from 6% in 2000 to 4% in 2001. During first Quarter 2002, DENS will expand to a national random sample of programs. This presentation will include data collected from the random sample, as DENS begins to provide information that truly represents clients presenting for treatment throughout the nation.

398 Objective motion detection and correction in time series fMRI experiments conducted on cocaine-dependent subjects

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Subject motion has been widely recognized as a source of artifact in functional magnetic resonance imaging (fMRI) data. This becomes particularly important in stimulant administration studies, where patients typically exhibit especially large movements. Methods for correcting for this motion exist; however, their relative merits remain unknown, largely due to the lack of accurate real-world motion standards. Motion correction algorithms differ widely in their results. For example, when applied to an fMRI data set, anterior-posterior motion estimates from AIR and DART had a correlation coefficient of only 0.388 (640 consecutive, T2* weighted, axial images). Such a low
correlation coefficient implies that the two methods return quite different estimates of subject motion; subsequent corrected images will differ significantly, as may statistical inferences derived from the corrected images. We have measured movement of human subjects in real time, and of phantoms, during MRI data acquisition using state-of-the-art infrared motion analysis. Based on this accurate motion standard, we evaluated several motion correction algorithms, and present their relative strengths and weaknesses.

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399 POLYDRUG ABUSE PATTERNS WITH MDMA (ECSTASY) AMONG YOUNG ADULTS
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In recent years there has been a significant increase in the incidence of using the ‘club drug’ MDMA (Ecstasy). It is generally believed that MDMA is frequently used in combination with other drugs, but the pattern of such combinations has not been empirically measured. The present study was conducted to document the actual use of MDMA with other drugs, craving for MDMA and sleep-wake patterns of young adults who report using MDMA on an occasional basis. Two adult male and three female volunteers (age 23.6±3.7 years) agreed to wear a small wrist actigraphy (ActWatch-Score™, MiniMitter) device for 4 weeks. This device contains an accelerometer and records sleep-wake activity on a continuous basis. The device has a numerical faceplate and a pushbutton that allowed the subjects to manually enter

consumption, few studies have investigated the effects of alcohol cue exposure on P300 activity. To investigate the effects of familial alcoholism on brain electrical activity in response to alcohol cue exposure, 23 female moderate social drinkers (aged 21–25 years) with a history of familial alcoholism (FHP, n = 10) and without such a history (FHN; n = 13) participated in an auditory oddball task following presentation both to neutral and alcohol-related visual, tactile, and olfactory cues. Preliminary analyses of data from 14 subjects (7 FHP and 7 FHN) have been completed. Baseline values were subtracted from values obtained following neutral cue exposure and alcohol cue exposure to yield change from baseline scores for each condition. A 2 (FHP vs 2 (cue) repeated measures MANOVA conducted on CZ, FZ, and PZ revealed a FH × cue interaction on PZ, indicating that P300 activity over the occipital cortex was attenuated in FHP females subsequent to alcohol cue exposure relative to neutral exposure. Conversely, FHN females had an increase in P300 activity following presentation of alcohol cues compared to neutral cue presentation. These data suggest that alcohol cue exposure can elicit a physiological response similar to that observed after actual alcohol consumption in FHP females. The findings also support the potential utility of the P300 paradigm with alcohol cue exposure as a biological marker in the identification of individuals at risk for developing alcohol problems.

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401 CHANGES IN ADDICTION SEVERITY BETWEEN ADMISSION AND RE-ADMISSION
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‘Revolving door’ treatment is a problem familiar to everyone in the substance abuse field. At our inner-city intensive outpatient clinic, for example, some 16% of intakes are re-admissions. Are these patients likely to be better or worse in addiction severity than at their first admission? A case could be made for either: Better, because they may be more stable and willing to seek help. Worse, because of relapses and a longer history of substance abuse. Success in the first treatment or length of time between admissions might also affect differences. We compared Addiction Severity Index scores at admission and re-admission for 72 patients (mostly cocaine abusers) admitted over the past 6 years. As expected, admission and re-admission scores tended to be highly correlated (highest: Legal Composite, r = 0.86, P < 0.001), but there were exceptions: 3 of the 7 (interviewer-rated) severity scores (Employment, Drug, Family/social) were non-significant. Overall, there was no consistent change for better or worse between admissions (11 of 14 scores NS by paired-sample t-test). Legal and Family/social Composite scores did worsen (respectively, 0.034–0.058; 0.061–106, both P < 0.05). However, the Drug Severity score improved between the two admissions, from 6.73 to 6.06 (P < 0.05). The above patterns tended to be stronger for brief intervals between admissions. Time in treatment at first admission and other measures of treatment success were largely unrelated to changes by the second admission. We find these results intriguing, and hope to separate psychometric and severity-related effects in future work.

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402 BEHAVIORAL AND MOTIVATIONAL EFFECTS OF ‘RINGE’ COCAINE SELF ADMINISTRATION IN MALE AND FEMALE RATS
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Although several studies have shown that individuals with a family history of alcoholism show an attenuated P300 response to alcohol consumption, few studies have included females and none have...
Chronic cocaine self-administration can produce profound behavioral and motivational changes, and these changes may differ between males and females. The purpose of the present experiment was to characterize the effect of 'binge' cocaine self-administration on subsequent responding for cocaine under both fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. A discrete trials (DT) procedure was used that allowed rats 24-h access to cocaine for 7 days. Discrete trials were initiated every 15 min for a total of 4 cocaine injections (1.5 mg/kg) each h. Previous work with male rats has shown that under these conditions animals self-administer cocaine in noncircadian, ‘binge’ patterns and maintain high levels of intake. Responding under an FR and a PR schedule was assessed prior to and following the DT procedure. Preliminary results show that although females self-administer lower levels of cocaine, ‘binge’ self-administration has a greater effect on subsequent responding in females rats. Specifically, mean inter-injection intervals observed under the FR schedule and break points observed under the PR schedule were markedly reduced in females compared to males following ‘binge’ self-administration. These findings indicate sex differences in behavioral and motivational aspects of cocaine addiction following chronic intake. Whether these sex differences are due to differences in the development of tolerance or toxicity is currently under investigation.

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403 ESCALATION OF ILLICIT DRUG USE IN EARLY-ONSET CANNABIS USERS VERSUS CO-TWIN CONTROLS

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Previous studies have reported that early initiation of cannabis use elevates subsequent risks of other illicit drug use and drug-related problems. This study examines whether this association persists after controlling for genetic and/or shared environmental influences on both early cannabis use and drug related problems. 311 young adult MZ and DZ same-sex twin discordant for cannabis use before age 17 were compared on subsequent measures of illicit drug use and abuse/dependence. Individuals who used cannabis by age 17 had odds of other drug use and drug abuse/dependence that were 2.1–5.0 times higher than those of their co-twin who did not use cannabis before age 17. Controlling for known risk factors (parental conflict/separation, childhood sexual abuse, conduct disorder, major depression and social anxiety) had only negligible effects on these results. These associations did not differ significantly between MZ and DZ pairs and were also observed when analyses were restricted to discordant MZ twins. Associations between early cannabis use and later drug use and drug abuse/dependence cannot be explained by common predisposing genetic or shared environmental factors. The association may arise from the effects of the peer and social context within which cannabis is used and obtained. In particular, early access to and use of cannabis may reduce perceived barriers against illicit drug use and provide access to other forms of illicit drugs.

404 TEMPORAL LOBE BRAIN ABNORMALITIES IN OPIOID-DEPENDENT SUBJECTS OBSERVED WITH STATISTICAL PARAMETRIC MAPPING OF STRUCTURAL MAGNETIC RESONANCE IMAGES


Objective: To explore changes in gray matter density in opioid-dependent subjects using voxel-based morphometry. Methods: Brain MRI was performed using a 1.5 Tesla GE whole body imaging system. A three-dimensional spoiled gradient echo pulse sequence was used to produce 124 1.5-mm-thick contiguous coronal images (TE = 5 msec, TR = 35 msec, 256 × 192 matrix; FOV = 24 cm, Flip angle = 45, 1 NEX) for 36 opioid-dependent subjects, who were newly enrolled in methadone maintenance program, and 36 age- and sex-matched healthy comparison subjects. Images were spatially registered into a standardized proportional stereotaxic space, segmented into gray, white matter, and CSF. Segmented gray matter images were converted into binary images and then smoothed using a 8-mm full width at half-maximum isotropic Gaussian kernel. Statistical Parametric Mapping 99 was used to calculate differences in gray matter densities in the opioid group, relative to the comparison group. Results: Opioid-dependent subjects had significantly decreased gray matter density in both temporal lobe regions of the brain, as compared to healthy comparison subjects (corrected p-value = 0.01, height threshold t = 5.37, extent threshold = 50 voxels). Regions of decreased gray matter density include left superior temporal gyrus, left uncus, and right middle temporal gyrus. Conclusion: This study reports region-specific decreases in the gray matter density in opioid-dependent subjects. Findings of the current study may underlie the impaired cognitive performance observed in opioid-dependent subjects.

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405 COCAINE-INDUCED NORADRENERGIC AND METABOLIC CHANGES IN THE NONHUMAN PRIMATE BED NUCLEUS OF THE STRIA TERMINALIS

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The bed nucleus of the stria terminalis (BNST) has been shown to play a key role in the integration of limbic and neurovegetative functions, and in responses to stress. The BNST receives inputs from limbic regions, such as the amygdala, and sends projections to regions involved in drug reinforcement, including the nucleus accumbens shell and the ventral tegmental area. The BNST also possesses high densities of norepinephrine (NE) fiber inputs. NE and dopamine (DA) are both removed from the synaptic space by the norepinephrine transporter (NET). In fact, the NET possesses an even higher affinity for DA than for NE. Consequently, DA binding at the NET may contribute to the effects of cocaine. The role of the present experiment was to determine if cocaine induces significant functional metabolic and transporter changes in the monkey BNST. Rhesus monkeys self-administered cocaine (0.3 mg/kg per inf) for 0, 5, or 100 days. In vitro binding to the NET in the BNST was conducted using [3H]nisoxetine autoradiography, while local cerebral glucose utilization (LCGU) in the same subjects was determined using the 2[14C]deoxyglucose (2-DG) method. The results revealed that only chronic cocaine self-administration significantly increased NET binding site densities (up to 59%) in all examined subregions of the BNST. In addition, all subregions of the BNST displayed significantly reduced LCGU after both 5 and 100 days of cocaine administration (up to 31.6%). Negative correlations were found between NET density and LCGU in all subregions of the BNST. The results further indicate that the functional effects of cocaine on LCGU preceded its effects on NET density. The profound cocaine-induced changes in the density of NET binding site distribution in conjunction with considerable metabolic changes in the BNST strongly implicate the BNST as an important component in cocaine self-administration. Supported by DA09085 (LJP), DA06634 (CNI-DA), and DA07246.
406 THE TROPANE HORSE: A NOVEL COCAINE ANTAGONIST STRATEGY?

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The psychostimulant properties of cocaine have been attributed to blockade of the dopamine transporter in various brain regions. Based on this premise, compounds that target the dopamine transporter are prominently represented in medications development to treat cocaine addiction. In consideration of the diversity of addictions, cocaine drug therapies should contain an array of cocaine-like agonists with reduced addictive potential and cocaine antagonists. The design of a cocaine antagonist at the dopamine transporter is challenging. We devised compounds that theoretically would react covalently with reactive residues on the dopamine transporter, undergo a secondary reaction to release the bulk of the compound but allow a fragment to remain covalently linked to the transporter. This remnant would interfere with cocaine access to the dopamine transporter. HEK-293 cells transfected with the human dopamine transporter (hDAT) were incubated with ‘tropane horse’ candidates, control compounds or with vehicle for various times. The ‘tropane horse’ was removed by extensive rinsing of cells and both [3H]cocaine binding and [3H] dopamine transport assays were conducted. In control cells [3H]cocaine binding was significantly altered by the ratio of high and low affinity [3H]cocaine binding sites. These studies highlight the potential for developing cocaine antagonists, compounds that reduce the potency of cocaine for blocking dopamine transport.

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407 PARTICIPATION IN 12-STEP-BASED FELLOWSHIPS AMONG DUALLY DIAGNOSED PERSONS

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Participation in 12-step groups (12SG) has been found helpful in maintaining abstinence from substance use. Many substance users are dually-diagnosed with a comorbid psychiatric disorder. 12SG are underutilized by such persons. There has been little research about 12SG affiliation in this population. This paper examines participation in both dual focus and traditional 12SG among dually-diagnosed persons. 278 members of Double Trouble in Recovery (DTR), a 12 step-based fellowship addressing recovery from dual-diagnosis, were re-interviewed a year after baseline. 52% were members of underserved minority groups with long histories of substance abuse and mental health disorders. At follow-up, 71% were attending DTR, 67% a traditional 12SG (e.g., AA or NA); 51% were attending both. Frequency of attendance was high for both types of groups; meeting participation (e.g., speaking in meeting) was high for DTR, low for other 12SG. Level of engagement in 12-step recovery activities varied across behaviors (e.g., working the 12-step program, reading recovery literature). Recovery from addiction was cited as the main reason for attending DTR (57%) and traditional 12SG (76%). Dual diagnosis mentions were also cited for attending DTR (33%). Main obstacles to DTR attendance centered on availability. Main reasons for not attending other 12SG: Does not meet my needs and ‘don’t need it right now’. Most often cited DTR primary benefit: The focus on mental health. A diagnosis of schizophrenia and self-reported abstinence at baseline were significantly associated with greater DTR attendance at follow-up: being more troubled by substance abuse than by mental health at baseline was associated with greater attendance at both types of groups at follow-up. Dually-diagnosed clients can and do engage in both dual-focus and traditional 12SG. Clinical implications are discussed, including the need to find one’s own comfort level to maximize participation and resulting benefits.

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408 CHEMOKINES AND CHEMOKINE RECEPTORS IN LONG-TERM NON-PROGRESSORS (LTNP) OF HIV INFECTION: ROLE OF DRUG ABUSE

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Long-term non-progressors (LTNP) represent a minority of HIV infected patients in whom an effective immune response is known to play a significant role in prevention of disease progression. Previous studies showed that chemokines can suppress HIV infections and chemokine receptors function as co-receptors for HIV entry into target cells. Although drug abuse has been associated with increased HIV infection and progression of disease, the effect of drug use on the expression of chemokines and their receptors has not been extensively studied. We hypothesize that chemokines such as MIP-1b, and IL-8 may be upregulated in LTNP compared to patients with active HIV infections. Peripheral blood mononuclear cells (PBMC) cells from HIV infected LTNP (n = 8) and patients with active disease who are using cocaine (n = 8) and not using cocaine (n = 8) and normal controls (n = 8) were examined by flow cytometry for the phenotypic expression of the chemokines, MIP-1b and IL-8, and the chemokine receptors CCR5, CCR3 and CXCR2. Our results show that MIP-1b (P < 0.05) and IL-8 (P < 0.05) positive lymphocytes were significantly higher in LTNP compared to patients with active HIV infections irrespective of cocaine use. Further, patients with active HIV infections who are current drug users showed significantly higher percentages of CCR3 and CXCR2 positive lymphocytes compared to similar patients not using cocaine. No significant differences were observed for the expression of CXCR2 and CCR3 coreceptors between LTNP and drug using patients with active disease. These results support the premise that chemokines play a significant role in host defense against HIV infection and slow HIV disease progression in LTNP.

409 GROUP MOTIVATIONAL INTERVENTION IN DRUG ABUSE TREATMENT


This study examined the integrity of a new 20-session group motivational, cognitive-behavioral treatment (CBMT) for outpatient substance abusing clients, relative to a 20-session group CBT condition. Both interventions were theory based and manual driven. Hypothesis: Consistent with the Self Determination model of motivation upon which CBMT is based, we predicted that CBMT would be perceived by subjects as more ‘autonomy supportive’, while two additional constructs of the treatment process, (therapeutic alliance and group climate) would not be differentiated by group. Methods: Substance
abusing/dependent persons presenting for treatment were voluntarily randomly assigned to: (1) CBMT condition-a 4 session motivational group, followed by a 16 session cognitive-behavioral/motivational group, or (2) CBT condition-a 20 session cognitive-behavioral group. Motivational process data was collected at baseline, 2 and 10 weeks (end of treatment). Measures: the Health Care Climate Questionnaire (HCCQ) measures autonomy supportiveness; the Helping Alliance Questionnaire (HAQ-P) operationalizes patient-therapist alliance; and the Group Climate Questionnaire (GCQ) measures features of the therapeutic environment. Study subjects (N = 119) were clients who completed the 2 and 10-week follow-up interviews (N = 60 in CBMT, N = 59 in CBT). Results: The sample was 69% male, 67% Caucasian, 19% African-American, 10% Hispanic, mean age = 40 years. Patient autonomy ratings were higher in CBMT than CBT at 2 weeks (M = 6.2) versus (M = 5.9) P < 0.001. In contrast, both the therapeutic alliance and group climate measures rated by patients at 2 weeks were not different by condition, both measures being uniformly high in both groups. Conclusions: Results are consistent with our hypothesis that CBMT affects processes hypothesized to be central to this theoretical model of motivation and change. This positive difference between treatment conditions is contrasted by the lack of difference found between conditions on measures of therapeutic alliance and group climate, offering support for the unique role of autonomy supportiveness. Supported by NIDA grant number: R01 DA12209-01A1.

410 School-and home-based treatment for adjudicated youth and their families
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This review focuses on current research problems involving populations of substance abuse-involved youth in the criminal justice system and their families. Although these youth and their families need substance abuse services, there is a lack of systematic evaluation and controlled treatment interventions. This review describes methods to obtain basic research information on substance abuse histories while delivering an intervention that is sensitive to culture and gender differences; a description of how valid outcome measures can be obtained in the context of a controlled intervention is illustrated by presentation of the author’s recently approved HHS/CSAT funded project entitled LIFE (Life Interventions for Family Effectiveness). The program targets a population of 80 Hispanic and African American youth and their families; the population served are at-risk teenagers who are wards of the juvenile court for an array of offenses; the offenses include but are not limited to: substance use, abuse, and experimentation. The adolescents attend a day treatment school in the Los Angeles County Department of Education; the age range is 13–18 years; they are residents of the surrounding areas of South Central Los Angeles. The cornerstone of the treatment model is Multisystemic Therapy (a family preservation model) delivered at the students’ homes; the other essential components of the model are a computer literacy program, acting workshop, peer group, and parent drug education group (components are provided either at school, home or community). Forty adolescents who attend the intervention school and their families will receive the comprehensive treatment intervention. Their outcomes will be compared to 40 adolescents and their families at a control/comparison school who will receive social services as usual.

411 Influence of modafinil, 400 or 800 mg/day on subjective effects of intravenous cocaine in non-treatment-seeking volunteers
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Modafinil (M) is a putative treatment for cocaine (C) dependence. We hypothesized that subjective ratings of cocaine effects would be diminished in volunteers receiving M in a paradigm of cocaine given by intravenous (IV) infusion over 1 min compared to a baseline of no M. Non-treatment seeking volunteers with previous IV experience were hospitalized for 21 days and received randomized normal saline or C, 20 or 40 mg, in a double-blind design, at baseline and following 7 days of M, 400 mg/day, increased to 800 mg/day for 1 week. A battery of visual analog scales accompanied each infusion study along with continuous cardiac monitoring and blood sampling for subsequent pharmacokinetic analyses. Preliminary data from the first 5 completers indicated that M decreased visual analog ratings of ‘drug effect’, ‘high’ and ‘desire’ at 3 and 10 min after IV infusion following M at the 20 mg C dose compared to baseline (no M). These trends did not reach statistical significance except for ‘drug effect’ at 10 min and ‘high’ at 3 and 10 min (P < 0.05). Less remarkable differences existed with the 40 mg C dose. Subject accrual continues.

412 Chronic bupropion attenuates mecamylamine-precipitated nicotine abstinence syndrome in the rat
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Chronic bupropion treatment has been reported to reduce the craving and discomfort associated with tobacco smoking cessation. This study determined whether the rat model of nicotine dependence and abstinence introduced by our laboratory can detect the nicotine abstinence-alleviating effects of chronically administered bupropion. About 24 male Sprague–Dawley rats, weighing 389–454 g, were implanted s.c. with one 2ML Alzet osmotic minipump under halothane anesthesia on day 1 and 8. About 16 rats received 14 days continuous infusion of 9 mg/kg per day nicotine tartrate (3.15 mg/kg per day expressed as the base); beginning on day 8 of infusion, half of these rats received 20 mg/kg per day bupropion HCl in addition to the nicotine. A control group of eight rats were infused for 14 days with saline alone. On day 14 of infusion, all rats were injected s.c. with 1 mg/kg mecamylamine HCl and observed for 30 mins under ‘blind’ conditions for precipitated nicotine abstinence signs. Rats infused with saline alone and those co-infused with nicotine and bupropion had significantly fewer abstinence signs than rats infused for 2 weeks with nicotine alone, P < 0.01 and P < 0.05, respectively. These results are consistent with another study which found co-infusion of bupropion and nicotine significantly reduced the aversiveness of mecamylamine-precipitated nicotine withdrawal (Supported by GlassoSmithKline.).

413 Toxic effects of para-methoxyamphetamine (PMMA) in rats
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Para-methoxyamphetamine (PMMA), alone or associated with para-methoxymphetamine (PMA), is recently abused in Europe; tablets of PMMA are illegally sold as ‘ecstasy’. Several users died after ingestion of PMMA associated with PMA. There are few reports of experimental toxicity of PMMA. In a multiparametric study, we studied the animal behavior, arterial blood pressure, cardiac frequency, electrocorticograms, body temperature, blood arterial gas, before and after PMMA (2, 20, 40, 80 mg/kg) or saline injection (i.p.)
in Wistar rats. Even low doses of PMMA increased rat locomotion. Rats presented flat body posture, reciprocal forepaw treading, salivation and myoclonic movements which are consistent with serotoninergic syndrome. For higher doses (40, 80 mg/kg) tonic or tonic-clonic seizures occurred with spikes or spike-waves on ECOG. Body temperature quickly increased before the onset of hyperactivity and seizures. Arterial blood pressure and cardiac frequency increased in a dose-dependent manner. PMMA is a potent drug which has hypertensive effects, cardiovascular and neurotoxic effects. The PMMA experimental toxicity may explain the effects of PMMA in human fatalities.

414 MAGNESIUM L-ASPARTATE HYDROCHLORIDE FOR THE TREATMENT OF ILICIT OPIATE AND COCAINE USE IN METHADONE-MAINTAINED PATIENTS
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Magnesium (Mg) is the fourth most abundant mineral in the brain and plays a role in the functioning of opiate and cocaine-related neurotransmitter systems. Based on findings from pre-clinical studies suggesting that Mg reduces cocaine self-administration and potentiates the antinoceptive effects of morphine, we conducted a preliminary, randomized clinical trial investigating Mg in the form of magnesium L- aspartate hydrochloride for the treatment of illicit opiate and cocaine use. Eighteen methadone-maintained patients exhibiting unremitting cocaine and opiate use were randomized to receive either Mg (732 mg/day) or matching placebo for 12 weeks. Primary outcomes were opiate and cocaine use based on twice-weekly urine screens. Results showed that in the intention to treatment sample the percentage of urine screens testing positive for opiates in the Mg group (22.6%) was half that of the placebo group (46.4%), P = 0.04; the difference was even greater in the ‘compliant’ sample (Mg: 16.3%, placebo: 47.9%), P = 0.02. Although cocaine craving was lower in the Mg compared to the placebo group, there was no difference between groups in cocaine use. The Mg formulation was well tolerated. These preliminary findings are consistent with Mg having a beneficial effect on reducing illicit opiate use, and suggest that a larger controlled investigation of Mg for the treatment of opiate use in this population may be warranted. It is possible that a higher dose of Mg than was used in this study may be needed to decrease cocaine use.

415 A DESCRIPTIVE ANALYSIS OF PARTICIPANT CHARACTERISTICS AND PATTERNS OF SUBSTANCE ABUSE IN THE CSAT METHAMPHETAMINE TREATMENT PROJECT
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The Methamphetamine Treatment Study is an eight-site randomized clinical trial designed to compare the Matrix Model of treatment for methamphetamine dependent individuals with ‘Treatment As Usual’ at each site. The Matrix Model is a manualized outpatient treatment approach that integrates treatment elements from a number of specific strategies, including cognitive-behavioral therapy, motivational interviewing, psychoeducation, and 12-step program involvement. Treatment As Usual as a comparison condition varies by study site. Patients at each site were randomly assigned to either the Matrix Model (n = 75 per site) or Treatment As Usual (n = 75 per site). In addition to participating in treatment services, patients were asked to provide weekly data, including a urine specimen for drug testing. Data is also collected at discharge, 6 and 12-month follow-up interviews. This poster presents a demographic description of the cohort, and describes patterns of drug use, abuse, and related problems among the 1016 participants recruited between April 1999 and July 2001. Specific analyses include: demographic composition of the sample with respect to gender (55% female, 45% male), age (mean = 32.8 years), ethnicity (60% Caucasian, 17% Asian or Pacific Islander, Hispanic 18%, Native American 3%, and African American 2%), education completed (mean = 12.2 years), and income (mean = $1073.8 per month). Other descriptive analyses include: primary drug used, mean percent of days using various drugs including methamphetamine, alcohol, and marijuana, and percent of sample reporting various routes of drug administration. Mean baseline Addiction Severity Index composite scores describing medical, employment, alcohol, drug, legal, family/social, and psychiatric status are also presented. This research was supported by the Center for Substance Abuse Treatment collaborative agreement # T1 11440.

416 HIV RISK BEHAVIORS AMONG FEMALE INJECTING DRUG USERS IN PHILADELPHIA

Past research has indicated that not all injecting drug users are at equal risk of contracting HIV infection. Consequently, it is important to develop methods for locating and intervening with those IDUs at greatest risk of infection. The data presented here examines the demographic, psychological, drug use, and HIV risk characteristics of 122 injecting drug using (IDU) women. Subjects were recruited from three types of programs serving IDUs–methadone maintenance, detoxification, and needle exchange in Philadelphia, Pennsylvania during a 6-month period starting in November, 1997. Data were collected using self-administered questionnaires and personal interviews. About 38% of subjects reported sharing needles and 21% reported having multiple sex partners during the 6 months prior to interview. The Beck Hopelessness Scale was significantly related to both sharing needles (X² = 6.86, P < 0.05) and having multiple sex partners (X² = 4.0, P < 0.05). Recruitment site (X² = 6.1, P < 0.05) was related only to having multiple partners. In multivariate logistic regression analyses (controlling for race, education, recruitment site, age, alcohol use, and multiple drug use versus heroin only), the Beck Hopelessness Scale remained significantly associated with sharing needles and having more than one sexual partner. Younger age and recruitment from the needle exchange program were also significantly associated with having multiple sex partners. These data suggest that affecting hopelessness is an important goal for HIV prevention among IDU women. Also, these data suggest that younger women and those who use the needle exchange may be in particular need of prevention interventions addressing sexual risk.

417 A RANDOMIZED, CONTROLLED EVALUATION OF JUDICIAL STATUS HEARINGS IN DRUG COURT: 6-MONTH OUTCOMES AND CLIENT-PROGRAM MATCHING EFFECTS

We report on the first experimental study of judicial status hearings in a drug court. Consentng misdemeanor drug offenders were randomly assigned either to attend bi-weekly status hearings throughout their enrollment in drug court (N = 81) or to be monitored by their treatment case manager who petitioned for status hearings as needed (N = 99). Otherwise, subjects received the same treatment and case management services, random urinalyses, and rewards and sanctions for their performance in the program. We maintained excellent experimental control, with bi-weekly subjects attending substantially more status hearings than as-needed subjects (4.07 vs. 0.16, P < 0.0001). Last year at CPDD, we reported no between-group differences
in counseling attendance, urinalysis-confirmed abstinence or self-reported drug or alcohol use or criminal activity during the first 14 weeks of drug court. Current analyses similarly reveal no differences in graduation rates or 6-month follow-up ASI data or urinalysis results. Importantly, however, there were significant interaction effects between certain client characteristics and the schedule of judicial status hearings. Subjects with antisocial personality disorder (ASPD) or a prior history of failed efforts in drug abuse treatment achieved significantly greater abstinence during drug court when assigned to bi-weekly hearings. Moreover, subjects without ASPD or a prior drug treatment history graduated significantly more often and achieved significantly greater abstinence during the program and at 6-month follow-up when assigned to as-needed hearings. This suggests that antisocial offenders or those with prior negative treatment experiences may require greater structure and judicial supervision to perform adequately in drug court, whereas ‘naïve’ offenders may respond negatively to intensive criminal justice interference with their treatment. These findings have important implications for drug courts. Status hearings are expensive and time consuming for both clients and staff and should be targeted to clients who need them most.

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418 CogNITIVE capABILITIES AMONG SCHOOL-AGE CHILDREN PRENATALLY EXPOSED TO COCAINE


Now in its final year, this study is an ongoing evaluation of development and performance in two cohorts of children who have reached age nine. A cocaine exposed cohort (n = 42), on whom four different gestational exposure measures are available, was studied as part of a perinatal research program in the early 1990s; age mates who were not similarly exposed now serve as a contrast (n = 39). Children were all born in Maryland suburbs adjacent to Washington DC, live in the same neighborhoods and go to the same schools. Findings are summarized in three different ways: a two group contrast with covariates controlled, examination of the relationship between level of prenatal exposure and level of cognitive abilities, three group comparison in which the exposed cohort is broken by maternal postnatal drug use. Mothers of the unexposed contrast group are healthier in several ways, differing strongly on prior drug use and on Milon Depressive and Cluster C factors, Kbit IQ, somewhat on education, some measures of neighborhood and life events, but not on ASI medical, psychiatric, legal or family scales, financial strain, or five of seven HOME subscales. Children in both groups perform below standard on assessments, the cocaine-exposed group had much poorer performance on cognitive related assessments: CELF3, WISC, WAIT, and visual motor integration. In MANOVA, controlling for maternal IQ, smoking, education, and postnatal cocaine use eliminated all exposure effects in the general cognitive vector; specific verbal effects of prenatal exposure level persisted. Prior to covariate control, the WAIT math composite and the WISC verbal comprehension scores were the most different with Cohen’s d > 0.95. The overall strongest predictor of poor cognitive performance was mother IQ. In general cessation of cocaine during the postnatal years was found to be associated with much better child cognitive scores, but strong prenatal exposure effects on verbal scores persist and this is associated with maternal depression.

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419 CONSIDERATION OF A CANADIAN HEROIN TRIAL

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Chronic, untreated opioid dependence, and particularly injection heroin dependence, is associated with dramatically elevated morbidity and mortality. Potential complications include overdose, acquisition of blood–borne infections, disruption of social functioning, drug-related crime and drug acquisition crime, social marginalization and disenfranchisement. In addition opioid dependence leads to extensive costs to the public health, welfare and criminal justice systems. While methadone maintenance therapy (MMT), the current standard of care, is effective in many cases, a significant number of those who enter MMT are not retained long enough to maximally benefit, and many others show ongoing problematic drug use despite months of treatment. Moreover, a significant number of potential MMT patients reject this treatment completely. In February 1997 the, then Addiction Research Foundation hosted a meeting initiating discussions on the feasibility of Canadian trials of alternative opioid maintenance agents in the treatment of opioid dependence. About 18 months later those engaged in the discussions joined a larger body of clinicians, scientists and ethicists to form the North American Opiate Medication Initiative (NAOMI). Members of NAOMI developed a rigorous protocol for a multi-site heroin prescription trial. The general objective of this randomized controlled trial is to determine whether the closely supervised provision of injectable, pharmaceutical-grade heroin (in combination with oral methadone) is more effective than methadone therapy alone in recruiting, retaining, and benefiting chronic, opiate-dependent, injection drug users who are resistant to current standard treatment options. This draft NAOMI protocol has been reviewed by several ethical review boards as well as by a panel of scientific and clinical experts in the field and by drug user and patient representatives and advocates. In addition to presenting the details of the NAOMI protocol, this presentation will summarize the arguments for and against the trial in Canada as they have been developed during protocol development and review.

420 METHYLPHENIDATE EFFECTS ON TASK PERFORMANCE IN ADHD ADOLESCENTS

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This ongoing study is evaluating behavioral effects of methylphenidate in ADHD early and mid-adolescents recruited from pediatric and child psychiatry clinics based on a history of therapeutic use of stimulants. Subjects completed two 5–h laboratory sessions. Methylphenidate (0.25 mg/kg) and placebo were each administered under double blind conditions on one morning session, and stimulant therapeutic medications were withheld until after daily assessments were completed. To date, 17 subjects, ages 11–15, have completed the protocol. Using repeated measures analysis of variance, significant dose X time interactions were obtained on CPT performance, including does-related decreases in the hit rate standard error [F(2,14) = 4.87, P < 0.05] and increases in the attentiveness factor (d’) [F(2,14) = 5.94, P < 0.01]. One-way repeated measures ANOVA revealed a significant main effect of dose on performance on a Risk Taking Task, F = 15.91, P < 0.001, as the relative number of risk choices was significantly decreased by methylphenidate. This preliminary study supports the utility of laboratory performance assessment to evaluate behavioral response to medication in early and mid adolescents with ADHD.
EFFECTS OF D2-RECEPTOR ALKYLATION IN THE NUCLEUS ACCUMBENS ON COCAINE SELF-ADMINISTRATION IN RATS: COMPARISON WITH EFFECTS ON D2 BINDING

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Receptor alkylating antagonists have proven to be useful research tools for determining functional involvement of receptor systems in complex behaviors. The role of D2-receptors in the NAcc was investigated using NIPS, a selective irreversible inhibitor of D2 receptors. Rats were trained to self-administer cocaine on an FR2 schedule of reinforcement and given vehicle (20% DMSO) or 0.3 or 1.0 nmol of NIPS into each side of the NAcc. Anatomical specificity and D1/D2 selectivity was determined in separate groups of animals given vehicle or 0.1 or 1.0 nmol of NIPS using quantitative receptor autoradiography. Administration of 1.0 nmol of NIPS reduced D2 density by up to 95% throughout the NAcc while leaving D1 receptor binding unaffected. D2 receptor density was unaffected in the caudate putamen and olfactory tubercles. D2 receptor density was decreased by approximately 40% following administration of 0.1 nmol of NIPS in the NAcc. NIPS (1.0 nmol) decreased self-administration of 0.17, 0.33 and 0.67 mg per infusion of cocaine by 40% for up to 7 days after administration, with a gradual return to baseline values thereafter. The effects of 0.3 nmol of NIPS were significantly less than those of the higher dose and persisted for less than 4 days in most animals. The effects of administration of NIPS into the NAcc on cocaine self-administration were less pronounced than when given into the ventral pallidum, suggesting that dopaminergic innervations of the ventral pallidum may be more critically involved than those in the NAcc.

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COCAINE USERS HAVE AN OVEREXPRESSION OF ALPHA-SYNUCLEIN IN DOPAMINE NEURONS: PATHWAY TO PARKINSON’S DISEASE?

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Overexpression of human alpha-synuclein induces dopamine nerve terminal degeneration, and the native protein is a major component of nigral Lewy bodies in Parkinson’s disease. We report here that alpha-synuclein levels are elevated in dopamine neurons from chronic cocaine abusers. Quantitative Western blot and immunocytochemical studies were carried out on postmortem specimens of the substantia nigra from cocaine users and normal age-matched drug-free subjects. Alpha-synuclein levels in the dopamine cell groups of the substantia nigra and ventral tegmental area were elevated 2-fold in chronic cocaine users compared to normal age-matched subjects (N = 10; P = 0.01). Victims of agitated cocaine delirium were not significantly different from control values, but there was a trend toward lower levels of expression in Western blot assays of the S1 soluble fraction. The upregulation of alpha-synuclein protein in cocaine users was accomplished by changes in nigral mRNA levels. The neurotrophic gain of alpha-synuclein function with chronic cocaine abuse may be toxic and place aging cocaine addicts at risk for developing the motor abnormalities of Parkinson’s disease.

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COST AND COST-EFFECTIVENESS OF LONG-TERM METHADONE DETOXIFICATION VERSUS STANDARD METHADONE MAINTENANCE TREATMENT


We evaluated the difference in health care costs incurred through 12 months between 180-day methadone detoxification enhanced with psychosocial treatment (M180) and standard methadone maintenance treatment (MMT). About 179 patients were randomized to one of the two treatments. Program activity logs, computerized billing records, and patient self-report were used to gather information about in and out-of-study medical, substance abuse, and mental health treatment services received for the 12-month study period. MMT had significantly higher within study costs than M180 treatment, $4,739 and $2,855 (P < 0.001), respectively. The MMT ($2,371) and M180 ($2,437) treatment groups did not differ with respect to medical care costs incurred. However, the M180 group had significantly higher out-of-study substance abuse and mental health care costs than the MMT group, $1404 and $455 (P = 0.001), respectively. The difference in total health care costs between the two groups was $867; health care costs for the MMT group were 13% higher. We will present the results of an incremental cost-effectiveness analysis based on a model that projects opiate use observed during the study to expected years of survival.

ALCOHOL CONSUMPTION AMONG CHILD-BEARING AGE AND OLDER FEMALES WITHIN FIVE TRIBES OF PLAINS INDIANS

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Research on the epidemiology and prevention of Fetal Alcohol Syndrome (FAS) within six American Indian communities is ongoing in Montana (2 sites), North Dakota (1 site), and South Dakota (2 sites). This study of adult drinking and substance use includes the largest randomly-selected sample of American Indian adults (N = 1800 +) ever collected. Data about females from the first four sites were divided into four age groups: 16–24 (n = 170), 25–34 (n = 200), 35–44 (n = 186), and 45+ (n = 294). Data reveal statistically significant differences on the number of lifelong abstainers, mean age started drinking, mean age began drinking regularly, number of drinks consumed in the 30 days preceding interview, and prevalence of drinking within the year preceding interview. Of importance for FAS prevention, females currently in the child-bearing ages (16–44) began drinking 2 years earlier than older women. The current 16–44 year olds also began drinking regularly 3 years before the older cohort. As expected, the 16–44 year olds consumed more alcohol in the 30 days preceding their interview with the highest use among the 25–34 year olds. Data from the fifth tribe were recently collected and are being added to our database; analysis continues.

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KALETRA (LOPINAVIR/RITONAVIR) DECREASES METHADONE EXPOSURE AND MAY PRODUCE OPIATE WITHDRAWAL

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Funding provided by the NIAAA (RO1 AA09440 and RO1 AA11685) and the NIH Office for Minority Health Research.
Background: Drug interactions between methadone and antiretroviral medications can result in toxicity or opiate withdrawal. Cytochrome P450 3A4 is important to the metabolism of methadone and protease inhibitors. Inhibition or induction of this enzyme with lopinavir/ritonavir treatment could affect the therapeutic response to these medications. Methods: This within-subject study (n = 15) in HIV-negative, methadone maintained individuals examined methadone pharmacokinetics with timed blood sampling over a 24 h dosing interval before and following 7 days of lopinavir 400 mg per ritonavir 100 mg twice daily administration. Opiate withdrawal symptoms were recorded pre- and post-antiretroviral administration. Results: Methadone area under the time-concentration curve was reduced following lopinavir/ritonavir treatment. Methadone minimum concentration (Cmin) was significantly reduced (mean: 301 u/l pre antiretroviral, 217 u/l post antiretroviral) (P = 0.018), as was maximum concentration (Cmax) (531 u/l pre and 362 u/l post (P = 0.012). Mild opiate withdrawal was observed clinically and Objective Opiate Withdrawal Scores increased with lopinavir/ritonavir administration (P = 0.013). Conclusions: Lopinavir/ritonavir at standard clinical doses decreased methadone serum concentrations and may induce withdrawal symptoms in opioid dependent patients. Clinicians should be aware of the potential for precipitation of opiate withdrawal and the need for methadone dose adjustments if lopinavir/ritonavir is to be used in HIV disease treatment in methadone-maintained patients.

426 CHARACTERISTICS OF FIRST-TIME AND REPEAT DRUG-TREATMENT SEEKERS: SIMILARITIES TO THE SMOKING CESSATION LITERATURE

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Literature on smoking cessation indicates that depression and anxiety have a direct and significant effect on nicotine dependence. We questioned whether similar relationships existed with drug use. Data from the Drug Evaluation Network Study (DENS), a nationwide electronic system providing clinical information on substance abuse patients, was used to compare the nature and severity of problems among first time and repeat drug treatment-seekers. Data are from an ongoing sample of 24877 patients entering 48 substance abuse treatment programs between 1996 and 2001. Four groups were compared: patients entering with no prior drug treatment (N = 8643), one prior treatment (N = 5712), 2–4 treatments (N = 6098), and five or more (N = 3524). Analyses of the data, using ASI composite scores, revealed statistically significant differences between the four groups overall (MANOVA, P < 0.000), and in all domains (ANOVA, P < 0.000). The magnitude of these differences, however, was small. The scores showed that severity in medical, drug, family, and psychiatric domains increased linearly with the number of treatments (P < 0.000). Specifically, patients who had five or more treatments were more likely to have current, recent, or lifetime problems with anxiety, depression, or chronic medical issues. This group also had a longer lifetime history of heavy drug use (heroin, cocaine, alcohol to intoxication, opiates) (P < 0.000). These results are similar to findings in the smoking cessation literature, and suggest a relationship between depression, anxiety and need for repeated attempts for successful termination of drug use.

427 INJECTION DRUG USE AND CRACK COCAINE SMOKING: INDEPENDENT AND COMBINED RISK FACTORS TO HIV INFECTION

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Purpose and Hypothesis. Previous studies have examined the practices of injecting drugs or smoking crack cocaine as high-risk, but independent, factors for HIV transmission. To explore the independent and combined risks of injection practices and crack smoking, this study examined HIV seroprevalence rates among distinct drug user groups, based on patterns of ingestion. Because previously reports found that crack use among injection drug users is associated with lower levels of HIV infection, it was hypothesized that in this sample, those who both injected drugs and smoked crack-cocaine (dual users) would also have lower HIV seroprevalence rates compared to those drug users who only inject. Procedures. A sample of 3555 drug users and neighborhood controls in urban Miami, FL and rural Belle Glade and Immokalee, FL were partitioned into four mutually-exclusive groups: (1) injection drug users (IDUs), (2) crack-cocaine smokers, (3) dual users who both smoked crack and injected drugs; and (4) non-drug user controls. Analyses and Results. HIV seroprevalence rates were 45.1% for IDUs, 30.5% for dual users, 20.1% for crack smokers and 7.3% for controls, respectively. Multivariate logistic regression analysis found that after controlling for demographics and risk behaviors, when compared with controls odds ratios for HIV seropositivity were 9.81 for IDUs, 5.27 for dual users and 2.24 for crack smokers, respectively. In terms of HIV risk behaviors, IDUs had a higher injection rate compared to dual users, but dual users were more likely to engage in high risk sexual practices including unprotected sex, have more than one sex partner, exchange sex for money and/or drugs, and have a history of STDs than IDUS and crack smokers only. Implications. These findings provide evidence of (1) behavioral and structural co-factors that influence HIV exposure patterns among different drug user groups and (2) the substantially higher risk of HIV infection among IDUs compared to other drug users. Intervention strategies must be tailored for the specific drug use subpopulations to optimize efficacy.

428 THE RELATIONSHIP OF CHILD ABUSE AND PEAK AGGRESSION IN ADOLESCENTS WITH SUBSTANCE AND CONDUCT PROBLEMS

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Childhood exposure to abuse/neglect is associated with high-risk behaviors (e.g., violence, aggression and substance use) in adolescents. We previously reported that adolescents with drug and conduct problems report more abuse and neglect experiences than controls, but the relationship of abuse and neglect to aggression in this population is unknown. Aims: To investigate the relationship of self- and parent-reported aggression and child abuse and neglect exposure in a sample of adolescents with substance use problems and controls. Methods: About 98 patients in an adolescent substance treatment program and 102 controls (both groups 40% female) were given an extensive assessment battery, including the Colo. Adolescent Rearing Inventory (CARI), the Peak Aggressive Incident Scale, and the Child Behavior Checklist (CBCL). Results: Total abuse and neglect scores and physical abuse scores were significantly associated with self- and parent-reported aggression for the total sample (r: 0.263–0.406). In separate analyses of controls and patients, total abuse and neglect, and physical abuse scores significantly correlated with self-report of aggression only in controls. Parental report of aggression (CBCL) did not correlate significantly with self-report of aggression in either patients or controls. Conclusions: These results suggest that exposure to abuse/neglect is not associated with elevated aggression among adolescent patients with conduct and substance problems. However, abuse and neglect in other adolescents may increase aggressiveness or aggressiveness may increase their risk for abuse and neglect experiences. Further study is warranted.

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This study compared three 12-week continuing care interventions for 243 cocaine dependent patients who had completed a 4-week intensive outpatient program (IOP) at a VA or community-based treatment facility. The three conditions were standard group addictions counseling (STND; two groups per week), relapse prevention (RP; one individual and one group session per week), and brief telephone counseling/case management (TEL; one 15 min call per week). The RP and TEL treatments were manualized, and were more highly structured than STND. Follow-ups were done at 3, 6, 9, 12, and 18 months post entry into continuing care, and rates of contact were higher than STND. Additional analyses did find evidence of two interaction effects. First, patients with greater cocaine use severity prior to and during IOP had better outcomes in RP out to 12 months than in either STND or TEL, whereas those with low cocaine severity did better in TEL and RP than in STND. Second, there was a site by treatment interaction, in which cocaine use outcomes in TEL were relatively good at the community site and poor at the VA site, whereas outcomes in RP and STND were similar at each site. These findings suggest that the effectiveness of different models of continuing care may vary as a function of patients’ characteristics and initial progress in treatment.

The purpose of this study was to examine the impact of stress on smoking status to determine if there was a sex-specific response to life stress. Sex differences in event-related risk for changes in smoking status were examined by means of a secondary analysis from the Americans’ Changing Lives study. A community based sample of smokers (N = 1539, 46% female) was used to examine the interactive effects of sex and stressful life events on the likelihood of two outcomes; relapse among former smokers and failure to quit among current smokers. To improve recall bias, indicators of stressful life events (interpersonal loss, financial events, change of residence, health events) were confined to the 12-month period preceding the Wave II interview. Logistic regression procedures were used to calculate odds ratios. In the sample of former smokers (n = 757), change of residence and financial events were associated with increased occurrence of relapse, however, women were more likely than men to relapse in response to a financial event. In the sample of current smokers (n = 782), financial events were associated with continued smoking whereas heath events were associated with increased likelihood of quitting. However, women were more likely to continue smoking in the presence of an adverse financial event and less likely than men to quit in response to an adverse health event. Overall, stressful life events appear to have a greater deleterious effect on continued abstinence and the ability to quit smoking for women when compared to men.
Discrimination assay will be especially useful for studying the neuropharmacology of Δ9-THC dependence and withdrawal.

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433 DISCRIMINATION OF DRUG MIXTURES UNDER A FOUR-CHOICE DRUG-DISCRIMINATION PROCEDURE

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Pigeons were trained to respond on one key after 5 mg/kg pentobarbital, on a second key after 5 mg/kg morphine, on a third key after a mixture of these two drugs, and on a fourth key after saline. When responding stabilized, birds made 92% of their responses on the appropriate key. Lower doses of all drugs produced responding primarily on the saline key. Higher doses of pentobarbital and clordiazepoxide produced responding on the pentobarbital key and higher doses of morphine produced responding on the morphine key. Methamphetamine produced responding only on the saline key. A wide range of dose combinations of pentobarbital and morphine, or of clordiazepoxide and morphine, produced responding on the mixture key. Combinations of methamphetamine with pentobarbital or morphine produced responding only on the pentobarbital or morphine keys respectively. That birds respond on the mixture key after a wide range of doses not previously presented as mixtures suggests that they can detect the simultaneous presence of two drugs in a mixture even if the doses were not previously combined as mixtures.

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434 GENDER DIFFERENCES IN RESPONSE TO THE COLD PRESSOR TEST

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The relationship between stress, alcohol use disorders, and relapse to alcohol use is not yet well understood. In this study, hypothalamic-pituitary-adrenal axis response and subjective stress and craving ratings have been obtained in individuals with alcoholism (n = 13), alcoholism and posttraumatic stress disorder (PTSD) (n = 11), PTSD (n = 14), and a normal control group (n = 11) after completion of a physical stressor, the cold pressor task. Significant baseline gender differences were found prior to completion of the cold pressor task. Males had higher baseline ACTH levels than females (P = 0.007) and also reported higher baseline craving (P = 0.09). Females reported higher baseline pain (P = 0.09) and stress (P = 0.01) ratings and had a higher baseline heartrate (P = 0.02). However, after completion of the stress task, there is not a significant gender difference between change from baseline to maximum value for any of these variables. This suggests that although baseline differences may exist, males and females have similar magnitude of responses to the cold pressor test. This study is ongoing; the sample size is expected to increase by the presentation date. At that time, additional data will be presented including analyses of each diagnostic group.

435 RELATIONSHIPS BETWEEN INTIMATE PARTNER VIOLENCE AND BARRIERS TO EMPLOYMENT AMONG SUBSTANCE-DEPENDENT WOMEN ON WELFARE

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Substance abuse and domestic violence are both recognized by the welfare reform legislation of 1996 as barriers to employment. However, the two problems are not independent, as indicated by the high comorbidity (61%) found in this sample of 175 women with partners enrolled in a Substance Abuse Research Demonstration Project (SARD). While substance-dependent women already encounter significant barriers to employment, we hypothesize that substance-dependent women who have experienced intimate partner physical aggression in the past year encounter a larger and more severe constellation of barriers. Women were classified as victims of aggression based on their responses to the Modified Conflict Tactics Scale (Pan and Neidig, 1994). Clients were assessed using two scales measuring their perceptions of employment barriers they have encountered (Allen, 1995; Olson and Pavetti, 1996), as well as measures covering the domains of substance abuse, education, work skills, physical health, mental health, family, recent stressful events, legal problems, housing/neighborhood, childcare and transportation. Differences between groups were tested using standard parametric and non-parametric methods. Preliminary data indicate that victims of aggression have been living with their partner over the previous 3 years at twice the rate of women who have not experienced aggression (30 vs. 14%). They report somewhat more barriers to employment (3.9 vs. 3.2), and are also more likely to have moved in with friends in the past year (39 vs. 23%), and to have problems with both drugs and alcohol (31 vs. 25%). Significantly more victims of aggression report problems with the cost of childcare (27 vs. 13%), recent pregnancy or newborn care (14 vs. 4%), and having been arrested (20 vs. 6%) as reasons they have not been working. Further analysis will indicate domains where targeted interventions are required to address the special needs of women affected by both substance dependence and intimate partner aggression.

436 RETENTION AND TREATMENT SERVICES RECEIVED IN THE CASAWORKS FOR FAMILIES PROGRAM

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This presentation focuses on the treatment services received by women participating in an initial study of CASAWORKS for Families (CWF), a program designed to provide a wide range of services to women with substance use disorders who were attempting to move from welfare to work. The CWF program was recently evaluated in 11 sites around the nation. Predictors of retention in the program were examined, as was the relation of retention and services received to employment and substance use outcomes at 12 months. Data on services received at 1, 3, 6, and 12 month post-intake follow-ups indicated that the program was successful in delivering services. Most women received services to address medical, employment, basic needs, alcohol and drug, family, and psychiatric problems during the first 6 months of the program. The clients also had frequent contact with their case managers, and were retained in the program for an average of 222 days. Better retention in the program was predicted by a number of factors at baseline, including heroin use, higher psychiatric severity, and greater basic needs problems. Poorer retention was predicted by greater alcohol and cocaine use, more severe problems with children and other family members, and worse employment status at baseline. Longer retention was associated with better alcohol use outcomes, but was unrelated to employment or drug use outcomes. More alcohol and drug treatment services received in the first month predicted better substance abuse status at 12 months, but none of the other treatment service measures predicted substance use or employment outcomes.
Implications of the findings for further development of the CASA-WORKS program are discussed.

437 MATHEMATICAL MODELLING OF NICOTINE REPLACEMENT THERAPIES (NRT): INCREASED RELAPSE RATE AFTER STOPPING TREATMENTS

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Hypothesis: A mathematical model has been developed to assess the evolution of relapse rate on NRT and placebo (P) during treatment and to test whether relapse rate is similar or not after stopping treatments. Methods: The model estimates the hazard ratio (HR) of relapse of NRT compared with P. Two HR were considered, one accounting for during treatment effects the other for after treatment effects. An exponential kinetic model was used which included the type and duration of treatments. The model was then validated using published, randomized, double blind studies, comparing NRT to P on biochemically verified continuous abstinence. Results: About 22 studies published between 1984 and 1999 in smokers without specific disease condition were included. The sample contained subjects having similar characteristics and treated either with P (n = 2766) or NRT (n = 6644). After treatments’ initiation HR was 0.62 (95% CI: 0.58 – 0.67) and progressively increasing to 0.80 (95% CI: 0.69 – 0.96), at end of treatments. After treatment cessation, HR was 1.44 (95% CI: 1.18 – 1.76), thus, abstinence rate after NRT was 44% lower than after P suggesting a ‘rebound effect’ after cessation of NRT. Conclusion: Our model showed that NRT prevent relapse but in contrast to our hypothesis, stopping NRT may lead to increased relapse rate. Further studies have to assess whether long term NRT may prevent this rebound phenomenon.

438 HEALTH DISPARITY BETWEEN COURT-AND COMMUNITY-RECRUITED SUBSTANCE-ABUSING WOMEN ENROLLED IN A COMMUNITY HIV PREVENTION STUDY

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NIDA has highlighted the need to focus on research areas where gaps or disparities in prevention and treatment are evident. As part of an ongoing NIDA-funded study of cocaine, heroin or amphetamine using women, 18–44 years old, in St. Louis, Missouri, we were introduced to the City Court System and the presiding judge of the St. Louis drug court. This introduction resulted in the opportunity to augment our community-based sample with a sub-group of court-referred women. Based on involvement with the criminal justice system, these women represent an especially vulnerable population with potentially elevated risks for health issues. To date, our preliminary sample is comprised of 165 drug-using women. Although court (N = 21) and community (N = 144) respondents did not differ in terms of number of lifetime arrests, court referred respondents reported more nights in jail or prison. They were also likely to test positive for a sexually transmitted disease, including Hepatitis C (43 court vs. 22% community) and syphilis (10 court vs. 2% community). Sexual risk behaviors were significantly elevated in court referred respondents: four or more sex partners (29 court vs. 10% community); and sex trading (95 court vs. 50% community). Moreover, reported substance use differed by recruitment method. Community referred respondents were more likely to report lifetime alcohol use (57 court vs. 58% community) and cannabis use (33 court vs. 57% community). Although nearly the entire sample reported lifetime cocaine use, court respondents were more likely to meet criteria for cocaine dependence (95 court vs. 77% community). Based on preliminary results, it is clear that continued efforts to evaluate the differential risk factors for health issues in women are a fundamental focus for the research community.

439 IMMUNOSUPPRESSIVE EFFECT OF DELTA9-THC IN AN IN VITRO ANTIBODY-FORMING CELL SYSTEM

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Our laboratory has carried out extensive studies on the immunosuppressive effects of opioids, including morphine, U50,488H, and deltorphin. In these studies we used a system in which mice were immunized in vivo with sheep red blood cells (SRBC) 14 days prior to spleen cell harvest, when splenocytes were placed in culture with SRBC, and the capacity to make antibody measured in a secondary plaque-forming cell assay (PFC). In this assay, all of these agonists gave maximal 50% immunosuppression that followed sigmoidal dose-response curves, with maximal suppression at 10\(^{-7}\) – 10\(^{-9}\) M. As mu, kappa and delta2 agonists were active in this system, and delta9-tetrahydrocannabinol (THC) has been reported to be immunosuppressive in other assays of immune function, we decided to test it for capacity to alter PFC responses. We found that THC produces 50% immunosuppression with a sigmoidal dose-response curve showing maximal effect at concentrations between 10\(^{-7}\) and 10\(^{-5}\) M, and loss of suppression at concentrations of 10\(^{-11}\) M and lower. The dose-response curves are almost identical to those of the opioids. The THC-induced immunosuppression could be blocked by pre-incubation of the spleen cells with SR144528, an antagonist specific for the CB2 class of cannabinoïd receptors, but not by preincubation with SR141716, an antagonist specific for CB1 receptors. We have also used THC and these antagonists in cultures containing spleen cells from unprimed mice. The results observed in these primary assays are similar to those seen in the secondary MD assay. This contrasts with the effect of morphine, which is inactive when unprimed spleen cells are used. These studies show that THC can induce immunosuppression in the PFC assay that is cannabinoïd-receptor specific.

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440 OVARIAN STEROID HORMONE MODULATION OF THE ACUTE EFFECTS OF COCAINE ON ANTERIOR PITUITARY HORMONES IN OVARIECTOMIZED RHESUS MONKEYS

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Cocaine increases LH and decreases prolactin in gonadally intact rhesus monkeys but not in ovariectomized females (Mello and Mendelson, 1997). These findings suggested that ovarian steroid hormones may contribute to the endocrine effects of acute cocaine administration. The effects of cocaine and placebo-cocaine on LH and prolactin were examined in five ovariectomized rhesus females during saline maintenance and during three chronic hormone replacement conditions: estradiol (E2B) treatment (0.0015 – 0.006 mg/kg per day, i.m.); progesterone treatment (0.32 mg/kg per day, i.m.) and combinations of progesterone (0.32 mg/kg per day, i.m.) and E2B (0.004 mg/kg per day, i.m.). Before hormone replacement, neither cocaine (0.8 mg/kg, i.v.) nor placebo-cocaine altered basal levels of LH and prolactin, and this finding is consistent with our previous report (Mello et al. 1995). Cocaine significantly reduced prolactin under all hormone replacement conditions (P < 0.05 – 0.001). In contrast, cocaine stimulated LH release only during low dose estradiol treatment and during maintenance on progesterone alone. These data suggest that physio-
logically relevant doses of ovarian steroid hormones modulate cocaine’s effects on anterior pituitary hormones.

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441 NON-AMINES: A GENERALIZATION TO METHYLPHENIDATE AND INDATRAIN ALINE

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Methylphenidate and ndatrainl bind stereoselectively and enantioselectively to the dopamine transporter. Prior to our work on 8-oxa- and 8-carboxybicyclo[3.2.1]octanes it had been assumed that a nitrogen, such as exists in cocaine, methylphenidate and indatraline, was essential for interaction with monoamine transporters. Since we have shown unequivocally that the nitrogen ‘anchor’ point is not needed for potent biological activity in the bicyclo[3.2.1]octane series, we wished to probe the generalizability of exchange of oxygen, or carbon, for nitrogen in other monoamine uptake inhibitors. We therefore explored the substitution of the nitrogen in the piperidine ring of methylphenidate for an oxygen and a methylene, and the secondary amine in indatraline for a methyl ether. We now report that, again, nitrogen is not a prerequisite for binding potency, and these potent and selective (DAT:SERT) oxamethylphenidates and oxaindatralines bind enantio- and stereoselectively to the DAT.

442 CIGARETTE SMOKING AND COCAINE EACH STIMULATE RAPID RELEASE OF LUTEINIZING HORMONE (LH) IN MEN


Acute administration of cocaine (0.2 and 0.4 mg/kg, i.v.) rapidly stimulated significant increases in LH in male cocaine abusers (Mendelson et al., 2001). This study compared the effects of cocaine with another psychostimulant, smoked nicotine on LH. Six nicotine-dependent men (DSM-IV/criteria) smoked high yield (15.48 mg nicotine) cigarettes after 12 or more h of abstinence from cigarettes and caffeine (baseline CO₂ levels < 10 ppm). Subjects took one puff every 30 s; held it for 5 s, and took a total of 24 puffs over 12 min. A new cigarette was presented after every 4 puffs. Blood samples were collected at baseline and at 2 min intervals for 20 min after initiation of smoking, then at 10 min intervals for 120 min. Preliminary data indicate that plasma nicotine levels were detected within 2 min after smoking began, and peak nicotine levels were measured within 12–14 min. LH increased significantly within 14 min after smoking and remained significantly higher than baseline levels for 60 min (P < 0.01–0.004). Similarly, after i.v. cocaine (0.4 mg/kg, i.v.) administration to six cocaine abusers (DSM-IV criteria), LH increased significantly within 12 min and remained significantly above baseline for 30 min (P < 0.02). These findings suggest that cigarette smoking and i.v. cocaine have similar effects on LH in men and extend previous reports of the similarities in the subjective and physiological effects of cocaine and nicotine (Jones et al. 1999).

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443 SIMULTANEOUS SUBLINGUAL ADMINISTRATION OF MULTIPLE SUBOXONE TABLETS DOES NOT ALTER BUPRENORPHINE PHARMACOKINETICS OR THE DELIVERED DOSE

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Suboxone, a new opiate dependence pharmacotherapy, is a combination of buprenorphine and naloxone in a fixed 4:1 ratio. Two tablet strengths will be available—one with 8 mg buprenorphine and 2 mg naloxone and another with 2 mg buprenorphine and 0.5 mg naloxone. Buprenorphine doses between 8 and 32 mg are usually needed for opiate dependence treatment. Because many (most) patients will require administration of several sublingual tablets, we compared the effects of dosing four tablets (two 8 mg Suboxone tablets followed by two 2 mg Suboxone tablets; total 20 mg Suboxone) administered sequentially (doses separated by 15 min) or simultaneously (all four tablets at once). Non-opiate using subjects were dosed after naltrexone pretreatment using two dosing variations. In six subjects in the sequential condition, subjects were allowed to swallow 5 min before placement of the final two 2 mg tablets. In eight additional subjects, swallowing was not permitted between doses. Plasma buprenorphine levels were determined with LC/MS/MS and pharmacokinetic results analyzed with WinNonlin Pro. Results show no differences in AUC, Cₘₐₓ, Tₘₐₓ or bioavailability between dosing techniques. Absorption was rapid in all conditions with Tₘₐₓ occurring between 1 to 1.2 h. Pretreatment with naltrexone was safe and blocked all opiate agonist effects. In both conditions tablets dissolved slowly, often leaving a gelatinous mass beneath the tongue until cleared by swallowing. Clinicians should be reassured that minor variations in the sequence and timing of sublingual dose administration will have little effect on drug delivery.

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444 DRAMATIC INCREASE IN MORTALITY RATES AMONG INJECTION DRUG USERS: A FOLLOW-UP STUDY IN PHILADELPHIA, 1990–1997

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Objective: To describe recent mortality trends in a follow-up study of injection drug users (IDUs). Methods: 415 IDUs recruited in Philadelphia from a methadone treatment program and its surrounding neighborhood (out of treatment), between June and December 1989 (n = 255) and between June and December 1992 (n = 160), followed up to July 1997. Vital status was assessed by searches in the National Death Index up to June 2000. Death rates were estimated for each 18 month interval by the actuarial method; variables associated with risk of death were identified through multivariate Cox regression including time-dependent covariates. Results: Death rate increased 7-fold from the first to the last time interval, and among HIV-negative as well as HIV-positive subjects. Risk of death was significantly associated with HIV status and age; after adjustment for these variables, it was still increasing significantly across time periods. Conclusion: Mortality among IDUs, which had increased in the 70s and 80s, has continued to escalate. Detailed analysis will be provided to elucidate possible mechanisms for this recent trend.
445 Correlates of recidivism for women parolees from prison-based treatment in California

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The extent to which traditional therapeutic community (TC) methods meet the specialized treatment needs of drug-dependent women in prison is largely unknown. Drug-dependent women offenders entering prison-based TC treatment programs often report severe levels of polydrug abuse, psychological impairment, and histories of sexual/physical abuse. Very little research has been conducted specifically with this population and the degree to which these factors are related to recidivism is uncertain. The purpose of this study is to identify critical factors that are related to the reincarceration rates of women offenders who paroled from prison-based TC treatment programs. Extensive treatment intake interview data for 2512 women from eight prison-based TCs in California was compared using $\chi^2$ analysis and t-tests to identify preexisting differences for those who were (19%) and those who were not (81%) returned to custody within 12-months of their parole date. Intake data come from a five-year process and outcome evaluation of the California Department of Corrections’ (CDC) treatment expansion initiative. The return-to-custody data come from the CDCs Offender Based Information System (OBIS). Logistic regression analyses was used to indicate which women are at greater risk of reincarceration. Preliminary findings show that women with psychological impairments were most likely to be reincarcerated within 12-months of their parole, compared with women with no psychological impairments. Sexual/physical abuse and polydrug use were unrelated to reincarceration. These findings indicate a need for developing more comprehensive and effective treatment plans for dually-diagnosed women offenders. Future exploration from this study could provide valuable information on the types of services and approaches that should be emphasized when treating dually-diagnosed women in prison-based TCs.

446 MET and UNMET NEED FOR DENTAL SERVICES AMONG ACTIVE DRUG USERS IN MIAMI, FLORIDA

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In May, 2000, David Satcher, Surgeon General, released the first ever report on oral health in the United States, a report which emphasized the inextricable link between oral health and general health and identified existing disparities in oral health. According to this report, poor dental health has been linked to mortality, morbidity, poor nutrition, speech impediments, reduced employability, and low self image. Within this context, a University of Miami study considered both met and unmet need for dental services within a sample of chronic users of opiates and/or cocaine in Miami, Florida and compared them to the needs of non-users who were recruited from the same neighborhoods ($N=1479$). Three primary findings emerged from the study: (1) dental problems were among the most frequently reported health problems, (2) drug use was independently associated with need for dental services, and (3) injection drug use was independently associated with increased odds of unmet need for dental services. In view of the very limited Medicaid funding available for dental care of adults, our findings suggest that health care providers, managed care organizations, and policymakers should consider policies that promote increased access to dental services for drug users and other disadvantaged groups. These services could be integrated into existing behavioral health programs already targeting active drug users such as drug treatment, methadone maintenance, and risk reduction programs.

447 IMPACT OF MALE PARTNERS’ PSYCHOPATHOLOGY ON SUBSTANCE USE DISORDER FROM ADOLESCENCE TO YOUNG ADULTHOOD IN WOMEN

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This study determined the contribution of male partners’ substance use disorders (SUD) and psychiatric disorders [anxiety, depression, and conduct disorder (CD)] to the association of female adolescents’ SUD and psychiatric disorders with severity of SUD from adolescence to young adulthood in women ages 19–23. The sample included 85 couples. The age range of the females was between 14–18 and their average education level was ninth grade. All male partners were assessed when the females were young adults. The results of the moderating analysis controlling for female adolescents’ SUD revealed that: (1) SUD (Beta$F=0.32$, $P=0.02$; Beta$M=0.57$, $P=0.00$) and CD (Beta$F=0.29$, $P=0.01$; Beta$M=0.31$, $P=0.002$) in both members of the couple are related to severity of SUD in the young adult females, and (2) male partner CD increased the strength of the relation between female adolescent SUD (Beta $=0.40$, $P=0.005$) and CD (Beta $=0.43$, $P=0.003$) and her SUD in young adulthood. In conclusion, the results underscore the value of the interaction of SUD and CD, rather than anxiety and depressive disorders, in both members of the couple in predicting the severity of SUD in women.

448 PARENTAL SOCIAL STATUS AND ADOLESCENT COCAINE USE

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Adolescent use of both powder and ‘crack’ cocaine appears to be more common in families that have lower socioeconomic status (SES). However, most measures of parental SES in this field are limited to parental education or parental income, and the influence of parental occupation as a SES indicator remains largely unknown. Hypothesis: Measures of occupational status will contribute significant information to the prediction of adolescent cocaine use, even after controlling the influence of parental education and income. Procedure: The analysis compares the relative influence of five different occupational status measures: occupational prestige, the Duncan socioeconomic index (SEI), occupational education, occupational income, the Blau Group II classification. Statistical Analyses consist of logistic regressions and center on the National Longitudinal Survey Youth 1979 survey; specifically, the analyses focus on both the respondents to the main survey and also the interviews of their children ($n=10000+$). Results indicate that occupational SES indicators contribute independent information to the models, with occupational education making the strongest contributions. These findings are important to provide empirical information on the best SES indicators for analyses of family SES and adolescent drug use.

449 HOUSING CONDITIONS AFFECT RESPONSE TO DAY TREATMENT OF COCAINE-DEPENDENT HOMELESS

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A three group randomized controlled study examined the effect of housing conditions in outcomes of behavioral day treatment. Subjects were non-psychotic dually diagnosed homeless persons, with cocaine use disorders. Two, 6 and 12-month abstinence outcomes were examined for the three groups: Abstinence Contingent Housing (ACH), Non-abstinence contingent housing (NACH), and No housing (NH). Proportions of clients entering 12-month treatment, provided housing groups were hypothesized to show better outcomes. All groups participated in the same day treatment, work therapy, and aftercare programs, and were treated by the same counselors at the same times and setting. Observed urine specimens
were tested randomly 2 per week throughout the first 6 months of treatment and aftercare and 1 per week at aftercare to 12 months. Missing urine tests were considered drug positive. Based on generalized linear model analyses, average abstinence levels declined in all treatment groups over the course of the study. In the NH group abstinence levels declined from 23.6% to 12.6 to 3.5% for Months 1 and 2, 4–6, and 6–12, respectively. Over the same periods abstinence rates for the NACH group were 45.5, 32.9, and 13.5% while for the ACH group rates were 53.0, 40.4, and 15.6%. Abstinence rates for both the ACH and NACH groups were significantly different from those for the NH group at all time points (P < 0.001). While abstinence rates for the ACH group were somewhat higher than those for the NACH group during the early study phases, the differences were not statistically significant. Results suggests providing housing and housing contingencies for homeless substance abusers in treatment may play a role in abstinence outcomes and has implications for the utilization of housing in substance abuse treatment programs.

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450 GENDER DIFFERENCES IN GENETIC AND ENVIRONMENTAL RISK FACTORS FOR ADOLESCENT TOBACCO, ALCOHOL, AND ILLICIT DRUG USE

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The purpose of the present study is to estimate the contribution of genetic and environmental factors to tobacco, alcohol, and other substance use in adolescent boys and girls. Multivariate genetic structural equation models will be fit to longitudinal data collected in extensive home interviews with adolescent twins (aged 12–17 years old) from the Virginia Twin Study of Adolescent Behavioral Development (VTSSABD). Two waves of data are available from 1071 twin pairs (307 monozygotic male; 392 monozygotic female; 185 dizygotic male; 187 dizygotic female). For both boys and girls, of those who smoked cigarettes or drank alcohol without parental permission at the time of the first assessment (roughly 10%), the majority were still smoking and drinking alcohol at the last assessment; however, many adolescents began smoking and drinking between assessments, reflecting a large rise in substance use over this age period (roughly 20%). An increase in illicit drug use was also found, although to a lesser extent, with less than 5% of the sample reporting any illicit drug use at the last assessment. The patterns of correlations across the two waves of the study allow examination of the extent to which each type of substance use may lead to later substance use. For both sexes, the correlation between early alcohol use and later smoking/drug use were greater in magnitude than those between early smoking/drug use and later drinking, suggesting that alcohol use may be a potential gateway to further substance use. The extent to which genetic and environmental factors are shared across substances and specific to each type of substance will be explored through comparison of a common pathway model and an independent pathway model. The role of gender in the magnitude of genetic and environmental parameter estimates will also be assessed. Results from this study will lead to a better understanding of the comorbidity of substance use and the underlying genetic and environmental factors that may contribute to later substance use in adolescent males and females.

451 MECHANISM OF BUPROPION AND ROBOXETINE ANTAGONISM OF NICOTINIC RECEPTORS IN RAT BRAIN

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Bupropion (BUP) is an effective smoking cessation agent. Both BUP and reboxetine (RBX) are efficacious antidepressants. BUP nonselectively inhibits both dopamine and norepinephrine transporters (DAT and NET, respectively); reboxetine selectively inhibits NET. We previously reported that BUP inhibited both nicotine (NIC, 10 μM)-evoked [3H]dopamine ([3H]DA) overflow (IC50 = 1.3 μM) and [3H]norepinephrine ([3H]NE) overflow (IC50 = 323 nM) at BUP concentrations at least 100-fold lower than that eliciting intrinsic activity, suggesting antagonism of z3β2* and z3β4* nicotinic receptors (nAChRs), respectively. In contrast, RBX potently inhibited (IC50 = 7.3 nM) NIC-evoked [3H]NE overflow, but did not inhibit NIC-evoked [3H]DA overflow, suggesting selective antagonism of the z3β4* nAChR. The present study evaluated the mechanism by which BUP and RBX inhibit NIC-evoked [3H]neurotransmitter release from striatal and hippocampal slices using Schild analysis. To eliminate interaction with DAT or NET, nomifensine or desipramine, respectively, was included in the buffer. Schild analysis revealed that BUP (1–10 μM) shifted the concentration-response curve for NIC (1 nM–100 μM)-evoked [3H]DA overflow parallel and to the right, suggesting competitive inhibition of z3β2* nAChRs. Furthermore, BUP (0.1–1.0 μM) shifted the concentration-response curve for NIC (10 nM–100 μM)-evoked [3H]NE overflow parallel and to the right; however, the inhibition produced by 10 μM BUP was not surmounted by increasing NIC concentrations, indicative of spare nAChRs. Alternatively, the BUP-induced inhibition of [3H]NE overflow may involve two different nAChRs subtypes, competitively inhibiting one subtype and noncompetitively inhibiting the other. RBX (10 nM–1 μM)-induced inhibition of NIC (1 nM–100 μM)-evoked [3H]NE overflow was not surmounted by increasing NIC concentrations, indicative of noncompetitive inhibition of the z3β4* nAChRs. Thus, BUP and RBX inhibit nAChRs via complex mechanisms, and moreover, across the same concentration range at which they inhibit DAT and NET function. A combination of these actions may mediate their efficacy as antidepressants and smoking cessation agents.

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452 GENETIC DIVERSITY OF DRUG TARGETS IN THE BRAIN: SIMILARITIES BETWEEN HUMAN AND RHESUS MONKEY MU-OPIOID RECEPTOR VARIANTS

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A major target of opiate drugs are proteins in brain encoded by the mu-opioid receptor gene (MOR-1). Based on extensive studies in mouse, MOR-1 is a very large (~ 250 kb) and complex ( > 13 exons) gene, that gets translated into numerous variant mu-opioid receptors by alternative splicing. In humans, a splice variant (MOR-1A) has been described which lacks exon 4 and utilizes 12 bases of intron 3, resulting in a receptor with a different C-terminus tail sequence. Also in humans, but not found in mice, are single nucleotide polymorphisms (SNPs), that differentiate individuals and have been associated with various parameters of opiate response and addiction. Both splice variants and SNPs are highly relevant to drug addiction because the specific mu-opioid receptor proteins that an individual expresses may underlie their sensitivity and responsiveness to opiates and their susceptibility to becoming addicted. Monkeys, widely used in models of opiate addiction and medications development, are more closely related to humans and are amenable to objective phenotyping of some parameters of drug abuse. We hypothesized that MOR-1 splice variants and SNPs are present in monkeys, are closely related to human variations, and may affect mu-opioid receptor proteins. RESULTS: We cloned and sequenced MOR-1 coding regions from monkey brain and found > 98% homology to human MOR-1. Similar to human, we found an alternatively spliced MOR-1A with the
identical tail amino acid sequence to human, and a common SNP (5/16 animals) that changes an amino acid in the N-terminus (P26R). Cloning of additional splice variants, identification of SNPs, pharmacological characterization, cellular localization and ligand-induced receptor internalization studies are in progress. As MOR-1 splice variants and SNPs are relevant to receptor function, the findings support the validity of comparing genotype with phenotype parameters of dose response, self administration and relapse in non-human primates, of relevance to human addiction.

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453 ADDICTION AND CRIME CAREERS OF HEROIN AND CRACK ADDICTS ENTERING DETOXIFICATION

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Careers of addiction and crime will be described in a sample of 371 heroin and/or crack addicts who entered one of two detoxification units in 1998–1999 in the borough of Bronx in New York City. A specific hypothesis predicts that the subgroup of addicts who are involved in violent crime show indicators of deviance earlier in life than addicts not involved in violent crime. The participants were interviewed about different areas of life experiences, including family of origin, onset of drug and alcohol use, adolescent deviance, history of drug abuse, and history of criminal involvement. All data are based on retrospective self-report, and were collected as part of a study investigating entry into long-term treatment from detoxification. The sample had the following characteristics: 75% were male, 58% Hispanic, and 33% African American. The average age was 37, ranging from 20 to 62, with 47% within the 30–39 range. The primary drugs of abuse were heroin for 41%, crack for 23%, and both heroin and crack for 36%. This study describes selected key predictors and indicators of drug and crime involvement in the sample, including early family structure, age of onset of alcohol and drug use, indicators of conduct disorder in adolescence, onset of criminal justice involvement, length of addiction to primary drug of abuse, length of time incarcerated, and types of criminal offences arrested for. Associations among these variables are examined by means of path analysis. The analyses show that a high score on the adolescent conduct disorder scale (SCID) is significantly associated with a likelihood of having been arrested for a violent offence, such as assault, rape or homicide, lending support to the specific hypothesis of early indicators of violent deviance in a subgroup of addicts. The implications of the findings on prevention and treatment programs, and on tailoring interventions for specific subgroups are discussed.

454 SLOW-RELEASE ORAL MORPHINE AS A MAINTENANCE PHARMACOTHERAPY FOR OPIOID DEPENDENCE

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Alternative treatment options for patients responding poorly to methadone maintenance treatment are presently limited. This study investigated slow-release oral morphine (SROM) as an alternative maintenance pharmacotherapy to methadone in the treatment of opioid dependence. In a non-blinded, randomised, cross-over study, fourteen methadone-maintained patients were transferred to once-daily SROM (Kapanol™) for approximately 6 weeks. The mean (range) SROM:methadone dose ratio was 3.5 (3.0–3.75) upon commencement of SROM maintenance and 4.6 (3.8–8.0) after dose stabilisation. Mean (range) daily doses during methadone and SROM maintenance were 78 mg (25–120 mg) and 349 mg (120–570 mg), respectively. Subjects included those reporting adequate withdrawal suppression between doses on methadone (holders) and those reporting inadequate withdrawal suppression (non-holders). Plasma drug concentrations and indices of opioid effect (withdrawal severity, pupil diameter, respiratory rate) were measured throughout a single 24-h dosing interval at steady-state for each medication. Plasma concentrations rose and declined more gradually for SROM compared to methadone, with maximum concentrations being reached later in the dosing interval (6.5 vs. 2.5 h, P < 0.001). Withdrawal severity, pupil diameter and respiratory rate were inversely related to plasma drug concentrations and were of a similar overall magnitude for methadone and SROM. Compared to methadone maintenance, the mean number of self-reported withdrawal symptoms prior to dosing during SROM maintenance was reduced for non-holders (9.0 vs. 3.4, P < 0.01) and equivalent for holders (4.0 vs. 4.4, P > 0.05). Twelve of the fourteen subjects expressed a preference for SROM over methadone. In conclusion, SROM was at least as effective as methadone in suppressing opioid withdrawal between doses. Thus, once-daily SROM (Kapanol™) represents a safe and efficacious alternative for patients responding poorly to methadone.

455 GENDER, ETHNICITY, AND RECRUITMENT SITE AS PREDICTORS OF ENROLLMENT IN A STUDY ON LINKAGE METHODS

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Background: We examined the factors that predict participant enrollment in an ongoing study investigating the effectiveness of methods for linking heroin-injecting patients to substance abuse treatment. The current data reflect patients screened over 18 months through 12/01 (168 screened, 128 eligible, 71 enrolled). A total of 120 subjects are expected to enroll. Procedure: Patients were screened for eligibility in the Integrated Soft Tissue Infection Services (ISIS), the Emergency Department (ED), and the inpatient units (Inpt), all at the San Francisco General Hospital (SFGH). Patients eligible were adults that met state methadone maintenance requirements. Demographic information was collected. Once eligibility confirmed, an interview was scheduled within the next few days. Hypotheses: (1) Female and minority patients are less likely to enroll, (2) Enrollment success depends on recruitment site, in descending order from ISIS, to ED, to Inpt, because patients are more alert in an outpatient setting than at an acute inpatient or trauma unit. Results: 71% women vs. 78% men eligible (χ2 = 1.05, DF = 1, P = 0.305), 57% eligible women vs. 55% eligible men enrolled (χ2 = 0.035, DF = 1, P = 0.852). 75% White, 79% African-American, 71% Latino/a, 80% Mixed/Other eligible (χ2 = 0.79, DF = 3, P = 0.853). 61% White, 50% African-American, 58% Latino/a, and 38% Mixed/Other of eligible enrolled (χ2 = 2.49, DF = 3, P = 0.48). Female and minority patients were just as likely to be eligible for and enroll in the study. Our first hypothesis was not supported, indicating that in respect to gender/race our sample was representative of the larger sample. The second hypothesis was reflected in the data. Patients recruited at ISIS, though as likely to be eligible (ISIS 84%, ED 68%, Inpt 74%, χ2 = 4.35, DF = 2, P = 0.114), were more likely to enroll in the study (ISIS 70%, ED 53%, Inpt 38%, χ2 = 10.17, DF = 2, P < 0.006) than patients seen in ED or Inpt. Conclusions: There were no apparent biases in study enrollment according to gender/ethnicity. The outpatient clinic appears to be a promising setting for participant recruitment.
456 CA2+ SIGNALINGS MEDIATED BY DOPAMINE RECEPTORS IN THE CULTURED RAT HIPPOCAMPAL ASTROCYTES

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A recent new insight into the astrocytes physiology has emerged, leading to a different view of its role in the CNS, i.e., ‘regulation of neuronal function’. Dopamine regulates a variety of functions in the brain including locomotor activity, emotion, positive reinforcement and endocrine regulation. However, little is known about its effect on glial cells in spite of the fact that astrocytes possess dopamine receptors. Using a fura-2 Ca2+ imaging technique, we investigated the dopamine-evoked increase in intracellular Ca2+ concentration ([Ca2+][i]) in cultured rat hippocampal astrocytes and clarified mechanisms underlying the [Ca2+][i] elevation. Dopamine produced the increase in levels of [Ca2+][i] in a concentration-dependent manner. This elevation was not dependent on extracellular Ca2+, whereas it was inhibited by inhibitors of phospholipase C, inositol 1,4,5-trisphosphate receptor (InsP3R) and Ca2+/ATPase in stores, suggesting an involvement of Ca2+ mobilization from InsP3R in this event. These results suggest that astrocytes could be a target for dopamine, and astrocytic Ca2+ responses may modulate some neuronal functions in the rat hippocampus.

457 THE EFFECTS OF NON-CONTINGENT ELECTRIC FOOTSHOCK ON THE ACQUISITION OF INTRAVENOUS METHAMPHETAMINE SELF-ADMINISTRATION

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Previous research has indicated a role for the hypothalmo-pituitary-adrenal axis in the acquisition of intravenous cocaine self-administration. For example, data from our laboratory has shown that exposure to non-contingent electric footshock facilitated the acquisition of cocaine self-administration. This experiment was designed to determine whether footshock stress produces similar effects on the acquisition of methamphetamine self-administration. Male Wistar rats (n = 11) were surgically implanted with indwelling jugular catheters. The rats were randomly assigned to one of two test groups (footshock, control) prior to any training sessions. The rats in the non-contingent footshock group received approximately 50 random footshocks (0.6 mA) during a 1-h session prior to all food training and self-administration sessions. The rats were initially trained to respond for food during daily training sessions. The first day of the week remained a food training session throughout the experiment to maintain lever-pressing behavior and to examine possible nonspecific effects of the treatments. Methamphetamine was available 4 days a week starting at 0.075 mg/kg per infusion with weekly doubling of doses ending at 0.12 mg/kg per infusion. Plasma corticosterone was measured prior to any pretreatment on the first day of the week and post-session on the last day of each dose. Exposure to non-contingent electric footshock shifted the ascending limb of the methamphetamine dose-response curve upward and to the left, indicating that these rats were more sensitive to the reinforcing effects of methamphetamine at lower doses than control rats. In contrast, the descending limb of the acquisition dose-response curve was unaffected. Studies are currently underway to further elucidate the role of corticosterone in this effect.

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458 NEUROPSYCHOLOGICAL MEASURES OF VENTROMEDIAL PREFRONTAL CORTICAL FUNCTIONING PREDICT CUE-REACTIVITY

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Drug dependent populations perform poorly on neuropsychological decision-making tasks sensitive to functioning of the ventromedial prefrontal cortex (VMPFC). It has been hypothesized that VMPFC dysfunction disposes patients to poor decision-making, and thus to relapse. On the other hand, the VMPFC is activated during cue-induced craving states suggesting that robust VMPFC functioning might enhance the strength of the drug-appetitive response. In this study we examine the relationship between VMPFC functioning and both subjective reports and neural markers of craving in response to cue-related stimuli in the lab. About 30 drug-dependent subjects (20 cocaine-dependent and ten heroine-dependent) completed a neuropsychological test battery containing two measures recently validated as sensitive to VMPFC functioning: the Gambling Task (GT) and the Rogers Decision-Making Task (RDMT). A single VMPFC measure was obtained by converting performance into Z-scores and averaging across the tasks. On a separate study day, all subjects participated in an fMRI experiment in which they watched a video containing scenes of drug use, as well as a control video of neutral stimuli. Subjects were probed to report their craving during the videos. Correlational analysis indicated a highly significant positive relationship between VMPFC functioning and subjective reports of craving in response to drug cues (r = 0.48, P < 0.01). At the time of this submission, examination of the relationship between VMPFC functioning and the neural signature of craving (e.g. activation of the amygdala and anterior cingulate) is still underway and will be reported in the presentation. Given the importance of the VMPFC in supporting motivation for less immediate reward, it is possible that mounting a craving response in the setting of an fMRI scan (in which drug is not available) may require good VMPFC functioning. A positive relationship between high cue-reactivity in the lab and good decision-making would have important implications for attempts to use cue-reactivity for treatment outcome prediction.

459 MOTIVATIONAL INTERVIEWING FOR ADOLESCENT SMOKERS: PRELIMINARY RESULTS FROM A RANDOMIZED CLINICAL TRIAL

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Because 80% of tobacco use begins before the age of 18 in the United States, it is estimated that approximately 5 million adolescents will die prematurely in adulthood from smoking-related diseases (MMWR; 2000). In response, clinical researchers have been focusing considerable effort to address and intervene with adolescent smoking. We examined the relative efficacy of a brief motivational interview (MI) versus standard care (SC) for adolescent daily smokers who were not necessarily interested in quitting. Adolescents recruited from medical settings, schools, and the community were randomly assigned to either MI or SC after completing assessment. Preliminary results are available for 95 teens who have completed 3-month follow-up; recruitment and enrollment of additional participants in the study is expected to conclude in the spring of 2002. Consistent with our prior research (Colby et al., 1998), teens in both conditions significantly decreased number of cigarettes smoked per day as the DV, re...
smoked five or fewer cigarettes per day at baseline, 23% in SC versus none in MI had increased smoking by follow-up. For those who smoked 6–10 cigarettes/day at baseline, 14.3% in SC had decreased smoking at follow-up, compared to 41.2% in MI. For heavier smokers (11 or more cigarettes/day at baseline), 13.3% in SC decreased use versus 33.3% in MI. Results highlight the benefits of MI and the need for more intensive interventions for heavier smoking adolescents.

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460 THE TERMINAL ELIMINATION HALF-LIFE OF BUPRENORPHINE

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The terminal elimination half-life (t1/2) for a drug is an important pharmacokinetic parameter used to determine loading and maintenance doses, and the volume of distribution for the drug. Buprenorphine t1/2 s reported in the literature vary from 2.3 to 44 h. This variation in reported t1/2 s probably arises from the length of time that buprenorphine could be detected in plasma after administration. The appropriate detection time should encompass proposed durations between dosings of 1–3 days. We have now further evaluated previously published data (Chawarski et al. Drug Alcohol Depend. 55 (1999) 157-163) on buprenorphine plasma concentrations from 24, 48 and 72 h after dosing. Samples were from eight subjects who received three sublingual doses of liquid buprenorphine (32, 40 and 44 mg/70 kg) in different study sessions. Within and between subjects the t1/2 s varied, but mean values of 38.2, 30.1 and 30.2 h did not differ significantly between doses of 24, 48 and 72 mg/70 kg, respectively, using one-way analysis of variance with the Tukey post-hoc test (P < 0.05). These data present t1/2 s that would be relevant for multi-day dosing intervals of buprenorphine, and show that the t1/2 is independent of a sublingual dose.

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461 POST-CESSATION versus 3-MONTH FOLLOW-UP SMOKING STATUS OF TEEN TOBACCO SMOKERS AS A FUNCTION OF MARIJUANA USE


MARIJUANA (MJ) use is more prevalent in teen tobacco smokers compared to nonsmokers, yet little research has examined the impact of marijuana use on tobacco cessation outcomes. We compared the degree of change in tobacco smoking—as assessed by self-report of cigarettes per day (CPD) and expired air carbon monoxide (CO)—over 2 time intervals: after 3 months of treatment and after the 3-month follow-up following treatment. We divided participants into two groups: MJ smokers (at least one use during the 2-week period preceding enrollment) versus non-MJ smokers at baseline. We also compared participants on the basis of number of days of MJ smoking at baseline to assess whether frequency of MJ use correlates with change in tobacco smoking. We analyzed data from 26 teen smokers (mean age 14.8 ±1.4 years, CPD 19.5 ±9.4, 77% female, 23% African American, mean Fagerström Test of Nicotine Dependence 6.72 ±1.14); 14 (54%) of these subjects had reduced MJ preceding their intake. Results for all subjects indicate a mean reduction of 85% in CPD during treatment with no significant increase evident at follow-up. There were no significant changes in CO levels during treatment or follow-up. At baseline, Spearman correlation coefficients indicated nomanly significant associations of MJ use frequency with higher CPD (r = 0.38, P = 0.05), higher CO (r = 0.34, P = 0.09) and lower motivation to quit (r = 0.41, P = 0.07). However, preliminary findings indicate tobacco outcomes to be no worse for MJ users compared to non-MJ users.Data on motivation to quit as a mediating factor of cessation outcome will also be presented.

462 PREDICTING RELAPSE FOLLOWING SUCCESSFUL OUTPATIENT MARIJUANA TREATMENT

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Research on cigarette smoking, and alcohol, heroin, and cocaine dependence suggests that relapse following treatment is predicted by a number of factors. These include the amount of abstinence achieved during treatment, proximal events such as recent stressors and mood changes, and cognitive appraisal variables such as motivation to change and confidence in abstaining from use in high-risk situations (i.e., situational-confidence). However, little research has examined relapse with marijuana dependence. The current study examined predictors of relapse to heavy marijuana use (>15 days/month) for individuals who were abstinent at the end of a 14-week outpatient marijuana dependence treatment. 35 adults (28 men and 7 women) were abstinent at the end of treatment and had achieved two or more weeks of continuous documented abstinence during treatment. More than 50% (n = 18) returned to heavy marijuana use within 8 months after treatment and over a third (n = 12) within 4 months. Univariate comparisons between relapers and non-relapers were conducted on demographics, marijuana history, abstinence during treatment, and psychosocial functioning and cognitive appraisal variables at the end of treatment. Survival analysis of time to relapse to heavy use was conducted using Cox regression controlling for treatment assignment. From both univariate and survival analysis tow factors, situational-confidence at the end of treatment and sex significantly predicted relapse and time to relapse. Being male and higher situational-confidence ratings were associated with delayed relapse. The influence of an individual’s rating of situational-confidence is consistent with Stephens et al. (1994) who examined predictors of marijuana treatment outcome. The relapse rates found in the current study are similar to those of other substances of abuse, and suggest that even for marijuana dependent individuals who achieve abstinence during treatment, relapse to heavy use is common and occurs relatively quickly following treatment.

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463 BARRIERS TO EMPLOYMENT FOR INDIVIDUALS WITH HIV/AIDS: ALCOHOL AND DRUG USE

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Individuals with HIV/AIDS face numerous obstacles to employment even as their conditions become more manageable with advancements in anti-viral medications. Quantitative and qualitative data from 51 subjects with HIV/AIDS through a series of three comprehensive interviews during 2000–2001. About 74% of the subjects were male, 59% were ethnic minorities, 82.4% had multiple disabilities, and approximately 53% were symptomatic of AIDS (e.g. CD4 cell count <200 cells/microliter plasma). About 63% of the subjects scored higher than ‘live’ on the short version of the M.A.S.T. Employment outcomes, and employability ratings, between subjects reporting
alcohol and other drug (AOD) use and those subjects reporting no AOD use were comparable. Subjects cited fatigue, fear of being exposed to illness, discrimination, need for new training, disclosure issues, potential loss of benefits, and a need for flexible work hours as major barriers to employment. Substance abuse was determined to be one of several factors adversely impacting employment and quality of life among study subjects.

464 OPPOSING MECHANISMS MAY REGULATE COCAINE SELF-ADMINISTRATION IN G-PROTEIN-GATED POTASSIUM CHANNEL SUBUNIT KNOCKOUT MICE

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G protein-gated, inwardly-rectifying, K⁺ (GIRK) channels are potently activated by a2-adrenergic, cannabinoid (CB1), D2-4 dopaminergic, opioid (μ, γ, κ), 5-HT1A, GABAB, m2 muscarinic, and somatostatin receptor stimulation. GIRK channels are hetero- and homotetrameric complexes formed by a family of four related subunits, three of which (GIRK1, GIRK2, GIRK3) exhibit overlapping but distinct expression patterns in the rodent central nervous system. The purpose of the present experiment was to examine the behavioral effects of cocaine on mutant mice lacking GIRK2, GIRK3, and both GIRK2 and GIRK3. We show that intravenous cocaine self-administration in mice lacking GIRK2 or GIRK3 is virtually abolished. In animals lacking both GIRK2 and GIRK3, however, self-administration of cocaine is observed at approximately half the level of wild-type control mice. The observed effects appear selective for the rewarding effects of cocaine, as all of the knockout lines tested show apparently normal behavior maintained by 'natural' rewards such as food and water. Knockout mice can also exhibit cocaine-induced locomotor sensitization at rates and magnitudes comparable to wild-type mice. Our findings suggest that channels composed of GIRK2 and/or GIRK3 contribute to distinct neural circuitries and/or neurotransmitter pathways that may exert important influences on the rewarding effects of cocaine.

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465 TOLERANCE TO THE REINFORCING EFFECTS OF COCAINE AFTER BINGE SELF-ADMINISTRATION

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Repeated administration of a drug can produce tolerance or sensitization to the behavioral effects of the drug depending on many factors. However, self-administered cocaine under typical session conditions (i.e. 2–3 h/day) fails to produce dramatic changes (i.e. tolerance or sensitization) in the potency or efficacy of the drug. Recent data suggest that increasing access conditions (e.g. session length) increases levels of cocaine-maintained behavior on a fixed ratio (FR) schedule. It is not clear whether this is an instance of tolerance (to the rate-decreasing or reinforcing effects) or sensitization. In this study, changes in cocaine-maintained breakpoints on a progressive ratio (PR) schedule were examined after one of two models of binge self-administration. Sprague–Dawley rats were implanted with intravenous cannulae and trained to self-administer cocaine (1.5 mg/kg per infusion) on a FR1 schedule of reinforcement. Subsequently, breakpoints were determined for three doses of cocaine (0.375, 1.5 and 3.0 mg/kg per inf) in separate groups of rats. Once stable, a discrete trials procedure was instituted for three groups of rats. In this procedure, a retractable lever was inserted into the chamber (signaling the start of a trial), five times per hour, 24 h a day, for five consecutive days. A trial ended with a lever press (and subsequent infusion) or after 10 min, whichever occurred first. These schedule conditions typically result in a 2–3 day ‘binge’ where almost every trial ends with an infusion, followed by a self-imposed abstinence and subsequent re-initiation of drug-taking. Another group of rats were given access to cocaine on a FR1 schedule for 24 h (binge self-administration). In all cases, the cocaine-maintained breakpoint decreased (i.e. the dose-response curve shifted downward), indicating tolerance to the reinforcing effects of cocaine. Together, these data show that binge self-administration produces tolerance to the reinforcing effects of cocaine.

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466 EVALUATING THE PROGRESS OF RESIDENTIAL AND OUTPATIENT TC TREATMENT

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Hypotheses-The Client Assessment Summary (CAS) and Staff Assessment Summary (SASS) assist therapeutic community counselors and clients to evaluate treatment progress. This study examines whether the previously found four-factor structure with residential facilities holds with an outpatient population. In addition, the study aims to replicate the finding of Kressel (2000) highlighting clients, rather than counselors, as initially rating treatment progress as more advanced. Species–Daytop Village clients and counselors from residential and outpatient New York City area facilities. Number of subjects-205 pairs of clients and counselors completing the instruments for the first time. Procedures-As part of a NIDA funded project, counselors were trained on how to use the SAS and teach their clients the CAS. Following training, both separately completed their instrument and discussed results. Results-Failed to find four-factor model on CAS or SASS. Two-factor (developmental and psychological) and three-factor (developmental, psychological, and programmatic) models best accounted for total variance. Confirmed that clients, not counselors, rated higher perceived treatment progress (P < 0.05). CAS and SASS, across facilities provided good reliability alphas on all items and on overall scores (0.77–0.91). Statistical Analyses-CFA, ANOVA, Reliability Analysis. Importance of Findings-Provides theoretical and psychometric evidence indicating the similarities and differences between residential and outpatient TC treatment. This psychometric data will benefit the use of instruments in future TC work.

467 DETERRENCE AND PREVENTION OF DRUNK DRIVING AMONG REPEAT DUI OFFENDERS


Laws may deter illegal behavior if they are widely perceived to result in swift, certain, and severe sanctions. This type of deterrence may be conceptualized as an external behavioral control. DUI laws may also modify behavior by changing drivers’ internalized norms and values concerning drinking and driving (internalized control). We asked multiple DUI offenders (DO; N = 135) questions used by Berger and Marelich (1997) to assess the external and internalized behavioral controls produced by DUI laws on the drunk driving behavior of California drivers (CD). We find that whereas attitudes consistent with internalized behavioral controls are similar across groups, DO exhibit
fewer attitudes consistent with effective external controls. CD and DO describe drunk driving as morally wrong (93 and 93%, respectively), and support random breath tests (71 and 75%) at equivalent rates, suggesting comparability in their internalized controls. In contrast, DO regard arrest for drunk driving as less likely, and the consequences of arrest as less certain than do CD. Despite holding normative beliefs consistent with internalized control, DO report frequent drunk driving offenses in the past year, and we find no significant correlation between internalized control and the number of self-reported drunk driving offenses in the past year. Similarly, we find only weak evidence that attitudes consistent with external control correlate with the frequency of reported drunk driving offenses. The results suggest that self-reported attitudes toward the law and drunk driving may be weak indicators of external and internalized behavioral controls.

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468 LONGITUDINAL FINDINGS FROM 4 MONTHS THROUGH 3 YEARS OF AGE

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The influence of prenatal cocaine exposure on children’s language functioning was evaluated longitudinally at six time-points from 4 months through 3 years of age. Methods: The Miami Prenatal Cocaine Study prospectively enrolled 476 full-term, African–American infants at birth, categorized as cocaine-exposed (CE: n = 253) or noncocaine exposed (NCE; n = 223) by maternal self-report and bioassays (maternal/infant urine, meconium). The Bayley Scales of Infant Development (BSID), scored using the Kent Scoring Adaptation for Development (BSID), scored using the Kent Scoring Adaptation for Language Fundamentals-Preschool (CELF-P) was administered at 3 years. From the original sample, 464 children received at least one language assessment during the longitudinal study period and were included in the present analyses. Results: Using General Estimating Equations (GEE) longitudinal analyses, CE children had lower overall language skills than NCE children (D = −0.151; 95% CI = −0.269, −0.033; P = 0.012). Longitudinal findings remained stable after evaluation of potential confounding influences including other prenatal drug exposures and sociodemographic factors. Preliminary evidence also suggested possible mediation through an intermediary effect involving cocaine-associated deficits in fetal growth. Discussion: Although the cocaine-associated language deficit is subtle, it may have important ramifications for long-term academic and social adaptation, particularly when taken into consideration within the broader context of other potential risk factors.

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469 DEVELOPMENTAL TRAJECTORIES OF DEVIANT PEER AFFILIATION IN CHILDREN OF DRUG-DEPENDENT FATHERS AND CONTROLS

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Affiliation with delinquent peers has been shown to be a major risk factor for the development of antisocial and substance abuse behaviors in adolescence. Children of drug dependent fathers are at elevated risk for becoming substance abusers as a consequence of the interactions of both genetic and environmental factors. However, little data is available concerning the developmental trajectories of deviant peer affiliation in this high-risk group from pre-adolescence into adolescence. In this study, we have prospectively examined the density of peer deviant peers among the social networks of children of drug dependent fathers at ages 10, 12 and 16 years, and compared them with those of control children. Using a repeated measures general linear model, we found a significant group × time interaction such that greater deviant peer affiliation among the high-risk children was found at each time point. However, the trajectory of deviant peer affiliation showed an increasingly augmented level of affiliation maximizing at age 16 among high-risk youth. Associations between the magnitude of deviant peer affiliation, the severity of problem behaviors, and drug use are also examined. The study highlights the importance of this social developmental process in the liability for substance abuse and antisocial behaviors, and suggests that this could be a critically important target for prevention efforts.

470 SIDE-EFFECT PROFILES OF ISRAIDIPINE IN PHASE II CLINICAL TRIALS OF POSSIBLE EFFECTIVENESS FOR COCAINE TREATMENT

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Two double-blind, double-dummy studies were conducted to assess whether Isradipine pretreatment blocked the acute effects of i.v. doses of saline, 0.325, or 0.65 mg/kg cocaine in cocaine-dependent research volunteers who were not seeking treatment. In study 1, 13 males and 5 females, 19–44 years of age received acute doses of 0, 15, and 30 mg isradipine sustained release (three dose levels) as a 5-h pretreatment before the three cocaine doses in a 3 × 3 factorial design testing acute effects of the drug interaction. The primary side effect complaint of clinical significance was headache which tended to emerge in the afternoon hours about 3 h after cocaine or 8 h after isradipine dosing. This occurred in only six subjects without isradipine treatment and in 15 and 17 of the 18 participants receiving the low and high dose pretreatments, respectively. The second study tested repeated oral doses of 30 mg isradipine sustained release plus 15 mg immediate release in eight males, 19–44 years of age. Placebo or 30 mg isradipine sustained release were administered q.HS for 4 days before beginning an ascending series of cocaine doses (saline, 0.325, and 0.65 mg/kg, respectively) across the next 3 days. About 2 h before each i.v. dose, participants also received 15 mg immediate release isradipine or placebo. Again, headache was the primary complaint of significance for six of the eight participants. In both studies, headaches were frequent enough for participants to seek tylenol treatments, p.r.n., although no subject found them intolerable enough to cause study drop-out. These results suggest that chronic high dose isradipine treatment can be tolerated by cocaine-dependent patients.

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471 PSYCHOLOGICAL DYSREGULATION AND RISK OF DRUG INVOLVEMENT: TEST OF THE RELATIONSHIP AMONG 10,429 CENTRAL AMERICAN ADOLESCENTS

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Poor self-regulation (‘psychological dysregulation’—PD) in early childhood has been posited (Tarter et al. 1999) to presage later problem behaviors, including drug use and abuse. This model hypothesizes that infants with a difficult temperament are more likely to manifest conduct problems in childhood, drug involvement by early adolescence and drug dependence by young adulthood. To promote research in this area, Mezzich et al. (2001) developed the Dysregulation Inventory (DI), a self-report index of affective, behavioral, and cognitive dysregulation. To test whether PD is related to the likelihood of drug (alcohol, cigarette, inhalant, marijuana, cocaine, crack, and ecstasy) use and abuse among 12–19 year old adolescents, we administered an abbreviated Spanish language version of the DI to 9936 students, 258 drug abusers, 131 street children, 64 offspring of addicts, and 30 juvenile delinquents in Panama and Costa Rica. In support of the discriminant validity of the DI, highly significant group differences were found ($F = 74.67, 4 df, P < 0.0001$). Students had the lowest mean dysregulation score and drug abusers the highest (Effect size $ES = 1.01$), while the other high-risk groups had approximately equivalent intermediate scores. Female and Costa Rican students had slightly higher mean dysregulation scores ($ES = 0.13$ and 0.19, respectively). DI scores showed an ‘inverse U’ relationship with age, peaking at 15 (maximum $ES = 0.16$). Among students, the likelihood of lifetime drug use and problems increased monotonically with increasing quintile of dysregulation ($P < 0.0001$ for all substances studied). Overall, the probability of drug involvement was three to seven times greater among youths with the highest versus those with the lowest DI scores. This relationship did not differ by sex or country. The Dysregulation Inventory may represent a valuable screening tool, permitting public health workers to identify youths at markedly increased risk of drug involvement.

**472 Comparison of clinical outcomes for addicted patients, in Bristol UK, on drug treatment and testing orders or standard health treatments, over a 3-year period**

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**BACKGROUND:** Between 1998–2001, 50 patients have been treated under Drug Treatment and Testing Orders (CJ). The treatment plans conformed with treatment as offered to health referrals to the Service (BSDS). We wished to critically ascertain whether the CJ referrals were a different population and additionally to examine the clinical outcomes for this population. **METHOD:** CJ and BSDS notifications between 1998–2001 to Regional Database were compared for age, gender, race, main drug/mode of consumption. Additionally 50 patients were matched from each cohort by age, gender, race and main drug/mode of consumption, compared from case records, (a) at assessment; for daily drug use, actual combinations of drugs used daily, registration with GP, dual diagnosis (ICD10), criminal activity, significant PH of amphetamine misuse, (b) at review; for retention, completion, ongoing treatment, requests for further treatment on relapse, physical health, mental health, housing, employment, social integration and ongoing criminal activity. **RESULTS:** Clinical Outcomes; both cohorts showed improvement in clinical outcomes, completion rates the same, retention CJ 63% BSDS 50%, marked improvement in physical and mental health CJ, marked improvement in housing and social integration CJ, less criminal activity BSDS with health treatment. Differences between cohorts; CJ narrower age range and narrower profile of drug misuse, CJ more males and fewer dual diagnosis, CJ lower engagement with primary health care, fewer significant amphetamine problems but both CJ and BSDS failed to retain significant numbers of patients. CJ patients being in breach of court order BSDS patients failing to attend. **CONCLUSIONS:** Despite the different routes of referral it is noteworthy that 71.7% of BSDS were criminally active at assessment. These results suggest there is a need for access to secondary treatment services both via health referrals and Criminal Justice referrals.

**473 Schedule-induced alcohol consumption in fischer and lewls rat strains**

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Although the Fischer (F344/N) and Lewis (LEW/N) rat strains have been reported to differ in their tendency to self administer a variety of recreational compounds (including cocaine and morphine), little has been reported regarding such reactivity to alcohol, partly due to the fact that it is generally difficult to get rats to self administer alcohol. One procedure in which rats reliably consume alcohol is schedule-induced polydipsia (SIP), a design in which the animal is provided with access to a fluid (in this case, alcohol) under conditions of the spaced delivery of food pellets. This procedure was used in the present experiment to assess whether F344/N and LEW/N strains differ in alcohol consumption. Initially, rats from each of the two strains were reduced to 85% body weight by food restriction and given daily sessions of non-contingent pellet delivery (a single 45 mg pellet once every 30 s for a total of 60 pellets) during which water was freely available. Once the strains displayed SIP (approximately 25 days), saccharin (the alcohol vehicle) replaced water during the scheduled food deliveries (14 days). Alcohol was then gradually added to saccharin (1% increments approximately every 1–2 weeks) until 5% ethanol was available. Both strains acquired SIP, displaying the typical post-pellet pattern of licking. The two strains differed significantly in its acquisition, however, with the F344/N strain consuming greater amounts of water than the LEW/N strain. When saccharin was made available, both strains increased fluid consumption, but under this condition there were no significant differences between the two strains. When alcohol was added to the saccharin solution, the LEW/N strain drank significantly more than the F344/N strain (when the concentration of alcohol was 2, 3, 4 and 5%). Under this procedure of drug intake, it appears that the LEW/N rat is differentially responsive to alcohol, a difference noted for other drugs within other self-administration designs.

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**474 Cocaine inhibits dendritic cell functions in long-term non-progressors of HIV infection**

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Dendritic cells are efficient antigen presenting cells and potent stimulators of antigen specific T cell responses. Functional deterioration of this population is associated with rapid progression of HIV disease. Long-term non-progressors (LTNP) represent a minority of HIV infected patients in whom an effective immune response, including intact dendritic cell function, may play a significant role in prevention of disease progression. Although drug abuse has been associated with increased HIV infection and progression of disease, the effect of drug abuse on dendritic cell numbers and functions is not known. We hypothesize that drugs of abuse, such as cocaine, may negatively affect the function of dendritic cells leading to immunosuppression and progression of HIV disease. Peripheral blood mononuclear cells (PBMC) from LTNP and normal controls were cultured...
in vitro with different concentrations of cocaine (10−7−10−12 M) and examined for dendritic specific markers (CD11c, CD1a, CD80 and CD84) by flow cytometry. Further, PBMC derived dendritic cells from LTNP were examined for their capacity to process HIV specific antigen on irradiated 8E5/LAV cells to stimulate lymphocyte proliferation in vitro. Our results show that the CD11c positive subpopulation was significantly lower (P < 0.05) in LTNP compared to controls. No significant differences in CD1, CD80 and CD84 expression was observed between LTNP and normal controls. Cocaine treatment produces only a moderate reduction in CD11c marker expression in LTNP. In proliferation assays, LTNP showed higher antigen specific stimulatory responses compared to normals. However, cocaine-induced inhibition of LAV specific stimulatory responses was significantly greater in LTNP than normals. Studies, using CD4/CD8 depleted PBMC populations are currently underway to determine T cell specific responses. Our results suggest that dendritic cell numbers and functions are relatively intact in LTNP and cocaine may significantly downregulate dendritic cell functions. These results support the premise that cocaine may modulate dendritic cell functions and progression of HIV infections.

475 MOLECULAR BASIS OF THE IN VITRO EFFECT OF IL-16 ON MORPHINE- AND DAMGO-INDUCED GENE EXPRESSION OF HIV-CXCR4 CO-RECEPTOR IN HIV-1 TRANSFECTED 8E5/LAV T-CELL LINE

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Interleukin (IL)-16, a proinflammatory cytokine produced mainly by CD8+ T cells has been found to affect T-lymphocyte function and to inhibit human immunodeficiency virus type 1 (HIV-1) replication in vitro. Previous studies showed that HIV-1 T-tropic co-receptors CXCR2 and CXCR4 play a significant role in susceptibility to infection. Although drug abuse, particularly with opioids has been linked as a cofactor in the immunopathogenesis of HIV-1 infections, the underlying molecular mechanism(s) has not been fully elucidated. Previous studies have shown that morphine plays a significant role as a cofactor in susceptibility and progression to HIV infection possibly by modulating HIV coreceptors. We hypothesize that IL-16 mediates its anti-HIV effects through downregulation of the expression of the CXCR4 coreceptor and further reverses morphine induced upregulation of CXCR4. 8E5/LAV T cells were cultured with either IL-16, morphine or morphine agonist [D-Ala2, MePhe4, Gly(ol)(5)] enkephalin (DAMGO) or IL-16 plus morphine/DAMGO for 6-72 hrs. Total RNA was extracted, reverse transcribed and cDNA was amplified by PCR using CXCR4 and housekeeping b-actin primers. Our results show that morphine and its agonist DAMGO specifically upregulates CXCR4 gene expression and IL-16 significantly down regulates both constitutive and morphine/DAMGO induced CXCR4 gene expression in a dose and time dependent manner. Further FACS analysis using PE-conjugated anti-CXCR4 antibodies also confirmed the RT-PCR analysis demonstrating decreased number of CXCR4 positive 8E5/LAV cells treated with IL-16. These results demonstrate that drug use may upregulate HIV entry coreceptors that facilitate infection and suggest a therapeutic role of IL-16 against HIV disease progression.

476 MECHANISM OF CONTAMINATION OF US PAPER CURRENCY


Measurable amounts of cocaine (as well as methamphetamine, heroin, and other abused drugs) can be found on circulating paper currency. Contamination probably occurs after drug users handle currency, with drugs being deposited on currency after excretion into sweat. Studies have shown that cocaine is excreted into sweat. This preliminary experiment was designed to test the concept of direct transfer of cocaine from the user to money. New $1 bills (US Treasury) were covered with an impermeable dressing to minimize environmental losses, and placed (1 bill on two occasions) on the backs of four subjects. Each received either an intravenous infusion of cocaine (0.375 mg/kg per h) or placebo as part of an experiment on cocaine pharmacotherapies. To examine the effect of sweat rate on cocaine excretion, heating pads (42 ºC) were placed over the bills. Sweat rate (measured with a perspirometer) was significantly increased (P = 0.012) with heat (from 0.10 ±0.02 to 0.27±0.12 mg/min per cm²). Notes absorbed 36.7±17.4 mg unheated, and 66.9±5.6 mg when heated. Results with paper currency were compared with commercially available sweat collection patches. Cocaine levels are being measured using chiral capillary GC-MS following methanol extraction. Results will be available by March, 1 2002.

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477 EFFECTS OF CONTINUOUS INFUSION WITH AMPHETAMINE ON COCAINE SELF-ADMINISTRATION AND FOOD-MAINTAINED RESPONDING IN RHESUS MONKEYS

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Amphetamine is one ‘agonist substitution medication’ that is currently being evaluated clinically for its utility in the treatment of cocaine dependence. In the present study, the effects of continuous infusion with saline or amphetamine (0.01–0.1 mg/kg per h, i.v.) on cocaine- and food-maintained responding in rhesus monkeys were evaluated using two procedures. In one procedure, injections (saline or 0.001-0.1 mg/kg per injection cocaine) and 1 gm food pellets were available under a second-order schedule during alternating daily sessions of drug and food availability. Amphetamine produced a dose-dependent downward shift in the inverted U-shaped cocaine self-administration dose-effect curve, and these effects were sustained for up to 28 days. Doses of amphetamine that decreased cocaine self-administration produced smaller and transient decreases in food-maintained responding. In the second procedure, cocaine injections (0–0.1 mg/kg per injection) and food pellets were available under a concurrent choice schedule. Each daily 2 h session was divided into 5 cycles of cocaine and food availability. During each cycle, monkeys could respond on one key for cocaine injections or on a second key for food pellets. Under this choice procedure, increasing cocaine doses produced a dose-dependent and monotonic increase in the percent of reinforcers obtained on the cocaine key. Amphetamine dose-dependently decreased cocaine choice and usually shifted the allocation of responding to the food key. These results indicate that chronic treatment with amphetamine can produce dose-dependent and sustained decreases in cocaine self-administration in rhesus monkeys.

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478 A RANDOMIZED TRIAL OF NEUROLEPTIC VERSUS QUETIAPINE THERAPY IN DUAL-DIAGNOSIS

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Cocaine and amphetamine abuse is much more common in patients with major psychiatric disorders than in the general population with lifetime rates of abuse as high as 61% in bipolar disorder (BPD) and 47% in schizophrenia. Studies show that neuroleptic use (DA antagonists) increase, while atypical antipsychotics (5-HT/DA antagonists) decrease stimulant self-administration in rats. This finding is clinically relevant as patients with severe psychiatric illnesses commonly receive neuroleptics and those who abuse stimulants often receive higher doses than those without substance abuse. The present study examined the effects of chronic neuroleptic therapy versus the atypical antipsychotic, quetiapine, on stimulant cravings in dual-diagnosis outpatients over a 12-week period. Methods: 24 outpatients (15, male, 9, female; mean age = 36±8) receiving chronic neuroleptic therapy participated in the study. Diagnoses included 13 BPD, three schizophrenia, six schizoaffective disorders, and two major depressive disorders. All patients had stimulant abuse or dependence as confirmed by DSM-IV criteria. Patients were randomized to either continue (C) or discontinue (D) neuroleptics. Currently psychotic patients in the DC group (n = 8) were tapered off the neuroleptic and given quetiapine. The Hamilton Depression Rating Scale (HRSD-17), Brief Psychiatric Rating Scale (BPRS-18), and Cocaine Craving Questionnaire (CCQ-10) were primary outcome measures. Results: A reduction (P < 0.01) in drug cravings (CCQ-10) in the DC group (n = 12) as compared to the C group (n = 12) was noted. In the DC subgroup, those receiving quetiapine (n = 8) had reductions in CCQ-10 scores (P < 0.01) as well as BPRS-18 and HRSD-17 (P < 0.05) as compared to the neuroleptic C group. Discussion: This is the first randomized trial to explore the efficacy of neuroleptics versus atypical antipsychotics in dual-diagnosis patients. This preliminary data suggest that neuroleptic therapy may contribute to stimulant cravings in dual-diagnosis patients regardless of drug rehabilitation treatment. In contrast, quetiapine may have efficacy in treating both stimulant cravings and mood symptoms. Further investigation of this agent is warranted.

479 INVESTIGATION OF SEX DIFFERENCES IN THE ACUTE AND LONG-TERM EFFECTS OF MDMA ADMINISTRATION IN RATS

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Studies have shown robust sex differences in the behavioral and neurobiological effects of many drugs of abuse, including cocaine and alcohol. The current investigation extends these studies to 3,4-methylenedioxymethamphetamine (MDMA; ‘Ecstasy’). The use of MDMA is rising exponentially, and a newly released report suggests that women are more susceptible to neurobiological damage following MDMA usage. To investigate sex differences to the effects of MDMA in an animal model, male and female rats received a standard neurotoxic dosing regimen of MDMA (15 mg/kg, ip, every 12 h for 4 days). Locomotor activity and core rectal temperature increased similarly in MDMA-treated males and females directly following drug administration. Daily administration of MDMA resulted in an attenuation of drug-induced increases in locomotor activity and temperature. Tests of anxiety were conducted on MDMA-treated rats 2 weeks following drug administration. All MDMA-treated rats spent significantly less time on the open arms in the elevated plus maze, suggesting that MDMA treatment was anxiogenic. Male and female-treated MDMA rats were not different. Additional tests of anxiety using the lightdark box and the social interaction test revealed no effect of MDMA treatment. Thus, the long-term effects of MDMA on anxiety are not universal. The specific effect of MDMA on a single test of anxiety resembles similar effects on specific tests of memory and may reflect the subtle long-term functional effects of MDMA usage. These results suggest that the effects of a neurotoxic dosing regimen of MDMA are not sexually dimorphic in the measures of acute locomotor activity and core rectal temperature nor in the long-term effects of MDMA on a variety of measures of anxiety.

480 BRAIN AUTORADIOGRAPHY OF INTRAPERITONEALLY INJECTED C-14 ETHANOL IN MICE


The mechanisms of action of ethanol in the brain are not fully understood. Recent hypotheses on the neurochemical mechanisms of ethanol are: (A) stimulation of GABAA/glycine receptors; (B) inhibition of NMDA receptors; or (C) interaction with opioid receptors. None of these have conclusive experimental support. Nuclear magnetic spectroscopy experiments indicate that a significant proportion of brain ethanol (20–40%) is ‘invisible’ to spectroscopy. Hypothetically, this ‘pool’ of ethanol could be detected by autoradiography. Thus, we hypothesized that ethanol binds to a heterogeneously-distributed, novel brain substrate and used autoradiography with C-14-ethanol to map the distribution of exogenously introduced ethanol in the murine brain. Mice (C57Bl6 strain) were injected intraperitoneally with 20–25 ucurie of C-14 Ethanol. A scintillation counter was used to create a standard curve of blood [C-14 Ethanol] to maximize the blood concentration (found experimentally to be 20 min after injection). CuSO4 and sodium pyrazole were used to inhibit alcohol dehydrogenase. Mice were sacrificed by cervical dislocation under CO2 anesthesia. Cold 0.9% w/v NaCl (2 ml) was perfused transcardially. Brains were immediately removed and snap-frozen. Thereafter, mice brains were cut on a cryostat at 30 microns. Select slides were thaw mounted onto subbed, labeled microscope slides, which were then placed into a cassette with Kodak BioMax TranScreen LE intensifying screens and Hyperfilm MP (35 x 43) autoradiography film. In on-going and future studies we will examine different strains of mice and improve the experimental manipulation of the brain post-mortem. Preliminary results (N = 3) do not show focal uptake, which may suggest that our hypothesis is not supported. This negative result, if confirmed, will help direct future human research in the field.

481 PATTERNS AND DETERMINANTS OF DRUG USE AMONG ADULTS IN ISRAEL: RESULTS OF A NATIONAL HOUSEHOLD SURVEY

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Little is known about the epidemiology of drug use in Israel. We analyzed data from the 1998 national household survey to provide insight into patterns of use in the two major population groups-Jews and Arabs. A total of 2199 persons completed the survey (81% Jews, 19% Arabs). Respondents were chosen from a national multi-stage probability sample designed to represent Israeli household residents between the ages of 18–40, excluding those living in cooperative (kibbutz) communities, individuals in compulsory military service not living at home, and institutionalized persons. Women were oversampled to constitute 60% of the sample. Drug use is defined as past-year use of any illicit drug. Socio-demographic and economic determinants included age, marital status, religiosity, education, household income, and occupation. The associations between SES indicators and drug use were assessed univariately, and multivariately through logistic regression models controlling for the effects of other factors. About 4% of Jewish men and women, and 1% of Arabs, who have never used drugs report a willingness to do so. Past-year drug use was reported by 5% of Jews (7.2% men, 4.0% women. OR = 1.8, 95% CI = 1.2–2.7) and 7% of Arabs (11.4% men, 4.6% women, OR = 2.7, 95% CI = 1.2–5.9). Marijuana is the predominate drug used by Jews (91%) and Arabs (69%). The majority (63%) of male drug users was...
between 25 and 34 years, whereas most female drug users (66%) tended to be younger (18–24 years). Results of multivariate modeling indicate that occupation (manual vs. professional) was the strongest predictor of drug use for Jewish men and women, with significantly lower rates among professionals. Household income was similarly negatively associated with drug use in both sexes. Little differences were noted across education groups. Analyses of the 1998 US-NHSDA data reveal similar relationships with the socio-economic indicators although at higher rates of use. These cross-cultural similarities will be considered. The utility of a national survey for public health policy-making will also be addressed.

482 QUANTITATIVE EEG ABNORMALITIES IN RECENTLY ABSTINENT METHAMPHETAMINE-DEPENDENT INDIVIDUALS

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Methamphetamine exposure is associated with long-lasting reductions in markers for dopaminergic neurons in preclinical models and probably in humans. Quantitative electroencephalography has been used to characterize abnormalities in brain function in a number of disorders, including cocaine dependence. To our knowledge, quantitative EEG has not been used to characterize abnormalities associated with methamphetamine dependence. Methods: The sample included 11 methamphetamine dependent subjects and 11 non-drug using volunteers. Methamphetamine dependent subjects were hospitalized for 4 days to document abstinence; non-drug using volunteers were studied as outpatients. EEGs were recorded in the eyes-closed resting state using a Pz reference, and EEG power in each frequency band (0.5–4 Hz, 4–8 Hz, 8–12 Hz, and 12–20 Hz) was quantitated using a fast Fourier transform. Results: Methamphetamine dependence was associated with globally increased EEG power in the delta and theta bands. There were no differences between the groups in higher (alpha and beta) frequency bands. Conclusions: Recently abstinent methamphetamine dependent subjects demonstrated QEEG abnormalities that are consistent with a generalized encephalopathy. These neurobiologic changes may underlie other previously reported abnormalities in methamphetamine dependence, including depressed mood and impaired cognition. Development of treatments for methamphetamine dependence must take into account these underlying abnormalities.

483 CHARACTERISTICS AND NEEDS OF SUBSTANCE-ABUSING WOMEN ON WELFARE: FINDINGS FROM EVALUATION OF THE CASAWORKS FOR FAMILIES PROGRAM


States face a special challenge moving women with substance abuse problems from welfare to work under the requirements of the 1996 federal Temporary Assistance to Needy Families Program (TANF). Yet, little is known even about the characteristics and needs of this potentially important population. We examined the characteristics and needs of a large diverse sample of substance abusing women on TANF who entered the CASAWorks for Families (CWF N = 673) intervention from 11 sites in nine states. Sites were substance abuse treatment programs, mostly outpatient, specializing in women, and were situated in urban, suburban and rural locales. Substance abusing women on TANF were recruited from welfare offices, welfare employment programs, or other agencies serving this population (e.g., child protective services). This CWF group was compared with: (1) a general TANF sample (GTS N = 157) recruited at local welfare offices in 8 of the 11 sites without regard to clients’ use of addictive substances; and (2) a sample of substance abusing women on TANF entering 81 standard outpatient substance abuse treatment programs in seven metropolitan areas through the Drug Evaluation Network System (DENS N = 520). Findings indicated that substance abusing women on TANF in all samples had multiple, serious and generally chronic health and social problems that can be barriers to employment. In general, the CWF women showed the most severe domestic violence, legal, employment history and psychiatric problems. DENS clients showed the most serious addiction problems. GTS women showed the least severe health, social and addiction problems. Although none of the samples utilized can be considered truly representative, they do provide for the first time a multi-locale, diverse picture of substance abusing women on TANF as compared with other pertinent groups.

484 THE PHENCYCLIDINE (PCP)-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF DRUGS WHICH ALTER GLUTAMATERGIC NEUROTRANSMISSION IN RATS

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Excessive glutamate receptor activation, particularly of the NMDA receptor subtype, has been implicated in a number of neurological disease processes. Many potent NMDA antagonists produce phencyclidine (PCP)-like side effects limiting their clinical utility. Therefore, different approaches to modifying glutamatergic neurotransmission are being investigated. Interest in NMDA antagonists continues with a focus on those with binding characteristics purported to produce fewer PCP-like side effects. In addition, a number of nonNMDA glutamate receptor (AMPA, kainate, metabotropic) ligands and glutamate release inhibitors have shown efficacy in clinically relevant animal models. In this study the discriminative stimulus effects of drugs which decrease glutamatergic neurotransmission were tested in rats (N = 6) trained to discriminate 2.0 mg/kg, i.p. PCP from saline in a standard two-lever drug discrimination paradigm under a fixed ratio schedule of food reinforcement. Two NMDA antagonists with moderate selectivity for NMDA receptors containing NR2B subunits were tested. Felbamate and nylidrin which bind, respectively, to the glycine- and ifenprodil-associated sites on the NMDA receptor complex, produced less than 20% mean PCP-associated lever responding. The lack of PCP-like effects for these compounds may be related to their specific binding interactions with the NMDA receptor or may be due to overriding activity at other CNS sites. Testing of the AMPA antagonist NBQX and glutamate release inhibitor riluzole, both of which should result in an indirect decrease in NMDA receptor activation, resulted in virtually no responding on the PCP-associated lever. Further testing with nonNMDA glutamate receptor ligands and glutamate release inhibitors alone and combined with PCP will provide more information on interactions within the glutamatergic system. Overall, the data provide additional support for the specificity of the PCP-like discriminative stimulus cue not only for drugs associated with altered glutamate receptor activity, but even between drugs which bind to the NMDA receptor but differ in site of activity and receptor subtype selectivity.

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The use of psychostimulants in both children and adolescents is quite widespread. However, systematic studies examining behavioral and molecular effects of cocaine in different developmental stages of mice are limited. When cocaine is repeatedly given to adult animals behavioral sensitization occurs in which an animal becomes more responsive to the effects of the drug. To investigate developmental differences caused by the repeated administration of cocaine, three age groups of male CD-1 mice, post-weanling, peri-adolescent and adults, were administered cocaine IP (20 mg/kg) or saline once daily for seven days starting on postnatal days 24, 33 and 60, respectively. Locomotor activity was measured on days 1, 4 and 7. While on day one all of the mice showed increased activity after cocaine administration, post-weanling mice demonstrated no behavioral sensitization throughout the 7 days of treatment. In contrast, both the peri-adolescents and adults were sensitized to the behavioral effects of cocaine by day 4 of the study. On day 4, peri-adolescent mice showed an initially greater response to the locomotor effects of cocaine that quickly diminished over time. These results demonstrate that chronic cocaine causes behavioral sensitization in peri-adolescent and adult mice, but not in post-weanling mice. The pharmacological effects of cocaine are mediated by inhibition of the dopamine transporter, causing increased dopamine in the synapse. Adenylyl cyclase and DARPP-32 are both mediated by inhibition of the dopamine transporter, causing increased dopamine in the synapse. Adenylyl cyclase and DARPP-32 are both mediated by inhibition of the dopamine transporter, causing increased dopamine in the synapse. Adenylyl cyclase and DARPP-32 are both mediated by inhibition of the dopamine transporter, causing increased dopamine in the synapse. 

This work was supported by NIH/NINDS NS41871 (ME/EMU) and T32DA 07237 (MWA).

The cocaine priming threshold is defined as the minimal level of cocaine that induces reinstatement of self-administration. This value should be independent of whether it results from a series of injections or a single injection of cocaine. Rats trained to self-administer cocaine were placed in an operant chamber, cue-induced lever pressing was extinguished and the cocaine priming threshold was then measured using a series of escalating doses of cocaine. The cocaine priming threshold varied between days in individual rats and the frequency distribution was log-normal with a median of 0.21 mg/kg of cocaine (five rats, 252 sessions). Priming thresholds greater that 2 mg/kg were observed in less than 3% of sessions. If the assumptions used to calculate the priming threshold were accurate, a single injection of 0.21 mg/kg of cocaine should induce priming in 50% of the sessions. In the same rats, the proportion of sessions in which greater than five lever presses were observed following a single i.v. injection of cocaine at doses between 0.03 and 6 mg/kg was measured. The probability of reinstatement dose-dependently increased to 100% after 2.0 mg/kg. The ED50 for the single dose method was 0.23 mg/kg, not significantly different from the median priming threshold. The consistency between the results of these two methods indicates that the definition of the priming threshold is operationally appropriate.

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The continuous improvements of Reggio Emilia’s SERT started with The Q Club, then continued with the Italian Group on Standards followed by the definition of its product standards and finally, in 2000, ISO 9001 certification issued by DNV. Q corresponds to the difference between expected outcome and outcome and focuses on the difference between bearing emphasis and efficiency (the choice of using the ISO reference rather than credit). The keystone of the Q is the agreement with the client on the services to be supplied (increase in his right to citizenship. Lisbon Platform1992). The QS requires that function is tested through in-house and external tests (verifications of the 1st, 2nd and 3rd parts, non-conformity management); which calls for continuous assessment. It was set up to create a contrast with the fundamentalism that existed in early days when social fear was too strong. In the early nineties, the birth on European Policy on the subject was accompanied by Professionals’ Associations. ERIT (www.erit.org) is now a bench-marker. These experiences cannot be exported even under identical regulations (which certainly is not the case in Europe). The European group on project assessment has gathered approximately 30 tools currently in use (The Instruments ofRICS, Mucchi, 1997), compared them, found the ASI to be inadequate and then selected, adapted and validated the MAP (The Minima criteria, Mucchi, 1998). The Group banks on the growth of the philosophy of assessment of operators (Evaluation, Vademecum, Verso l’Utopia, 2000), because either they become leading characters, or the Welfare will be cut.

Supported by DA12043 and DA14189.
Lobeline (LOB) is an antagonist at \(\alpha_4\beta_2\) and \(\alpha_3\beta_2\) nicotinic receptors (nAChRs) and inhibits the dopamine (DA) transporter and the vesicular monoamine transporter (Teng et al., 1998; Miller et al., 2000, 2001). The present study determined the effect of structural modification of LOB by esterification of the 8-hydroxyl functionality. The LOB esters, \(\text{cis}\)-LiBu, \(\text{cis}\)-LAC, \(\text{cis}\)-LPR, \(\text{cis}\)-LBZ, \(\text{cis}\)-LTO, \(\text{cis}\)-LBU, \(\text{cis}\)-LTO, \(\text{cis}\)-LBZ, and \(\text{cis}\)-LAN were 3 to 1400-fold less potent than LOB inhibiting [3H]nicotine ([3H]NIC) binding to rat striatal membranes \(K_i = 0.06, 0.07, 0.15, 0.53, 1.6, 3, 28, 0.02\) \(\mu M\), respectively, probing the \(\alpha_4\beta_2\) subtype. Additionally, \(\text{cis}\)-LBZ inhibited NIC-evoked 86Rb+ efflux from thalamus, suggesting that these ester analogs also act as antagonists at \(\alpha_4\beta_2\) receptors. LOB inhibited [3H]nicotinic acetylcholine ([3H]MLA) binding to rat brain membranes \(K_i = 12\) \(\mu M\), probing the \(\alpha_7\) subtype and inhibited NIC-evoked striatal [3H]DA release \((IC_{50} = 1.8\) \(\mu M\), probing the \(\alpha_3\beta_2\) subtype). In contrast, none of the ester analogs inhibited \((K_i > 100\) \(\mu M\)) [3H]MLA binding or NIC-evoked [3H]DA release. Thus, 8-hydroxyl esterification of LOB decreased affinity, but increased selectivity, for the \(\alpha_4\beta_2\) nAChR subtype. In the transporter assays, \(\text{cis}\)-LTO, \(\text{cis}\)-LBZ, \(\text{cis}\)-LiBu, \(\text{cis}\)-LAC, \(\text{cis}\)-LBZ, and \(\text{cis}\)-LPR were 5 to 10-fold more potent than LOB inhibiting striatal [3H]DA uptake \((IC_{50} = 6.7, 7.5, 7.7, 12, 15, 16, 23, 90\) \(\mu M\), respectively). Furthermore, \(\text{cis}\)-LTO, \(\text{cis}\)-LBZ, \(\text{cis}\)-LAC, \(\text{cis}\)-LiBu and \(\text{cis}\)-LBZ were 2 to 25-fold more potent than LOB inhibiting hippocampal \([3H]\) serotonin ([3H]-5-HT) uptake \((IC_{50} = 2.3, 3.1, 4.5, 17, 31, 77\) \(\mu M\), respectively). \(\text{cis}\)-LAC and LOB were equipotent in the latter assay. These results demonstrate that structural modification of LOB by esterification of the 8-hydroxyl group affords decreased affinity and increased selectivity for the \(\alpha_4\beta_2\) nAChR subtype, and increased affinity at both DA and 5-HT transporters.

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### 491 Homelessness, Substance Misuse and Access to Public Entitlements in a Soup Kitchen Population

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The study examined the effects of homelessness on access to two public entitlements (Medicaid and Food Stamp programs) in a soup kitchen population. Data were collected from a sample of 342 adults at two soup kitchens in New York City. Five hypotheses related to access to Medicaid and Food Stamp programs were tested. Two hypotheses involved the effects housing status: (1) comparing the effects of literal homelessness and unstable housing with stable housing; and (2) comparing literal homelessness with unstable housing. The remaining three hypotheses were related to the role: (3) frequency of drug/ heavy alcohol use; (4) drug/alcohol treatment history; and (5) childcare responsibilities. Results. Sample characteristics were: 51% male; 80% African-American; 92% unemployed; mean age was 39 y. Substance use in the past 30 days was 83% cocaine (powder or crack), 20% heroin, 25% other drugs and 33% heavy alcohol use (five or more drinks per day). Rates of drug/alcohol treatment were 71% lifetime and 31% current. Half of the sample had Medicaid or Food Stamps. Multiple logistic regression analysis fully or partially supported four of the five hypotheses. Access to Medicaid and/or Food Stamps was associated with stable housing (both), lower frequency of drug/heavy alcohol use (Medicaid only), current drug/alcohol treatment (both), and caring for children (Food Stamps only). There was no difference between literal homelessness and unstable housing in their association with public entitlements. Conclusion: The findings support the crucial role of stable housing status and drug/alcohol treatment in mediating access to entitlements. A major policy implication of the study is the need to reduce health disparities through aggressive outreach programs designed to enhance homeless persons’ access to Medicaid and Food Stamp programs.

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### 492 The Brief Qualitative Assessment: Integrating Methods in Drug Abuse Research

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Despite the growing call for mixed-method approaches within the field of drug abuse research, quantitative and qualitative studies remain disconnected, in part because the process of melding the two is poorly understood. This paper illustrates one approach to bridging the two. It assumes that, while quantitative work identifies the symptoms or attendant behaviors of a disease, qualitative work can depart from this background to explore the sensitive and pertinent elements of meaning that shape drug abuse. However, a space must first be created within the quantitative instrument that facilitates the identification of contextual aspects that warrant further examination. The purpose of this paper is to describe the integration of a qualitative elicitation technique into a quantitatively structured study. This technique is part of our ongoing longitudinal study of methamphetamine use. It is a Brief Qualitative Assessment (BQA) that entails 10 min of unstructured interviewing and follows a 2 and 1/2 h Natural History Interview. Its design couples aspects of Kleinman’s Explanatory Model with Scrimshaw and Hurtado’s Rapid Assessment Procedure. First, we experience, psychological numbing, intrusive symptomatology, role impairment/distress) were not correlated with the number of days specific drugs (including alcohol) were used during the prior month. These data point to a clinically significant, albeit complex, association between substance dependence and PTSD in this population.
present examples of the interview topics, which developed along side the understanding of the technique, and interviewees’ responses. Topics included most salient themes of intense methamphetamine (MA) use periods, violence and MA use and sexual relationships, risk-taking behaviors and MA use. Second, because of the uniqueness of the procedure, the implementation protocol is outlined in detail, including special attention to training interviewers in qualitative techniques. Third, the challenges presented by the nonlinear nature of data collection and analysis are discussed. Fourth, the implications of qualitative training of the interviewers on the dynamics of the entire project are described. And finally, we present the concepts (such as the role of self-concept, power and sexual identity in MA use) identified for further qualitative exploration.

493 CHARACTERIZATION OF NICOTINE INTAKE, EXTINCTION, RE-INSTATEMENT AND PRECIPITATED WITHDRAWAL USING 23-H ACCESS TO NICOTINE SELF-ADMINISTRATION

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Few studies have focused on extended access to nicotine in rodents using the intravenous self-administration (SA) procedure. This study characterized nicotine intake using 23-h sessions of SA. Rats were trained to nose-poke for food and water in 23-h sessions for 5 days prior to and after recovery from surgical implantation of jugular catheters. A lever was then introduced and rats self-administered nicotine (0.01 mg/kg per 0.1 ml infusion per s; FR1) for 2 months. Extinction was examined for 1 week during which time nicotine was replaced by saline, and then for 2 weeks following the removal of drug cues (i.e. infusions and light cue). Somatic signs of nicotine withdrawal were examined after mecamylamine administration (0 then 1.5 mg/kg, IP) immediately after the last nicotine session and 3 weeks after extinction. Reinstatement was examined in separate tests after presentation of drug cues and after nicotine administration (0, 0.03, 0.001 mg/kg, IV). Nicotine SA decreased during the first week, increased gradually over the next 3 weeks, and then remained at a stable level. An analysis of the 1st h of drug access revealed a steady increase in nicotine intake after 3 weeks of SA. Extinction of drug-seeking behavior was observed, and this effect was facilitated by removal of drug cues. A mild reinstatement was observed after presentation of drug cues, and this effect was not altered by nicotine. Mecamylamine precipitated robust withdrawal signs immediately following the last nicotine session, and this effect was absent 3 weeks after extinction. These results suggest that rats will self-administer nicotine to the point of producing dependence, and that nicotine SA is increased at certain parts of the daily cycle of intake.

Supported by the Robert Wood Johnson Research Network on the increased at certain parts of the daily cycle of intake.
Objective: To describe club drug use among a cohort of non-injection (NIDUs) and injection drug users (IDUs) in Baltimore, Maryland. Methods: Adolescent and young adult (age 15–30) NIDUs and IDUs were recruited into an ongoing community-based cohort. IDUs must have initiated injection drug use ≤ 5 years prior to study entry. NIDUs must have initiated non-injected cocaine, crack or heroin use ≤ 5 years prior. Club drugs include: ecstasy, LSD, ketamine, non-LSD hallucinogens (i.e. mushrooms, mescaline, peyote), GHB, methamphetamines, and PCP. Drug use was assessed through interviewer-administered questionnaires. Continuous variables were compared using t-tests. Categorical variables were compared using χ² and Wilcoxon signed-rank tests. Results: To date, among 69 subjects, 33.3% were female and 75.4% were White. Median age was 24 (range 17–30). About 91% were IDUs. Half (50.7%) had used at least one club drug in their lifetime. Rates of use varied by type of drug: ecstasy (41.0%), LSD (37.7%), PCP (20.3%), non-LSD hallucinogens (17.4%), ketamine (13.0%), meth-amphetamines (10.1%), and GHB (1.5%).

Median age of first club drug use was 15 (range 12–26); 13.0% were currently using club drugs. Half of the IDUs initiated club drug use after they began injection and 11.3% were currently using both heroin and ecstasy. Conclusions: These preliminary data suggest that club drug use is becoming increasingly common among IDUs in Baltimore, and ecstasy. Conclusions: These preliminary data suggest that club drug use is becoming increasingly common among IDUs in Baltimore, and ecstasy.

498 Concordance rates between youth and parents: 5 years after treatment

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Every year, over 130,000 adolescents in the United States are treated for alcohol and and drug abuse problems, and the rate is increasing (SAMHSA, 2001). There is increased attention to the need for monitoring and reporting outcomes of treatment, and for improving research methodology (Winters, 1999). The purpose of this study was to evaluate the concordance between youth’s and parents’ report of the youths’ drug or alcohol use after treatment. As part of a larger study, outcome interviews via telephone were conducted with 97 young people and their parents an average of 66.1 months (S.D. = 5.69) post-treatment. Youth were administered the Adolescent Diagnostic Interview (ADI: Winters and Henly, 1993); and parents were administered a shorter version with parallel items. The youth sample was 52% female and 100% Caucasian. At the time of follow-up, they were an average of 23.7 years old (S.D. = 2.8). Post-treatment use included: alcohol (75%), marijuana (47%) or cocaine (28%), or amphetamines (25%). Youth/parent concordance was surprisingly high: agreement on whether youth had returned to use at any time during the follow-up period: (k = 0.78; P < 0.001); pattern of use since treatment (abstinent/use then abstinent/sporadic use/continuous use) (k = 0.39; P < 0.001); pattern of subsequent use after first relapse (quit/continued to use with problems/continued to use with no problems) (k = 0.39; P < 0.001); length of time between treatment and first use (r = .93; P < 0.001); length of longest abstinence during follow-up interval (r = .72; P < 0.001). Overall rating of alcohol/drug problem (five point Likert scale from ‘much better’ to ‘much worse’) was high (83%) though kappa was relatively low (0.14). Subsequent analyses (for the conference) will compare parent and youth self-perceptions of problem with additional data collected on DSMIV criteria for abuse and dependence.

499 Pharmacokinetic and behavioral mechanisms of antidepressant antagonism in a model of chronic (+)-methamphetamine use in rats

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These studies evaluated pharmacokinetic mechanisms involved in monoclonal antibody (mAb) antagonism of (+)-methamphetamine [(+)-METH]-induced locomotor effects in a rat model of chronic (+)-METH use. After determination of baseline (+)-METH-induced locomotor effects, rats received a single dose of high-affinity anti- (+)-METH mAb (Kₐ = 11 nM), equimolar in binding sites to 1 mg/kg i.v. (+)-METH. Rats were challenged with (+)-METH (0.3, 1.0, or 3.0 mg/kg, i.v.) the following day (day 1), and on days 4 and 7. On day 1, the mAb reduced 0.3 and 1 mg/kg (+)-METH-induced locomotor activity by 100 and 39%, respectively. However, the mAb did not provide protection against the 3 mg/kg dose. On days 4 and 7, the mAb had little effect. In the pharmacokinetic studies, rats (N = 3/time point) received the anti- (+)-METH mAb, followed the next day by (+)-METH (1 mg/kg, i.v.). The mAb did not significantly affect (+)-METH brain levels for the first 15 min after (+)-METH administration. However, the (+)-METH area under the concentration-time curve from 0–4.5 h (AUC) showed mAb pretreatment increased serum AUC by >6000% and decreased brain AUC by >60% compared with no mAb controls. These data suggest that although anti- (+)-METH mAb does not prevent (+)-METH’s initial rapid brain
penetration, it does increase the redistribution of METH out of the brain.

500 COMPARING EFFECTS AND COSTS OF ATOD ABUSE ON PREGNANCY OUTCOMES AT TWO ALTERNATIVE PRENATAL INTERVENTION PROGRAMS

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Alcohol, tobacco and other drug (ATOD) abuse during pregnancy can contribute to serious complications and health risks for both mothers and infants before and after delivery. This study compares the effects of ATOD abuse on outcomes at two prenatal intervention programs in the Washington, DC metropolitan area for mothers who delivered between January 1996 and December 2000. One center engages in prenatal care and medical problems prior to contact with either program. The paper will also use the programs’ records and Medicaid submissions to compare the costs of serving and treating women in both programs, including the costs of prenatal and ATOD programs to which they might be referred.

501 SUPPRESSION OF MORPHINE-INDUCED REWARDING EFFECTS AND MU-OPIOID RECEPTOR-MEDIATED G-PROTEIN ACTIVATION UNDER NEUROPATHIC PAIN

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We previously reported that the morphine-induced place preference was abolished in sciatic nerve-ligated mice. The present study was designed to investigate whether neuropathic pain state induced by sciatic nerve ligation could cause any changes in the opioid receptor-mediated G-protein activation in the mouse. The i.c.v. morphine-induced place preference was observed in sham-operated but not sciatic nerve-ligated mice. Under these conditions, the increase of [35S]GTPgammaS binding induced by mu-opioid receptor agonists to lower midbrain membranes including ventral tegmental area (VTA), which distributes high densities of mu-opioid receptors to produce the rewarding effect, was significantly attenuated in nerve-ligated mice as compared to sham-operated mice. In contrast, there were no significant differences in increases in [35S]GTPgammaS binding stimulated by delta- and kappa-opioid receptor agonists between two groups. These results suggest that the decrease of mu-opioid receptor-mediated G-protein activation in the mouse lower midbrain may be, at least in part, implicated in the inhibition of morphine-induced rewarding effect under neuropathic pain.

502 COMPARISON OF THE ANXIOLYTIC-LIKE ACTION OF SOME ABUSE INHALANTS IN THE BURYING BEHAVIOR TEST

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Inhalant share some effects with classical CNS depressant drugs, including anxiolytic-like actions. On the other hand, in vitro studies have reported that toluene and 1,1,1-trichloroethane (TCE) can interact with NMDA receptors with similar potencies. Hence, the main purpose of this study was to compare the anxiolytic-like actions of 3 different inhalants: toluene, TCE and diethyl ether using the burying behavior test. Swiss-Webster mice (25–35 g) were adapted on 2 consecutive days by placing them during 30 min in static exposure chambers inhaling air. On the third day, independent groups of animals were exposed to air (control group), toluene (1000–4000 ppm), TCE (2000–12000 ppm) or diethyl ether (10000–30000 ppm). Flurathyl (200–600 ppm) was included as a negative control. After 30 min of exposure, animals were tested in the burying behavior test. The parameters registered were burying behavior latency (BBL), cumulative burying behavior (CBB) and number of shocks (SH). Toluene, TCE and diethyl ether significantly increased BBL and decreased CBB, reflecting anxiolytic-like actions. The order of potency was toluene > TCE > ether. Interestingly, toluene was the only solvent that increased SH. No anxiolytic-like actions were found for flurathyl. Taken together, these results suggest that although in in vitro studies toluene and TCE presented similar potencies, in this in vivo study, inhalants presented different effects with different potencies.

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503 WHOLE-BODY DRUG LEVELS IN RATS DURING COCAINE SELF-ADMINISTRATION UNDER COMPLEX SCHEDULES OF REINFORCEMENT

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According to titration theories of self-administration, drug intake is regulated to maintain levels of drug (or drug effect) within a certain range. However, evidence for this view comes almost exclusively from studies using simple schedules of reinforcement, where drug is continuously available and response requirements are low. In the present study, whole-body drug levels were calculated based on rats’ self-administration performances under multiple schedules (where schedule components alternated automatically) and chained schedules (where progression through the components was contingent on lever-pressing). Cocaine was only available during certain components, according to variable-interval or differential-reinforcement-of-other-behavior contingencies. Unit doses were adjusted across sessions to maintain responding while response requirements were increased to successively approximate the final schedules. Drug levels were calculated retrospectively, only after training had been completed. Operant responding was robustly controlled by the exteroceptive stimuli associated with the schedule components, but no relationship was observed between local response rates and drug levels. Thus, titration did not contribute to the establishment of stimulus control. Nonetheless, under the unit doses and temporal schedule parameters used here, drug levels within sessions were typically maintained within a relatively narrow range. While these results are consistent with the hypothesis that drug ‘seeking’ may occur only while drug levels are within a certain range, titration theory cannot account for the patterns of behavior observed under these complex schedules of reinforcement.

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504 EFFECTS OF BUPRENORPHINE, NALTREXONE, AND MORPHINE IN MONKEYS TRAINED UNDER CONCURRENT FR SCHEDULES OF FOOD AND HEROIN AVAILABILITY

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The present studies examined the effects of buprenorphine, naltrexone and morphine on the relative reinforcing strength of heroin using a novel two-lever ‘choice’ procedure. Monkeys (n = 3) were trained to respond under concurrent fixed-ratio 30 (FR30) schedules of reinforcement during daily 60-min sessions. About 30 consecutive responses on one lever resulted in food delivery, and 30 consecutive responses on the alternative lever resulted in an i.v. injection of either saline or heroin; availability of each i.v. solution varied according to a double alternation schedule. Data were collected on four measures: overall response rates, percentage of total responses occurring on the injection-associated lever (%DLR), number of injections earned, and number of food pellets earned. We reported previously that the distribution of behavior depends on the unit dose of heroin available for self-injection. The %DLR increased from 21±12% when saline was available to 100% when 0.01 mg/kg/ijnj heroin was available. The dose-effect function for the number of injections earned was biphasic, with the peak (28±1 injections/session) occurring at a unit dose of 0.003 mg/kg heroin. Pretreatment with 0.01 mg/kg naltrexone produced rightward displacements of the heroin dose-effect functions for all four behavioral measures, resulting in increased heroin intake in the presence of naltrexone. Pretreatment with morphine, 0.1–3.2 mg/kg, dose dependently increased responding on the injection-associated lever during periods of heroin availability, but did not consistently alter heroin-maintained performance. Buprenorphine, 0.01 and 0.1 mg/kg, yielded results that were similar, in part, to both naltrexone and morphine pretreatments. Like morphine, buprenorphine produced increases in responding on the injection-associated lever during periods of saline availability and like naltrexone, buprenorphine increased total drug intake. This result is consistent with buprenorphine’s profile as a partial opioid agonist, and suggest that it is able to antagonize some direct effects of heroin without altering the relative reinforcing strength of high unit doses of heroin.

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505 CYTOKINE MODULATION BY NICOTINE AND LPS IN HUMAN CORONARY ARTERY ENDOTHELIAL CELLS

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Endothelial injury is a critical component of atherogenesis, the pathogenic process leading to cardiovascular disease and stroke. The immune system, by activating cells, generating inflammatory mediators, and impacting apoptosis is thought to modulate the integrity of the vasculature. These studies focused on the action of the bacterial cell wall constituent LPS in terms of production of cytokines and chemokines relevant to inflammation, using human coronary artery endothelial cells (HCAECs). It was found that LPS increased the numbers of HCAECs in culture, as well as the expression of the chemokine MCP-1, as assessed by RT-PCR studies. Such an alteration in cytokine production by HCAECs was seen also with nicotine, the addictive component of tobacco, such that the levels of MCP-1, IL-8, and Gro-alpha were enhanced. Correlations of these finding have been extended to protein measurements with ELISA. Nicotine has been shown to affect immunity against infections and may therefore impact on the course of inflammation, and therefore studies were performed in which both nicotine and TNF-α were used, and the data will be presented here. The prevalence of cardiovascular disease and stroke in this country remains a critical public health problem and the results of this study should give a better knowledge of the action on cytokine production in a model relevant to atherosclerosis and stroke. AHA FL 0051206B.

506 GENDER DIFFERENCES AMONG ADOLESCENTS WITH SUBSTANCE USE DISORDERS AND TRAUMATIC STRESS

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The purpose of this study was to examine gender differences associated with traumatic stress and substance use among adolescents in an urban, short-term residential drug treatment facility. This study is part of a larger, multi-site project examining adolescent addiction treatment outcome (Baltimore site N = 153, 120 males, 33 females). Drug use and traumatic stress were measured using the Global Assessment of Individual Needs (GAIN), a structured interview, self-report instrument. Females (M = 5.72) had significantly higher overall traumatic stress scores than males (M = 3.5, P < 0.01). Females reported significantly more instances of forced sex and emotional abuse, and males reported more instances of weapon attacks. More females than males had traumatic experiences prior to age 18, that lasted longer, and were perpetrated by someone they trusted. Females reported significantly more days of being disturbed by memories, feelings of being unable to go on, being frightened by their urges, exploding over minor things, and using drugs to forget the past. Since traumatic stress symptoms have previously been associated with the use of harder drugs (opiates versus marijuana), gender differences in heroin-using adolescents were also examined. About 45 of the 153 adolescents were treated for heroin use (females = 14, males = 31). Overall, those needing treatment for heroin had higher traumatic stress scores than those needing treatment for other drugs (F = 4.93, P = .03). There was a trend (χ² = 3.43, P = .06) of a greater percentage of females needing treatment for heroin abuse (42%) than males (26%). However, the interaction of gender and heroin use was not significantly related to traumatic stress. Severity of post-treatment drug use and traumatic stress on admission was only significantly correlated for males (r = 0.44) during the 3–6-month follow-up. These findings suggest that although adolescent females may be at higher risk for traumatic stress symptoms and need treatment for harder drugs, female substance use outcomes following addiction treatment may be less associated with traumatic stress at admission than males.

507 INTEGRATING SUBSTANCE ABUSE TREATMENT WITH HIV PREVENTION: TREATMENT OUTCOMES AMONG GAY MALE METHAMPHETAMINE ABUSERS IN HOLLYWOOD, CA

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Gay and bisexual men on the West Coast who abuse methamphetamines represent a group vulnerable to HIV infection due to critical associations between sexual risk behaviors, i.e. unprotected anal intercourse, and drug use. From 1997–2001, 162 gay male methamphetamine abusers were treated in a NIDA-funded (R01 DA10313) treatment/research clinic. Subjects were randomly assigned to four treatment conditions: standard relapse prevention (n = 41); contingency management (n = 42); a combined relapse prevention/contingency management condition (n = 39); and a condition that modified standard drug abuse relapse prevention with culturally specific materials that teach skills to reduce both sexual risk behaviors and drug use (n = 40). We predicted that assignment to contingencies would significantly enhance drug abuse treatment outcomes. The
It has been previously demonstrated that female rats acquire cocaine self-administration quicker and at a higher rate than male rats. In addition, female rats respond at higher levels than male rats during cocaine-induced reinstatement. Our laboratory, as well as others, have shown that the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the self-administration of cocaine in male rats. The current experiments were designed to combine and further examine these two areas by investigating the role of female gonadal hormones and the HPA axis on cocaine self-administration in rats. Female (n = 9) Wistar rats were implanted with indwelling jugular catheters. During the same surgical procedure four female rats also underwent bilateral ovariectomy (OVX). Rats were first trained on a fixed ratio 1 schedule of cocaine (0.25 mg/kg per infusion) self-administration. Following stable rates of self-administration, rats were then trained on an extinction procedure where lever-pressing had no programmed consequences. When the rates of responding during extinction were < 20% of baseline rates, reinstatement was tested using either an ip injection of cocaine (10 mg/kg) or by presenting cues that were previously associated with cocaine self-administration. Plasma corticosterone was also measured on the first and last days of cocaine self-administration, the first and last days of extinction and on the reinstatement test days. Intact female rats had a higher rate of cocaine intake and showed less lever pressing during extinction than OVX rats. In addition, OVX female rats had higher basal levels of plasma corticosterone than intact females. In summary, these data demonstrate that there is a difference in cocaine self-administration between intact and OVX female rats which may be influenced by the HPA axis.

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510 Short-term evolution of cocaine withdrawal and detection of benzoylcegonine in urine at treatment entry

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Background: Fluctuating (Gawin & Kleber, 1986) or gradually decreasing (Weddington et al., 1990; Satel et al., 1991) patterns of cocaine withdrawal have been described. Hypothesis: Different cocaine-withdrawal patterns are related to detection (Weddington et al.; Satel et al.) or non-detection of cocaine in urine at the start of assessment. Method: Short-term evolution (6 days) of cocaine withdrawal was assessed in 25 cocaine-dependent patients during hospitalization in a closed addiction unit. Cocaine withdrawal was measured using the Cocaine Selective Severity Assessment (CSSA). Benzoylcgonine (BEG) was detected in the urine of 19 participants (ten in methadone maintenance) at treatment entry (BEG-positive group); the other six participants (three in methadone maintenance) provided ‘clean’ urine specimens for the cocaine metabolite (BEG-positive group). CSSA scores of these groups were compared with repeated measures ANCOVA. Results: After adjusting for cocaine dose, a time by group interaction was detected (F (2.955) = 2.901; P = 0.04). The BEG-positive group showed a gradually decreasing cocaine withdrawal, whereas the BEG-negative group showed lower CSSA scores the first day of hospitalization than the other group. Afterwards, the BEG-negative group’s CSSA scores rose on the 2nd and 3rd days and gradually decreased until the 6th day. At the end of the assessment period, both groups showed comparable CSSA scores. Conclusion: Detection of BEG in urine at treatment entry is related to a different pattern of subsequent cocaine withdrawal.

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511 The effect of personality and family history of smoking on smoking severity in adolescent females

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Rates of adolescent female smoking are rising. The extent to which family history of smoking ([FHS]:parents-ever-smokers(both-BE, one-OE, neither-NE) or current smokers(both-BC, one-OC, neither-NC)
interacts with personality deviance to affect severity of smoking-behavior (never NS, regular/non-dependent-smoking RS, regular/nicotine-dependent-smoking ND) in young women has not been systematically examined. We tested the extent to FHS would moderate the effects of Extraversion (E), Neuroticism (N), Social-Nonconformity/Lie-scale (L), Novelty-Seeking (NS), Aggression, and Alienation on smoking. Interview and mailed-questionnaire data from a survey conducted in 1995–1997 (N = 1856 female like-sex twin pairs born 1975–1983) were analyzed by logistic-regression. Overall, high ( > 75th percentile) levels of: E (ORs = 1.81,1,61), N (ORs = 1.73,1,87), L (ORs = 1.38,1,82), and NS (ORs = 2.00,2,51) significantly increased risk for both RS and ND, respectively. Low-levels ( < 25th percentile) of E, N, L, and NS on the other hand appeared to significantly protect against development ND. After controlling for age, FHS, and personality, for FHS-ever smoking, low E ( < 25th percentile) interacted with BE to significantly increase risk of ND (OR = 2.68). For FHS-current-smoking: low E ( < 25th percentile) interacted with BC to significantly increase risk of RS (OR = 0.60), high E ( > 75th percentile) interacted with BC to significantly protect against ND (OR = .39), high L ( > 75th percentile) interacted with BC to significantly decrease risk of RS (OR = 0.20), and high NS ( > 75th percentile) significantly interacted with BC to increase risk of ND (OR = 3.02). These results suggest that in young females the effects of E, L, and NS on smoking depends upon FHS. In particular, when both parents are ever or current smokers, low levels of E, or shyness, appears to be a clear risk factor for RS and ND.

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512 THE INFLUENCE OF NRT RATE ON THE ACUTE SUBJECTIVE AND REINFORCING EFFECTS OF CIGARETTE SMOKING

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The subjective and reinforcing effects of many drugs of abuse, including nicotine, depend partly on their rate of onset, with faster acting formulations typically producing stronger effects than slower ones. In this study, we examined the effect of nicotine replacement therapy (NRT) pre-treatment on reducing the acute subjective and reinforcing effects of smoking, and whether these effects differ for the nicotine nasal spray (fast delivery) versus the nicotine patch (slow delivery). Smokers (n = 21 to date) participated in three sessions, each after overnight smoking abstinence, involving 14 mg nicotine (NicodermR) or placebo patch, followed 3 h later by acute administration of nicotine (NicotrolR) or placebo nasal spray. Thus, we examined the effects of nicotine patch vs nicotine spray vs double placebo. Subjects then engaged in smoke-reinforced responding on a progressive ratio procedure and rated subjective liking, etc. of the earned smoke puffs. Few differences were significant. ‘ Urge to smoke’ tended to decrease more and ‘liking’ of puffs was lower following nicotine spray versus the other conditions, but there was no difference in withdrawal or smoke-reinforced responding. Final analyses will control for plasma nicotine levels, which tend to be lower following nicotine spray vs patch.

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513 INCENTIVES IMPROVE ADHERENCE TO REFERRAL FOR CHEST X-RAY AMONG IDUS BEING SCREENED FOR TUBERCULOSIS AT A SYRINGE EXCHANGE PROGRAM

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Objective: Syringe exchange programs (SEP) have proven to be valuable sites to conduct tuberculin skin testing among active IDUs, and onsite delivery of TB preventive therapy (PT) at SEPs has been promising. However, those with reactive skin tests require chest x-rays (CXR) to exclude active TB prior to the initiation of TB PT, and adherence to referral for off-site CXRs has been problematic. Monetary incentives have been useful in improving adherence in various settings. Further, we have shown that monetary incentives could be justified on a cost basis if they had even a modest effect on CXR referral adherence. We compared adherence to referral among IDUs undergoing TB screening at a SEP before and after the implementation of incentives. Methods: TB screening was conducted at a storefront SEP in the Lower East Side in New York City. From 1995–1998, 106 IDUs were referred for CXRs based on skin testing. From 1999, 42 IDUs were referred for CXR with an incentive of $25 contingent on adherence. Results: The cohorts referred for CXR were comparable with respect to gender (28% vs. 31% female, P = 0.75), ethnicity (non-Hispanic white: 36 vs. 24%, P = 0.16), injecting daily (42% vs. 39%, P = 0.7), unstable housing (58 vs. 64%, P = 0.45), alcohol intoxication (45% vs. 52%, P = 0.44), crack use (31% vs. 35%, P = 0.65), and the proportion currently in drug treatment (41 vs. 31%, P = 0.25). However, the earlier cohort (1995–1998) was younger (mean age: 38.2 vs. 43.5, P = 0.009). Forty IDUs (38%) adhered to CXR referral prior to the use of incentives compared with thirty (71%) with incentives (C2 = 13.7, P = 0.0002, RR = 1.89, 95% CI = 1.39–2.58). CXR referral adherence was not related to age, gender, ethnicity, injecting daily, unstable housing, alcohol intoxication, crack use, or the proportion currently in drug treatment. Conclusions: IDUs have a high prevalence of TB infection and are at high risk for active tuberculosis. Successful screening programs are important to control the endemic and are shown to be cost-effective. Monetary incentives increase adherence of IDUs at SEPs to referral for CXRs.

514 PROBLEM SEVERITY, GENDER, AND REDUCTION IN COCAINE USE FOLLOWING BRIEF MOTIVATIONAL INTERVENTION

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It has been noted that women entering SA treatment often present with greater problem severity along a number of life dimensions, but that they also fare better in terms of retention and outcome. We sought to test whether street-recruited women cocaine users also showed greater problem severity than a sample of men recruited in a similar way and whether problem severity and gender predicted response to a brief motivational intervention. This analysis is based on initial and 1-month follow-up data from 113 participants in two groups of a three group randomized trial. Both groups completed an initial assessment plus feedback), but gender and...
515 BUPRENORPHINE VERSUS METHADONE IN OPIATE DETOXIFICATION

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This open study compared buprenorphine sublingual tablets with standard oral methadone in the treatment of opioid withdrawal in 37 inpatients dependent on opioids. The first dosages of the respective medications were determined with respect to the self-declared amount of heroin use. Reductions were guided by clinical judgement. Withdrawal symptoms were assessed by the Short Opiate Withdrawal Scale (SOWS), and monitoring vital signs. Toxicological investigations of urine were performed. Results: Rates of completion of detoxification did not differ significantly between the two treatments (BUP: 77%; METH: 89%), the average length of stay ranged from 10.9 (S.D. 4.9) to 12.7 (S.D. 4.3) days. Overall, the two groups did not differ in total withdrawal severity. However, significant levels of withdrawal symptoms were found on day 8 in the buprenorphine group (P < 0.05) compared to patients in the methadone group; whereas patients detoxified with methadone had significantly higher SOWS-Scores after the detoxification phase on days 13 and 16 (P < 0.05). Thus, buprenorphine tablets seem not to be more effective in alleviating withdrawal symptoms in opioid dependent inpatients during detoxification, but in shortening the duration of withdrawal treatment, compared to methadone.

516 LOW-COST CONTINGENCY MANAGEMENT REINFORCING DRUG ABSTINENCE VERSUS THERAPY COMPLIANCE

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Contingency management (CM) interventions are efficacious in reducing drug use, but they have rarely been implemented in community-based treatment programs, in part due to their cost. A lower-cost CM procedure that provides the chance to win prizes has been demonstrated efficacious in some community-based settings. The purpose of this study is to compare the efficacy of this lower-cost CM procedure when reinforcing drug abstinence directly or reinforcing compliance with goal-related activities. To date, 60 cocaine-dependent outpatients have been assigned to one of three conditions: standard outpatient treatment, standard treatment plus the opportunity to win prizes for submitting cocaine-negative urine specimens, or standard treatment plus the opportunity to win prizes for completing goal-related activities, such as attending a psychiatric appointment, completing a job application or taking a child to the library. None of the patients assigned to standard therapy have remained in treatment throughout the 12-week study, compared with 20 and 28% of those assigned to abstinent and activity CM conditions, respectively. Mean consecutive weeks abstinent are 3, 6 and 7 weeks in the respective conditions. These data suggest that reinforcing compliance with goal-related activities may be equally efficacious as reinforcing drug abstinence. This process of reinforcing compliance with goal-related activities may be suitable for use in community-based settings, as it is consistent with commonly used procedures such as treatment goal planning and it may not require frequent urine sample monitoring.

517 SEX DIFFERENCES IN OPIOID ANTINOCICEPTION: IMPORTANCE OF RODENT STRAIN AND OPIOID EFFECTIVENESS

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Sex differences in the antinociceptive effects of opioids have been reported previously in rats, with males being more sensitive to opioid antinociception than females. There is also evidence indicating that the magnitude of these sex differences can vary markedly across opioids as well as across rat strains. In the present study, the influence of rat strain (F344, F344 Sasco, Long Evans, Lewis, Sprague Dawley, Wistar) on sex differences in opioid antinociception were examined in the rat warm-water (50, 52, 55°C) tail-withdrawal procedure. Tests were conducted with a number of opioid compounds that included the highly effective mu agonist morphine, the less effective mu agonist buprenorphine, and the less effective µ/k agonists butorphanol and nalbuphine. Collapsed across all strains and sexes, the rank order of opioid effectiveness in producing antinociception was morphine > buprenorphine > butorphanol = nalbuphine. Sex differences were observed in all strains, and were largest with the less effective opioids buprenorphine, butorphanol and nalbuphine. Differences across strains were also apparent, as the opioids were generally most potent in the F344, F344 Sasco, Sprague–Dawley and Long Evans strains, and least potent in the Wistar and Lewis strains. Although sex differences were observed in all strains with at least one of the opioids tested, the magnitude of these sex differences was largest in the F344 rats and their substrain the F344 Sasco. In summary, the magnitude of sex differences in opioid antinociception varies across rat strains and across opioids that vary in their effectiveness in producing antinociception. That the largest sex differences were obtained with the less effective opioids suggests that these opioids may represent a sensitive pharmacological tool to study the mechanisms underlying sex differences in opioid antinociception.

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518 NICOTINE DELIVERY, PHYSIOLOGIC AND SUBJECTIVE EFFECTS OF CLOVE CIGARETTES


Clove cigarettes (kretaks) are alternative tobacco products from Indonesia, that have become increasingly popular among US teenage smokers. Their typical composition is 30% clove leaf and 70% tobacco components. About 10 adult chronic smokers (seven males, three females) were tested to assess nicotine delivery, physiologic and subjective effects of a clove cigarette (Djarum Special) compared to their own brand of cigarette. Average time to smoke the clove cigarette (549 s and number of puffs (15.1) were significantly larger than own brand (314 s and 9.4 puffs). Increases in venous plasma nicotine and exhaled CO after smoking the clove cigarette (17.4 ng/ml; 6 ppm) were not different than those after own brand (17.6 ng/ml; 4.5 ppm). Similarly, maximal changes in heart rate (8.0 vs. 6.6 bpm), systolic (10.8 vs. 6.8 mm Hg) and diastolic (2.3 vs. 3.7 mm Hg) blood pressures did not differ significantly between the clove and own brand of cigarette. The Duke Sensory Questionnaire and the Cigarette Evaluation scales were used to assess subjective effects of smoking. Compared to their own brand of cigarette, clove cigarettes were rated as more satisfying, better tasting, causing a greater reduction of cigarette craving and being distinctively different. The results of the study suggest that clove cigarettes... like other combustible tobacco products... deliver significant quantities of nicotine, CO, and presumably other toxic components of tobacco smoke. Their taste
satisfaction, aromatic odor and novelty may contribute to their appeal among US teens.

519 Substance use and other risk factors associated with physical injury among women

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Purpose: The objective of this study is to examine the relationship between substance use and other risk factors associated with physical injury (defined as trauma such as broken bones, concussion, gunshot or knife wounds, sport injuries, sexual assault in the last 12 months). Methods: Interview data from 633 female participants were collected in Miami-Dade County, FL, using a network-based sample. 59.4% of the sample were substance users (19.4% injection drug users and 40.0% other chronic drug users) and 40.6% were non-substance users. Bivariate and multiple regression techniques were used. Results: Approximately one-quarter (23.7%) of the sample experienced physical injury within the last 12 months. Bivariate analysis revealed that risk factors for physical injury within the last twelve months differed by ethnicity. White non-Hispanics (38.7%) were more likely than Blacks (30.0%), or Latina/Hispanic women (31.3%, P < 0.004) to experience physical injury. Substance users (28.7%) were more likely than non substance use (55%, P < 0.000) to experience physical injury. Persons who did not live in their own house or apartment (29.4%) were more likely than persons who lived in their own house or apartment (13.3%, P < 0.000) to experience physical injury. Persons who had been arrested in the past 12 month (38.8%) were more likely than those with no arrest (19.1%, P < 0.000) to experience physical injury. Age and education were insignificant. Multivariate logistic regression was used to identify the independent risk factors for physical injury. Injection drug use, not living in own house or apartment, and arrest in the last 12 months remained significant indicators of physical injury. Conclusion: The findings indicate that women substance users are at higher risk of physical injury compared to non-substance using women.

520 Effects of alcohol and THC on human risk-taking

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Risk taking is a conceptually and behaviorally broad phenomenon, and is of consequence from a public health perspective because excessive risk taking often results in harm to both individuals and communities. Epidemiological and clinical studies link certain drugs to excessive forms of risky behavior. Risk-taking can be understood as decision-making under conditions of uncertainty. It is described here as behavior that occurs in a context with two response options: (i) option 1 has a reinforcement probability < 1.0 and a probability > 0 of an aversive outcome, (ii) option 2 has a reinforcement probability = 1.0, but a smaller reinforcer value than option 1. Choosing option 1 is defined as risk-taking. We present results from laboratory studies of risk-taking with human subjects, whose choices were maintained by monetary reinforcers. In the experimental procedure, subjects were presented with a two-choice discrete trial task. The task presented subjects with repeated trials of a ‘non-risky’ option versus a ‘risky’ option (offering variable amounts of money at a gain/loss probability of 0.50). In two separate experiments, we assessed the effects of two disinhibitory drugs of abuse on risk-taking in adult subjects. Across three doses of alcohol (0.2, 0.4, and 0.8 g/kg) and smoked marijuana (half of 1.77, 1.77, and 3.58% THC), risk-taking behavior generally increased as a function of dose. Subjects were also more likely when intoxicated to make consecutive risky responses following a single gain on the risky option, compared to placebo conditions.

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521 Neurophysiology of motor function following cannabis discontinuation in chronic cannabis smokers: an fMRI study

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Hypothesis: Compared to no-smokers, during early withdrawal, chronic cannabis users were hypothesized to demonstrate decreased activation in the anterior cingulate gyrus during finger-tapping tests. Methods: About 16 chronic cannabis smokers, and eight psychiatrically healthy controls were included in these analyses. Scanning was performed on a GE I.5 Tesla scanner retrofitted with a whole body echo planar coil. Using a quadrature head coil, echo planar images and high resolution MR images were acquired. The challenge paradigm included finger tapping. Differences in cerebral activation reflected by changes in BOLD signal were examined in the left (L) and right (R) anterior cingulate gyrus above the corpus callosum (AAA) and the anterior cingulate gyrus anterior to the corpus callosum (VOA). Between group differences were completed using analyses of variance. Results: After 24 h of discontinuation, we found that in both the R and L AAA for both right and left-handed finger-tapping, chronic cannabis users demonstrated statistically significantly less activation than controls (P < 0.04 for all analyses and P ranging from 5.25×10−0.037). In the VOA, differences between chronic cannabis users and controls existed only on the right side (P < 0.02 for all analyses). Discussion/Significance: These results suggest that 24 h after cannabis discontinuation, chronic smokers produce reduced anterior cingulate activation in motor tasks compared to controls. The main finding of reduced activation in the anterior cingulate gyrus suggests subtle deficits in the attentional processing of motor function even 24 h after discontinuation of cannabis. These differences in regional brain activation even 24 h following discontinuation of use have important implications with regard to functional activities and subtle deficits that may be present when driving or in professional sport.

522 Cocaine-modulating effects of terguride in nonhuman primate models of cocaine abuse

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The D2 receptor partial agonist terguride has a profile of behavioral effects in rats that suggests potential benefit as a pharmacotherapy for cocaine addiction. The present study investigated the cocaine-modulating effects of terguride in squirrel monkeys trained to respond on a second-order schedule (FI 10 min, FR 30:S) of either i.v. cocaine injections or food pellet delivery (Platt et al., Psychopharmacology 157, 2001). Additional studies determined the effects of terguride in monkeys whose drug-seeking behavior was extinguished and subsequently reinstated by cocaine priming injections (Khroyan et al., JPET 294, 2000), and side effect profiles were evaluated using quantitative observational techniques (Platt et al., JPET 293, 2000). Under each procedure, the effects of terguride were compared with those of the reference D2 receptor antagonist nemonapride and the D2 receptor full agonists quinpirole and propylpynorapomorphine (NPA). Terguride and nemonapride, but not quinpirole or NPA, dose-dependently reduced cocaine self-administration and inhibited cocaine-induced reinstate-
ment of extinguished drug seeking. Effective doses of terguride had no systematic effect on locomotor activity or muscle rigidity, whereas effective doses of nemonapride virtually eliminated locomotor activity and induced severe catalepsy. The primary observable effects of terguride were a modest level of self-directed behavior (a D2 receptor agonist-like effect) at intermediate doses and a low level of catalepsy (a D2 receptor antagonist-like effect) at the highest dose tested. These findings suggest that terguride may have advantages over conventional D2 receptor antagonists and agonists as a candidate pharmacotherapy to combat cocaine abuse and relapse. In animals self-administering food, however, terguride decreased response rate at doses lower than those required to suppress cocaine self-administration, indicating limitations on the selectivity of terguride as a modulator of cocaine reinforcement.

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523 BASeline Smoking as a Predictor of Response to Vouchers in Pregnant Smokers


Effective interventions are available for pregnant cigarette smokers, but cessation rates are often less than 20%. As part of a pilot study examining the efficacy of a voucher-based incentive program for achieving higher cessation rates, 25 pregnant smokers earned vouchers contingent on smoking abstinence. The purpose of this study was to assess whether baseline smoking levels differed for women who did and did not achieve abstinence. To date, 12 of the 25 (48%) women have achieved abstinence, defined as self-reported non-smoking for at least 7 days verified by saliva cotinine analysis. Mean cigs/day among abstainers vs. non-abstainers were 4.8±2.9 vs. 11.9±12.1 at baseline (P = 0.03). Of those who reported smoking less than 15 cigs/day prior to pregnancy, 5/6 (83%) achieved abstinence vs. 7/19 (37%) among those smoking >15 cigs/day (P = 0.02). Among those smoking less than 10 cigs/day at baseline, 11/19 (58%) achieved abstinence vs. 1/6 (17%) of those smoking >10 cigs/day (P = .04). These preliminary results offer compelling evidence for baseline smoking frequency as a predictor of response to this voucher-based intervention.

524 Drug Use Prevalence Among Welfare Clients

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A representative sample of 511 applicants and recipients to the Temporary Assistance For Needy Families (TANF) welfare program in a large metropolitan Southern California county were interviewed between November 2000 and June 2001. Respondents were recruited at all 24 county welfare offices. Interviews were conducted in English and Spanish. Respondents were interviewed about their attitudes towards substance use, their use of alcohol, tobacco, and other drugs, and about other aspects of their lives including demographics, physical and emotional health, employment, and family status. In addition to participating in the survey, 95% of the participants participated in a Breathalyzer test and 77% provided a urine sample. Welfare reform and the increased emphasis on moving welfare recipients from welfare to financial independence has heightened interest in substance use among welfare recipients because of its perceived role as a barrier to employment. However, little objective empirical data is available on rates of drug use among TANF welfare recipients or their attitudes about drug use as a social problem. This paper presents data on rates of substance use among the TANF welfare population based on self-reports and urine test results. Three prevalence rates—low, intermediate, and high—are presented using different assumptions about rates of use among those who denied use, but did not provide a urine sample for testing. The intermediate method, the most realistic of the three estimates, uses logistic regression to adjust self-report data upward for drug use underreporting. Sample results are weighted to reflect the distribution of the population. The paper examines use of marijuana, opiates, amphetamines, cocaine, sedatives, and barbiturates. The data form this research are useful for planning welfare substance abuse programs by providing objective data on drug use in the TANF population.

525 Attention and Behavior of 9-Year-Old Children Prena tally Exposed to Cocaine

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The anticipated negative impact of prenatal cocaine exposure on attention and behavior during school years has not yet been empirically documented. This study of 9-year-old children is a part of an ongoing follow-up of a perinatal investigation of 120 infants born at a public hospital to low-income, primarily African-American, mothers living in a Maryland county adjacent to Washington, DC. Prenatal exposure levels were assessed using multiple hair and urine samples along with maternal self-report. In the present study, current maternal drug use was measured using hair samples from both the exposed cohort (n = 42) and a non-drug using comparison cohort. The comparison cohort (n = 39) consists of women of similar demographics whose children live in the same zip codes and attend the same schools. Attention and behavior are measured using the Conners’ Rating Scale, the Conners’ Rating Scale-Teacher Version, the Gordon Diagnostic System (GDS), the Guide to the Assessment of Test Session Behavior for the WISC-III (GATSB), and the Child Behavior Checklist (CBCL). Simple group differences using independent samples t-tests existed for the ADHD Index and Cognitive Problems subscales (Conners’ Scales) completed by both parent and teacher and three CBCL subscales (Thought Problems, Attention Problems, and Withdrawn). Cohen’s d scores ranged from 0.46 to 0.72). Means for both groups were below clinical levels for all attention and behavior rating scales. The commission scores on the GDS continuous performance tests, indicators of impulsivity and hyperactivity, had significantly more exposed subjects in the abnormal range. MANOVA analyses controlling for maternal IQ, maternal education, postnatal drug use, child gender, and smoking eliminated prenatal effects on both attention and behavior vectors. No group by gender effects were noted.

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526 Are Family Drinking Problems Among Probation Officers Related to Their Views and Practices?


Research suggests that a number of characteristics of treatment professionals are related to alcohol treatment outcome. However, studies have not assessed how the characteristics of other professionals affect services provided to individuals with alcohol problems. This analysis examines the relationship between family drinking problems among probation officers and their views and practices regarding alcohol problems among probationers on their caseload. The family
drinking measure includes both family of origin and present family. Approximately 200 probation officers in eleven California Counties are being surveyed using self-administered questionnaires. Preliminary data from 116 respondents found 82% (n = 95) of the probation officers had at least one family member with a history of a drinking problem and 51% (n = 53) considered family drinking problems to have a moderate or great impact on their lives. Those with more family drinking problems tended to report: (a) A perception of having larger proportions of probations with alcohol problems on their caseload (r = 0.26, P < 0.01), (b) A stronger view that treatment is effective (r = 0.22, P < 0.05), and (c) A higher level of alcohol related training and education (r = 0.21, P < 0.05). There was a negative relationship between family drinking problems and personal alcohol consumption during the past year (r = −0.21, P < 0.05). Multiple regression is used to assess whether family drinking problems predict a composite variable measuring the practice of referring probationers to alcohol treatment. Findings have implications for probation officer training/education, improving treatment utilization, and detecting and managing alcohol problems among probationers. Supported by NIAAA R03 AA12692-02.

527 CHARACTERISTICS OF GAMBLERS: HEALTH MEASURES AND GENDER DIFFERENCES

BACKGROUND: Gambling and drug use behaviors are prevalent and share multiple features. Approximately two of three adults have gambled recreationally within the last year. However, few studies have systematically investigated in a gender-sensitive fashion for health measures associated with recreational gambling. Methods: The random digit dialing database of 2417 adult respondents from the 1998 Gambling Impact and Behavior Study performed by the National Opinion Research Center was used, excluding data from subjects with current or past problem or pathological gambling. Multivariate analyses were used to identify characteristics distinguishing groups of past-year, prior and never gamblers. Multivariate analyses were also performed to identify characteristics distinguishing female and male past-year gamblers. Results: Past-year gamblers as compared with never gamblers had higher rates of substance abuse, depression, incarceration and good to excellent general health. Past-year as compared with prior gamblers had higher rates of bankruptcy. Female as compared with male past-year gamblers were less likely to report incarceration or problems with substance abuse and more likely to report lifetime depression (trend) and having sought mental health treatment. Female gamblers as compared with males were more likely to report gambling onset later in life, engaging in casino gambling, and describing non-strategic or machine forms as favorite. Male as compared with female gamblers were more likely to report engaging in strategic and non-casino forms of gambling and describing strategic forms as favorite. Conclusions: Both negative and positive measures of health and well-being are associated with past-year gambling. Significant differences exist in the gambling attitudes and behaviors of men and women. These findings highlight the need for more research into the nature of the associations between gambling, health, gender and substance use such that appropriate public health recommendations can be made.

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528 CIGARETTE SMOKING AND ATTENTION TO PLEASURE AND THREAT WORDS IN THE STROOP PARADIGM
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Hypothesis: It is predicted, based on biological incentive-sensitization models of addiction, that when tested immediately after smoking, smokers will show heightened attention to words with appetitive motivational significance compared with their performance during acute abstinence. Since the same neural pathways have been implicated in responding to cues with aversive motivational significance, responses to such cues may also be affected in a similar manner. Species: Humans. Number and characteristics of subjects: 21 smokers (9 men, 12 women) who had smoked at least 10 cigarettes per day for at least 6 months, and ten never-smokers (five men, five women). All were aged between 18 and 35 years. Procedures: Non-smokers were tested once and smokers twice, once immediately after smoking a cigarette and once after overnight abstinence (in counterbalanced order), on three versions of the modified Stroop task. They were required to colour-name words (not drug-related) with neutral, appetitive and aversive connotations. A blocked format was used, with word types presented in counterbalanced order; total response times for words of each motivational class were recorded. Statistical analyses: Analyses of variance were used to compare (a) smokers’ performance under conditions of abstinence and recent smoking (using condition and order as within subjects factors in a repeated measures design), and (b) the performance of smokers on their first occasion of testing (abstinent or after smoking) with that of non-smokers. Results: Smokers who had just had a cigarette were slower to colour-name both threat and appetitive words than neutral words, whereas there was no effect of word type in acutely abstinent smokers. Non-smokers performed more similarly to recent smokers. Conclusions: This suggests suppression of normal attentional biases to motivationally significant stimuli during smoking abstinence. Importance of findings: Dependence on cigarettes may in part reflect their ability to normalize smokers’ responsiveness to both incentives and threats. This may contribute to difficulties in maintaining abstinence, and highlights the need for further studies of motivational processes in smokers so that appropriate treatment strategies can be developed.

529 DETECTION OF COCAINE METABOLITE IN THE URINE OF CHRONIC COCAINE USERS DURING CESSATION

Following up on reports that elimination of cocaine and its metabolites is prolonged in chronic users, we have reported a study showing that cocaine’s plasma half-life was longer in active street users than that reported in studies of acute low-dose cocaine administration, though the half-life of the metabolite benzoylegonine (BZE) was similar (Moolchan et al., 2000). Here we report on BZE equivalent concentrations [BZE] and correction with creatinine in urine collected from the same individuals. All urine voids were collected in separate bottles for 2–14 days after admission of 20 chronic high-dose cocaine users onto a closed research unit. [BZE] was determined semi-quantitatively by FPIA. Mean [BZE] in the first voided urine post admission was 31.493 (range 630–277.709) ng/ml. At 24 and 48 h mean [BZE] had decreased to approximately 45% and 8% of [BZE] in the first voided urine, respectively. Mean (range) time to first negative specimen ([BZE] < 300 ng/ml) was 40.3 (16–66) h. Approximately half of the participants tested positive for BZE at least once after testing negative; mean time to last positive specimen was 53 (11–147) h after the first voided specimen. Mean creatinine concentrations ([CRE]) of individual participants ranged from 49 to 193 mg/dl. Mean [CRE] for specimens collected over 6 h intervals (12 AM – 6 AM, 6 AM – 12 PM, 12 PM – 6 PM, 6 PM – 12 AM) ranged from 75 to 83 mg/dl, with no differences
among the four intervals. Normalization with CRE ([BZE] \times 100/ [CRE]) and cutoff criterion set at 300 ng BZE/mg CRE increased the mean time to first negative specimen to 50 (11–80 h) and time to last positive specimen to 65 (7–147 h). Within the limits of this naturalistic study (e.g. unknown time of the last cocaine use), mean detection times were similar to the expected 48 h, though more than half of the participants tested positive longer than 48 h after admission to the unit, consistent with prolonged elimination times; [CRE] did not vary systematically with time of day; and CRE correction increased cocaine detection time when 300 ng BZE/mg CRE was used as the cutoff for positive and negative specimens.

In our continuing efforts to develop new potential stimulant abuse therapeutics, several 1-{[2-bis-(4-fluorophenyl)methoxyethyl]-4-(3-phenylpropyl) piperaziner (GBR 12 909) analogues were designed and synthesized. Our hypothesis was that structural modification of the GBR 12 909 molecule would alter the affinity and selectivity of this compound for the dopamine transporter (DAT) and serotonin transporter (SERT). It was thought that selected structural modifications (i.e. replacement of the piperazine ring with a piperidine ring) might enhance the affinity and/or selectivity for the DAT over the SERT. These new analogues were tested for affinity at the DAT and SERT present in rat caudate membranes using [125I]RTI-55 as radioligand. As a result of our work, several analogues containing oxygen in the phenylpropyl sidechain have been identified with subnanomolar affinity and/or increased selectivity for the DAT compared to GBR 12 909. These new analogues may prove useful as treatments for drug abuse and/or as pharmacological tools.

Persons of non-European backgrounds will comprise the majority of the U.S. population by 2050. The proportion of Asian Americans (AAs) will more than triple, increasing to an estimated 10% of the U.S. population. However, epidemiologic studies that document drug use and abuse among a wide range of AA sub-populations remain rare. Existing data from national surveys thus far have only been able to provide results for AAs as a whole; portraying AA substance abuse as the least problematic. To better understand the nature of differential rates of substance use and abuse among heterogeneous AA ethnic groups, we analyzed three recent large national surveys which contained ethnicity information on AA ethnic groups: the National Household Surveys of Drug Use (NHSDA), 1999 (N = 66,706), the National Longitudinal Alcohol Epidemiology Survey (NLAES), 1992 (N = 42,862), and the National Longitudinal Study of Adolescent Health (Add Health), 1995 (N = 90,118). The AA sample size varies from 900 to over 4500 across the three surveys. We examined use and problem use of a wide range of licit and illicit psychoactive substances across AA subgroups and in comparison with whites. Across major substances, results show that: (1) prevalence rates are the lowest in the aggregated AA among major racial groups; (2) using disaggregated AA subgroups, Japanese rates are the highest within AAs-very close to whites’ rates; (3) differential rates correspond to the ranking of several acculturation and socio-economic indices; (4) however, the differential rates are due in part to the size of mixed-race subgroups, among whom up to a 4-fold significant increase is observed; and (5) mixed-heritage AAs are at increased risk for substance use, even after controlling for cultural protective factors and socio-economic measures. The results point to the importance of rethinking ethnic/racial classifications in estimating the rates among ethnic/racial minorities, studying substance abuse problems in mixed-heritage adolescents, and studying detailed processes of decays in social-environmental and potentially genetic protective factors.

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531 4-[2-FLUOROPHENYL]METHOXETETHYLPIPERIDINES AS POTENTIAL COCAINE ABUSE THERAPEUTICS

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532 EXTENT OF PEER GANG INVOLVEMENT AS A RISK FACTOR FOR INDIVIDUAL DRUG USE AMONG CENTRAL AMERICAN SCHOOL CHILDREN

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Gang involvement has been shown to increase the risk of drug use among adolescents. However, peer gang participation have not been thoroughly investigated as a possible independent risk factor for youth drug involvement. In a cross-sectional study of 9930 randomly selected 12–19 year old school students from Panama and Costa Rica, self-reports were collected on extent of peer gang and drug involvement, and personal licit and illicit drug use (alcohol, tobacco, marijuana, ecstasy, cocaine). Self-reported extent of peer gang involvement was greater among boys (X2 = 86.87, 3 df, P < 0.0001), and increased with age (X2 = 79.34, 21 df, P < 0.0001), but did not differ by country. A subject’s report of the extent of gang involvement by their peers was found to be highly associated with the subject’s own drug use (P < 0.0001 for all drugs studied). This relationship held for girls and boys and youths of three developmental age groups, in both countries. Statistically significant relationships were found between extent of peer gang participation and peer licit and illicit drug use (Spearman r = 0.30–0.50, P < 0.0001) for all subgroups. The positive association between self-reports of peer gang involvement and subjects’ drug use did not remain after statistical adjustment, through logistic regression, for licit and illicit peer drug use, for most age, sex and country subgroups. Overall, self-reported peer drug use appears to mediate the relationship between extent of peer gang participation and the likelihood of drug use among Central American adolescent students.

533 TGAQAN PRIMER-PROBE DESIGN FOR NEUROBIOLOGICAL STUDIES

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Over the last several years a number of methods that utilize real time fluorescent PCR for a variety of different applications have been developed, including the TaqMan protocol for quantification of specific mRNAs. This method offers the promise of higher sensitivity of detection in comparison to pre-existing techniques, such as northern blot or even RNase protection assay. Increased sensitivity would allow measurement of multiple mRNAs in tissue extracts of small brain regions. Using empirical studies, we have developed guidelines for optimizing fluorescent TaqMan probe design. We created a set of primers and probes for quantification of mRNAs of neurotransmitter...
systems in the rat. These were tested in a study of alterations in gene expression in the caudate putamen of male Fischer rats induced by one 1-day or 3-day ‘binge’ cocaine administration (3 × 15 mg/kg cocaine or vehicle, spaced at hourly intervals). Total RNA isolated from caudate putamen was pooled from animals in each treatment group so that only variability in the measurement technique would be evaluated. Results of TaqMan measurements for five mRNAs were compared with results of RNase protection assays on the same pooled samples. Results: TaqMan assays yielded results that were highly reproducible; mean intra- and inter-assay coefficient of variation (%CV) were less than 8%, which is comparable to %CV values for our modified RNase protection assay. The TaqMan assay was much more sensitive than RNase protection assays; depending on the probe, 100–200-fold less input RNA than the RNase protection assay could be quantified. Both large (e. g. c-fos, 3.5–5.5-fold) and small (e.g. preprodynorphin, < 20%) alterations in gene expression caused by cocaine treatment were similarly detected by both TaqMan and RNase protection assays. We conclude that the TaqMan technique will be useful for the reproducible and accurate quantification of many mRNAs in small samples of tissue, such as from dissected brain regions of individual experimental animals.

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534 **NOVEL ISOThIOcyanate DERIVATIVES OF (+)-cis-3-METHYL-FENTANYL AS OPioid RECEPTOR PROBES**

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We previously identified SUPERFIT [(+)-cis-3-methylen-tan-yliso-thiocyanate] as a highly selective, irreversible delta opioid receptor ligand. Our subsequent studies revealed its receptor binding domain. The purpose of our current study was to identify new high-affinity, potentially irreversible delta opioid receptor ligands as research tools for further study of ligand interactions with the delta receptor. We synthesized the novel 2-and 3-iso-thiocyanate isomers of SUPERFIT (the 4-iso-thiocyanatophenethyl derivative) based on the idea that variation of the position of the iso-thiocyanate group might influence affinity and/or receptor selectivity and binding domain. In contrast to our previously reported de novo chemical synthesis of SUPERFIT, we utilized a seized sample of (+)-cis-3-methylfentanyl generously provided by the DEA as starting material. A novel degradative route was employed to obtain the key intermediate (+)-cis-3-methyl-4-phenylamino-piperidine. Sequential optical resolution, alkylation with 2-and 3-nitrophényl bromides, and acylation with propionic anhydride then provided the 2-and 3-nitro derivatives. Catalytic reduction reaction to the amines followed by reaction with thiophosphate gene then afforded the corresponding SUPERFIT isomers. We have found that some of these compounds have moderate selectivity and very high affinity for the mu opioid receptor. One of them, an ortho–

535 **INCONGRUENCE BETWEEN SELF-REPORTED AND USDT-CONFIRMED ILLICIT DRUG USE IN AN URBA*n* ER**

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We are examining the incongruence between self-reported and USDT confirmed illicit drug use in all patients who presented to the NYYAMC ER requesting drug detoxification or rehabilitation services for drugs other than ethanol in the year 2000. The Psychiatry Service offers OPD and inpatient drug-free treatment, OPD opiate detoxification and opiate substitution for patients using heroin and cocaine but not benzodiazepines, and inpatient detoxification for benzodiazepines. To date data from 83 subjects of the pool of many hundreds whom had urine toxicologies ordered have been examined for patterns of incongruence between self-report of use and UDST results. Rates of incongruence were highly variable, ranging from 10% for THC, to fully 50% for cocaine/crack cocaine. Specifically, 15% of subjects reported cocaine use in the face of a positive UDST, while 35% of the sample reported cocaine use with a negative UDST. For heroin, 15% of the sample denied use with positive UDST, and 20% had the reverse pattern. For methadone, the false negative report rate was 22%, while no patient reported use with a positive UDST. 26% had UDST positive for benzodiazepines while denying use, but no patient reported use in the face of a negative UDST. For THC, 7% of patients denied recent use when their UDST were positive for THC, and 2% of patients stated that they were using marijuana with negative UDST results. We hypothesize several reasons for these results: (1) Patients have inaccurate folk-knowledge about the sensitivity, specificity, and time course of UDST. (2) Patients adjust their self-reports to fit the services available, and/or requested. (3) Street drug content may not be as advertised.

536 **Gabapentin reduces cocaine use and cravings in addicts with chronic psychiatric disorders**

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Individuals with chronic psychiatric disorders display a high rate of cocaine use. It was hypothesized that gabapentin could reduce cocaine use by restoring an inhibitory GABAergic feedback on ascending dopaminergic projections to nucleus accumbens and cortical neurons. In a 24 week open label trial of gabapentin (800–2400 mg/day), involving five patients with paranoid schizophrenia, two with psychosis NOS, one with major depression and 1 with dysthymia, gabapentin was associated with a reduction in the number of cocaine positive urines, from a mean of 16.34 prior to gabapentin, to a mean of 8.11 after introduction of gabapentin (t = 6.12, n = 8, P < 0.001). About six/nine participants reported a noticeable decrease in their cocaine use throughout the 24 weeks. Several participants reported that the use of gabapentin also reduced the frequency and the intensity of urges to use. Blood levels of gabapentin ranged from 7.0 to 43 mg/l and did not correlate with the decrease in the number of cocaine-positive urine. Side effects reported were sedation and ataxia. Gabapentin proved to be a safe and efficacious medication to reduce cocaine usage in a community sample of psychiatric patients. Efforts towards double-blind replication are warranted.

537 **Why is withdrawal from morphine immunosuppressive in mice?**


Abstinence from morphine, by either abrupt withdrawal (AW) or precipitated withdrawal (PW) induces immunosuppression in murine spleen cells, as assessed by the capacity to mount an in vitro plaque-forming cell (PFC) response to sheep red blood cells. Mice were made dependent by implantation of a 75-mg morphine slow-release pellet for 96 h. At that time an abstinence syndrome was induced. For PW,
The present study determined the ability of bupropion, the nonselective dopamine/norepinephrine (DA/NE) uptake inhibitor and nicotinic receptor antagonist, to alter nicotine (NIC) self-administration in rats. To begin to differentiate the underlying mechanism(s) by which bupropion alters NIC self-administration, the effects of methamphetamine (an indirect DA agonist), apomorphine (a direct DA agonist), and reboxetine (a NE uptake inhibitor and nicotinic receptor antagonist) to alter NIC self-administration were also determined. Rats were trained to self-administer NIC (0.02 mg/kg/infusion, i.v.) on a fixed ratio 5 schedule of reinforcement. Upon reaching a stable baseline, groups of rats were pretreated 15 min before the session with vehicle, bupropion (1–78 mg/kg), methamphetamine (0.3–3 mg/kg), apomorphine (0.01–0.2 mg/kg) or reboxetine (0.3–17 mg/kg). Both bupropion and methamphetamine produced a biphasic dose-response pattern, increasing NIC infusions at low doses and decreasing NIC infusions at high doses; whereas, apomorphine and reboxetine only decreased NIC self-administration. These results implicate the DA transporter as mediating the bupropion-induced increase in NIC self-administration. To determine specificity, the ability of bupropion (1–78 mg/kg, 15 min pretreatment) to alter sucrose-or amphetamine (0.2 mg/kg per infusion)-maintained responding was examined. Bupropion did not increase responding for sucrose or amphetamine, suggesting that bupropion specifically increased NIC self-administration. The specific bupropion-induced increase in NIC self-administration may be the result of inhibition of the DA transporter.

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540 Cannabinoid CB1 receptors modulate morphine-induced hyperthermia

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Two subtypes of cannabinoid receptors, CB1 and CB2, mediate the physiological effects of cannabinoids. Recent evidence also implicates CB1 receptors in the reinforcing effects of morphine. In particular, mice lacking CB1 receptors failed to self-administer morphine or develop morphine tolerance. Although morphine induces hyperthermia via mu opioid receptors, and CB1 receptors mediate cannabinoid-induced hypothermia, the possible role of cannabinoid receptors in morphine-induced hyperthermia has not been investigated. Therefore, the present study investigated the effect of SR141716A, a selective CB1 antagonist, or SR144528, a selective CB2 antagonist, on morphine-induced hyperthermia in male Sprague-Dawley rats (250–350 g). Morphine (0.1–4 mg/kg, s.c.) evoked dose-dependent hyperthermia. The hyperthermia peaked 60 min following morphine injection and persisted for at least 180 min post-injection. Body temperature gradually declined to pre-drug levels. To determine whether CB1 or CB2 receptors modulated the hyperthermia, either SR141716A or SR144528, respectively, was injected intramuscularly 30 min prior to morphine. SR141716A (1–5 mg/kg, i.m.) attenuated morphine-induced hyperthermia. The effect was dose-dependent, and only the highest dose of SR141716A significantly attenuated the hyperthermia. SR144528 (5 mg/kg, i.m.) decreased slightly morphine-induced hyperthermia, but the effect was not significant. The administration of SR141716A or SR144528 by itself did not alter body temperature. The present data indicate that CB1, but not CB2, receptors modulate morphine-induced hyperthermia. These results demonstrate for the first time that cannabinoid receptors play a role in the hyperthermic response to morphine and provide further support that CB1 receptors modulate morphine-induced effects in rodents.

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541 AGGRESSIVE DRIVERS AND AGGRESSIVE DRINKERS


Drinking drivers are dangerous on the road not just because alcohol impairs their reflexes, coordination and judgment, but because they are frequently people whose customary driving style is aggressive and reckless. Alcohol, however, could aggravate this customary driving style, because alcohol consumption facilitates expressions of aggression for a subset of drinkers. We hypothesized that drinkers with alcohol use expectancies of aggression are especially likely to have dangerously aggressive driving styles. Multiple DUI offenders (N = 135) were administered the Driving Expectancies Scale (Deery and Love, 1996), and a seven-item alcohol-induced mood expectancies scale, factor analysis of which revealed two factors (Aggression and Euphoria) accounting for 59% of item variance. As expected, strong, significant pearson correlations were found between Aggression and typical driving styles that included disobeying road rules, anger at slow drivers, racing other cars, and driving fast. These findings suggest that alcohol use expectancies that emphasize aggression could help to identify a subset of DUI offenders requiring specialized anger management or driver training courses designed to improve their driving performance.

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542 A QUALITATIVE ANALYSIS OF DRUG AND SEXUAL HIV RISKS AMONG GAY MALE STIMULANT ABUSERS

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Stimulants, particularly methamphetamine, are used at high rates among gay and bisexual men in southern California and are tied to gay male sexual expression and identity. This presentation describes a qualitative study of 20 gay and bisexual men enrolled in a CSAT-funded outpatient behavioral treatment-research program for stimulant and/or alcohol abuse. Semi-structured, in-depth interviews were conducted at baseline and 26 weeks post admission. Ages ranged from 32 to 59 years, with a mean age of 40 years (6.39 = SD). 50% of the clients were Caucasian, 25% were African American, 20% were Latino, and 5% were Asian/Pacific Islander. About 65% were HIV infected. Sixty percent reported methamphetamine as their drug of choice, while 30 and 10% of the clients reported crack and alcohol, respectively. Qualitative data has been analyzed using grounded theory. Data describes clients’ relationship to their drug of choice as they proceed through treatment and associations between their sexual identity and sexual-related HIV risks before and after drug treatment. Findings are useful in designing culturally-specific drug treatment interventions.

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543 CUE-INDUCED ALCOHOL CRAVING, APPETITIVE OR WITHDRAWAL-BASED: ANALYSIS OF STIMULUS COMPONENTS, PATIENT CHARACTERISTICS, AND CUE REACTIVITY PATTERNS

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Cue reactivity studies have demonstrated robust subjective and physiological responses to alcohol cue presentation in alcoholic patients. Evidence for increased craving and positive drinking ex-pectancies, as well as elevated self-report of withdrawal symptoms and autonomic arousal, support both appetitive and withdrawal based theories of alcohol craving. Moreover, few studies have examined the impact of cue characteristics on cue reactivity. The present study has investigated cue-induced alcohol craving and withdrawal in alcoholics and non-alcohol drinking control subjects. Alcohol and non-alcohol beverage cues contained visual, tactile, olfactory and auditory components and cue reactivity measures included subjective ratings of alcohol craving, positive drinking expectancy, self-efficacy, anxiety, withdrawal symptoms, and physiological recordings of skin conductance and temperature, heart rate, salivation, and plasma cortisol and HVA levels. Thus far, 15 alcoholics (NY:10, Sweden: 5) and three control subjects (NY:3) have been tested, with alcoholics overwhelmingly more cue reactive than controls. Alcohol cue specific subjective responses were seen (in order of magnitude) with alcohol craving (P < 0.05), anxiety (P = 0.12), alcohol-like high, positive expectancy, self efficacy, and withdrawal symptoms. Alcohol cue specific physiological measures were seen with salivation (P = 0.09), and there were indications of an increase in skin conductance and plasma HVA. Analysis of cue components revealed that alcoholics were most responsive to olfactory stimulation, followed by video scenes from a bar, and guided imagery. Cue reactivity was positively correlated with scores from the baseline Alcohol Problems Questionnaire, and negatively correlated with number of days abstinent. Further analysis will examine positive and negative associations with the alcohol cue components and the nature of the craving response: withdrawal vs. appetitive.

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544 TEST OF ALTERNATIVE HYPOTHESES EXPLAINING THE RELATION BETWEEN MARIJUANA USE AND OTHER ILLICIT DRUG INITIATION IN ADOLESCENTS

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Several researchers have established that drug use in adolescence follows a sequential pattern, with alcohol or tobacco use preceding experimentation with marijuana and marijuana use preceding experimentation with other illicit drugs. Although marijuana has been described as a ‘gateway drug’ to other illicit drugs, conclusive evidence supporting a causal link between marijuana use and other illicit drug use is lacking. Hypothesis: Here, we tested 13 alternative hypotheses explaining the relation between marijuana use and other illicit drug initiation in adolescents. Method: The participants were 337 monozygotic twin pairs and 335 dizygotic twin pairs (age 12–18 years) assessed by the Colorado Center on Antisocial Drug Dependence. Marijuana use was defined as using marijuana more than five times during lifetime, and other illicit drug initiation was defined as any lifetime use of illicit drugs other than marijuana. A model fitting approach was used to test the alternative hypotheses. Results: Several hypotheses did not fit the data well and could be rejected. The best supported hypotheses were the correlated liabilities model with a very high correlation between the familial factors influencing marijuana use and other illicit drug initiation, a causal model where marijuana use is a cause of other illicit drug initiation, and a reciprocal causation model where marijuana use and other illicit drug initiation cause each other in a feedback loop. Conclusion: Although the hypothesis that marijuana use is a cause of other illicit drug initiation fit the data well, two alternative hypotheses were also consistent with the data.

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545 Drug use patterns observed in a research clinic
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Many variables may influence the type of drugs abused in a community at a given time: general economic status, drug availability, the prevalence drug enforcement efforts, and drug ‘fads.’ The Treatment Research Clinic at the University of Texas Mental Sciences Institute has been collecting substance abuse data since 1990 funded primarily by treatment research and medication development grants from NIDA. While the majority of patients have been recruited for cocaine or opiate dependent studies, use of other drugs are queried and measured. Demographic information, Addiction Severity Index, drug history information, and urine screens are also collected. Drug history information records reported current, past, and pattern of use for 16 drug categories. Total sample size of n = 4145 patients, spanning 12 years (1990–2001), will be presented. Analyses of these existing data will focus on assessing the patterns of reported and measured substance use, as well as any changes in the basic demographics of the subject pool. For example, for the 2-year block 2000–2001, the Age at cocaine first use averaged 26.0 (7.8) range 6 to 48 and patients reported using cocaine an average of 13.6 (9.3) times during the month before study participation. While local factors determine the unique characteristics of substance abusers seen in this clinic, the broader trends seen may reflect factors relevant to researchers in other locals.

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546 Human pharmacology of ayahuasca: subjective and cardiovascular effects and pharmacokinetics
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Ayahuasca is a shamanic psychotropic beverage used since pre-Columbian times in the Upper Amazon and Orinoco River Basins. This plant tea is obtained from Banisteriopsis caapi and Psychotria viridis and combines monoamine-oxidase-inhibiting beta-carboline alkaloids (harmine, harmaline, and tetrahydroharmine) with N, N-dimethyltryptamine (DMT), a hallucinogenic agent showing 5-HT2A/2C agonist activity. In recent years, the use of ayahuasca has spread outside South America, and groups of regular users of the tea have become established in several European countries. The subjective and cardiovascular effects and pharmacokinetics of ayahuasca alkaloids were assessed in a group of 18 healthy volunteers with previous experience in hallucinogen use in a double-blind placebo-controlled clinical trial, in which two doses of encapsulated freeze-dried ayahuasca (0.6 and 0.85 mg DMT/kg body weight) were administered. Ayahuasca produced dose-dependent perceptual, mood and thought modifications beginning 30–60 min after administration, peaking between 1.5–2 h, with an overall duration of 4–6 h. Significant dose-dependent increases were observed in the six subscales of the Hallucinogen Rating Scale, in the LSD, MBG and A scales of the Addiction Research Center Inventory, and in the ‘Liking’, ‘Good Effects’ and ‘High’ Visual Analogue Scales. Diastolic blood pressure showed a moderate though significant increase at the high dose (9 mm Hg maximal increase), while systolic blood pressure and heart rate were weakly and non-significantly increased. Non-compartmental pharmacokinetic analysis showed a linear pharmacokinetics for DMT and the beta-carbolines (harmaline and tetrahydroharmine). Plasma levels of harmine were negligible. Cmax values for DMT after the low and high ayahuasca doses were 11.85 ng/ml and 16.70 ng/ml, and Tmax was observed 1.5 and 1.75 h, respectively. The Tmax for DMT coincided with the peak of subjective effects.

547 Cocaine addiction at the millennium
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Thomas Jefferson University, Philadelphia, PA, There is a sizable body of research supporting the efficacy of substance abuse treatment (Kleber, 1989, McLellan et al., 1997). Research has also demonstrated that socio-demographic factors (McCauley et al., 2001), addiction severity (Carroll et al., 1993), and psychological functioning (Sterling et al., 1996) of the substance abusing individual can influence treatment outcome(s). Recognizing, however, that patient profiles evolve over time, the service community must be prepared to respond to the ever-changing needs of the treatment seeking substance abuser (Craddock, 1997). The current study seeks to identify whether the socio-demographic, addiction severity, and psychiatric symptomatology profile of individuals seeking outpatient cocaine addiction treatment 10 years apart at the same university based, inner city, outpatient treatment facility, has changed. There were 386 first admissions in 1990 and 58 in 2000 that contributed data to this study. At admission these patients provided basic socio-demographic information (i.e. race, gender, age, recent employment status, etc.) and were evaluated on a variety of psychosocial measures that included the Addiction Severity Index, SCL-90R, Beck Depression Inventory, and Risk for AIDS Behavior Inventory. Chi-square and t-tests were used to test for differences on categorical and continuous measures, respectively. Regarding the socio-demographic factors, results indicated that in 2000, new admissions were more likely to be married, older, working or seeking employment, and white. No meaningful differences in SCL-90-R or BDI assessed psychopathology were observed. While equivalent, in general, ASI composite and severity estimates appeared higher in 2000, perhaps the result of a longer and more extensive drug-use history. Interestingly, with respect to HIV risky behaviors, none of the 58 admissions in 2000 reported an intravenous route of cocaine administration as compared with 9% in 1990, X2 = 9.49, P = 0.008. Similarly, HIV risk as measured by the RAB dropped significantly over the 10 year period (M’s = 8.38 and 4.44, respectively) t (443) = 6.89, P < 0.001. The changing nature of the substance-abusing individual continues to define the challenges confronting the treatment community.

548 Could the length of time from onset of DSM-IV abuse to dependence (LOTAD) provide a measure of abuse liability of drugs in humans?
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Previous analyses suggest that the length of time between onset of DSM-IV abuse to dependence (LOTAD) is longest for alcohol disorders and progressively shortens for cannabis disorders to opiate disorders to cocaine disorders. This result is consistent with animal study findings concerning the abuse liability of these drugs. Abuse liability of drugs in humans is often measured using research designs that are similar to animal studies such as progressive-ratio schedules. LOTAD offers the advantage of measuring abuse liability in terms of drug-related diagnoses. Based on abuse liability animal studies, we hypothesized that LOTAD differences occur between (a) genders, (b) early initiators versus later initiators, and (c) route of use. Data for these analyses come from the DSM-IV Field Trials study (N = 1226), which used the CIDI-Substance Abuse Module. Substance-specific analyses included only those participants who were users of the drug.
(alcohol, cannabis, cocaine, or opiates). Analytical techniques included configurational frequency analysis and survival analysis. Compared to men, a greater proportion of women experienced dependence as their first disorder pertaining to alcohol use or cannabis use (i.e. negative LOTAD). Early initiators of use of alcohol, cannabis, and cocaine experienced shorter LOTAD than later initiators of use of these substances. Intravenous route of drug use was associated with shorter LOTAD than other routes. LOTAD was very short regardless of injection status for cocaine use, suggesting that cocaine is highly addictive (consistent with animal studies). Overall, these data suggest that LOTAD could provide a valid measure of a drug’s abuse liability in humans.

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549 THE INFLUENCE OF PARTNER DRUG USE AND RELATIONSHIP
POWER ON TREATMENT ENGAGEMENT

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Substance-using intimate partners negatively impact individuals’ substance abuse treatment engagement and drug use, but there is little research assessing the impact of other aspects of relationships on treatment. In this study we examine how partner drug use and relationship dynamics (power, control, dependence and insecurity) influence treatment engagement, and whether this differs by gender. 64 heroin users (42 men and 22 women) receiving methadone detoxification treatment were interviewed at treatment entry and submitted daily diaries of drug use throughout the 21-day treatment. Individuals reporting five or more heroin-free days in the first 14 days of treatment were characterized as treatment-engaged. Bivariate analyses revealed that among those with heroin-using partners, greater relationship power predicted treatment engagement, while among those with heroin-free partners, less relationship power predicted engagement. Women were more likely to have substance-using partners and reported greater power and control and less dependency in their relationships. Women who reported less dependency in their intimate relationships were more likely to engage in treatment. Men with heroin-free partners were more likely to engage than those with heroin-using partners. Relationship power and other dynamics may be important influences on the treatment process, though the impact may differ by gender.

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550 A RANDOMIZED TRIAL OF BUPRENORPHINE MAINTENANCE
COMPARED TO METHADONE MAINTENANCE: PSYCHO-SOCIAL OUT-
COMES

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Psycho-social outcomes from maintenance treatments reflect important individual and societal treatment impacts. An open-label, multi-site randomised controlled trial was conducted in Australian primary care settings. A total of 139 participants (57 existing methadone maintenance patients and 82 heroin users) were recruited and randomised to either methadone or buprenorphine maintenance. Patients were followed up at 3, 6 and 12 months post treatment commencement. Measures of psycho-social outcomes included HIV risk taking behaviour, social functioning and the SF-36. For those patients recruited from methadone maintenance, there was no change across the twelve months in psycho-social functioning between those randomised to buprenorphine maintenance and those randomised to remain on methadone. For heroin users, there were substantial improvements across all psycho-social domains within the first 3 months of treatment. However there were no significant differences between methadone and buprenorphine.

551 A HUMAN LABORATORY MODEL TO STUDY INTERNAL AND
EXTERNAL STIMULUS CUES IN COCAINE REINFORCEMENT AND RE-
LAPSE PREVENTION

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Eight cocaine-dependent research volunteers who were not seeking treatment participated in a laboratory study of cue-elicited craving and cocaine reinforcement. The study combined external and internal cocaine-related stimuli with a cocaine self-administration opportunity. Cocaine stimuli included a 10 min video tape of actors using cocaine (all S’s), manual handling of a syringe (3 S’s), and an i.v. injection of 40 mg cocaine (all S’s). Control stimuli included a 10 min nature video, manual handling of pencils, and an i.v. injection of saline. Following i.v. injections, all S’s completed the Multiple-Choice Questionnaire (MCQ) to express their preference to receive a 2nd injection versus varying amounts of money. In order to validate the MCQ as a reinforced operant response, one of the MCQ choices (of injection vs. money) was selected at random and S’s received it 15 min later. Visual signs and visual analog scales of subjective effects and craving were recorded repeatedly before, during, and after the procedure. Seven male and one female participants, 19–45 years of age, were hospitalized on a research unit for 4 days. The first day provided initial cocaine and control stimuli and the second day provided only control stimuli to demonstrate initial cue reactivity. Days 3–4 separately provided the cocaine and control stimuli in combination with MCQ reinforcement in counter-balanced order and under single-blind conditions. The results showed that external environmental cocaine-related cues produced only modest cocaine craving and physiological arousal in 4 S’s. In contrast, the i.v. injections of cocaine produced robust effects in all eight participants. Cocaine was reinforcing for seven of the 8 S’s (MCQ value of $0.40 for saline vs. $8.38 for cocaine). The 4 S’s who showed a craving response to external stimulus cues also reported greater MCQ values for cocaine ($11.44) as compared to the 4 S’s who were not responsive ($5.31). This procedure should aid the analysis of conditioned stimulus cues as triggers for relapse.

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552 DERIVED TRAIL MAKING TEST INDICES IN A SAMPLE OF
AMPHETAMINE ABUSERS: DEMOGRAPHIC EFFECTS

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Derived indices on the Trail Making test (TMT), a test often used for screening for cognitive impairment, are examined in a sample of amphetamine abusers in drug abuse treatment programs. The Trail Making Test (TMT) is a brief, portable and an inexpensive neuropsychological test that has been used to assess cognitive dysfunctions for over a half century. A mixed race sample (N=185) of subjects with a primary problem of amphetamine abuse was drawn from electronic
files of data from the Drug Abuse Treatment outcome Study (DATOS). The DATOS was a naturalistic, prospective cohort study that collected data from 1991–1993 in 96 programs in 11 cities in the United States. Data were analyzed to determine the effects of demographic variables on derived indices created by adding, subtracting, multiplying and dividing parts A and B of the TMT in this large treatment sample of substance abusers. The variables of gender, age, ethnicity and education were not statistically significant for selected derived indices of the TMT.

553 SAFETY AND IMMUNOGENICITY OF A HUMAN NICOTINE CONJUGATE VACCINE


TA-NIC is a novel nicotine vaccine composed of a nicotine derivative (nicotine butyric acid) conjugated to recombinant cholera toxin B. It is designed to induce nicotine-specific antibodies capable of binding nicotine in the blood and thereby preventing nicotine from reaching the brain. A double-blind placebo-controlled dose-escalation study was conducted among 50 adult smokers who were not attempting to quit and ten non-smokers. Cohorts were divided according to dose, dosing regimen and smoking status. TA-NIC was given by intramuscular injection at 0, 10 or 50 g doses with four dosing regimens (0, 2, 4, 6 weeks, 0, 2, 4, 8 weeks, 0, 2, 4, 6, 8 weeks or 0, 2, 4, 6, 20 weeks) tested. Safety and immunogenicity were assessed over a 24-week period. Injection site reactions and systemic adverse events were monitored. Immunogenicity evaluations were made prior to the first vaccination and following every vaccination. Immunogenicity was assessed by ELISA to determine antibody levels and competition assays were used to determine specificity of nicotine antibodies. 60 subjects were successfully followed to day 84. No serious safety issues were identified, detailed immunogenicity data will be presented.

554 FREQUENCIES OF MARIJUANA USE AMONG ADOLESCENT SMOKERS IN SMOKING CESSATION

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Adult studies suggest that marijuana (MJ) users in smoking cessation treatment consume fewer daily cigarettes than non-MJ users (Humfleet et al.1999; Willis and West, 1997). We hypothesized that MJ-using teen smokers in tobacco cessation treatment have increased frequency of MJ use as they reduce their cigarette use per day (CPD). Self-reported frequency of MJ use and CPD were obtained from 35 teen smokers (age 13–17 years, 77% female, 29% African-American) in a smoking cessation study through the first 6 weeks of a 3-month course. Participants characteristics included: enrollment age 15.2 ± 1.34 years, Fagerstrom Test of Nicotine Dependence (FTND) score 6.97 ± 1.32, baseline CPD 18.5 ± 8.86, age of onset of smoking 10.93 ± 2.0 years. From the total sample, 89% had ever smoked MJ, 27% had smoked MJ at least 2 days during last 2 weeks prior to their first visit, and 91% of MJ users smoked cigarettes prior to their onset of MJ use. Repeated measures linear regression showed a significant decrease in CPD (P < 0.0001) and an increase in the frequency of self-reported MJ use (P = 0.025) during this 6-week period. Furthermore, lower CPD in the prior week was associated with increased MJ use in the current week (P = 0.045), even after controlling for MJ use in the preceding week. These preliminary findings suggest the need for a closer look at potential compensatory MJ smoking among teenagers in smoking cessation treatment.

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555 PERINATAL BUPRENORPHINE ALTERS CHOLINERGIC NEURONS IN RAT STRIATUM

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The partial opioid agonist buprenorphine is under consideration for managing pregnant heroin addicts. In the rat, perinatal exposure to methadone disrupts the development of striatal cholinergic neurons. Buprenorphine was hypothesized to have an effect similar to that of methadone. The effect of perinatal buprenorphine exposure on striatal cholinergic neurons was determined in ‘weanling’ and ‘adolescent’ rats. On day seven of gestation, pregnant Sprague-Dawley CD rats under methoxyflurane anesthesia were implanted subcutaneously with 28-day osmotic minipumps delivering sterile water (w) or buprenorphine HCl (b, 0.3, 1, or 3 mg/kg per day). These doses spanned buprenorphine’s bell-shaped dose-effect curve. Within 24 h of birth, litters were culled to 10 and cross-fostered, resulting in the following prenatal/postnatal exposure groups: w/w, b/w, b/b, and b/b. New pumps were implanted in dams on postnatal day (PD) 10. On PDs 21 (n = 135) and 35 (0.3 mg/kg per day, n = 45), acetylcholine (ACh) content and turnover were determined. Rats were infused via the tail vein with deuterium-labeled phosphorylcholine (15 μmol/kg per minute) for 9 min and were euthanized by microwave radiation focused to the skull (7.5 kW, 0.75 s). Data were analyzed by ANOVA followed by Dunnett’s test with P < 0.05 considered significant. Buprenorphine’s effect on cholinergic activity differed from that of methadone, with the most pronounced effect being reduced ACh content following prenatal exposure to the 3 mg/kg per day dose on PD21. Like methadone, prenatal exposure to buprenorphine (0.3 or 1 mg/kg per day) increased ACh turnover on PD21. Unlike methadone, postnatal exposure to buprenorphine (3 mg/kg per day) increased ACh turnover. On PD 35, there were no effects of treatment on either ACh content or turnover; however a statistically nonsignificant increase in ACh turnover was observed in males exposed prenatally to buprenorphine, 0.3mg/kg per day. Unlike methadone, buprenorphine acts at δ, κ, as well as μ, opioid receptors, and is an antagonist at higher doses which may explain its different effect on cholinergic neurons.

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556 DELAY DISCOUNTING, IMPULSIVENESS, AND ADDICTION SEVERITY

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A number of studies have found that substance abusers show higher delay-discounting rates and impulsivity scores than non-abusing controls, and that the two measures are highly correlated; however, the nature of the relationship between addiction severity and delay discounting and impulsiveness has not been determined. This study compared stable methadone maintenance patients (n = 30) who had been drug-free for 2 or more years, to matched samples of drug-using methadone patients (n = 30), and non drug-abusing controls (n = 20) in terms of addiction severity, delay-discounting rate and impulsivity. Assessments included the Addiction Severity Index (ASI), a computerized delay-discounting procedure, and Eysenck’s T7 impulsivity scale. Results show that drug abstinent patients scored significantly lower on a number of addiction severity measures (the legal, family, psychiatric, drug and alcohol ASI composite scores, number of arrests, and drug-positive urine results) than the drug-using methadone patients. In addition, the radiation focused to the skull (7.5 kW, 0.75 s). Data were analyzed by ANOVA followed by Dunnett’s test with P < 0.05 considered significant. Buprenorphine’s effect on cholinergic activity differed from that of methadone, with the most pronounced effect being reduced ACh content following prenatal exposure to the 3 mg/kg per day dose on PD21. Like methadone, prenatal exposure to buprenorphine (0.3 or 1 mg/kg per day) increased ACh turnover on PD21. Unlike methadone, postnatal exposure to buprenorphine (3 mg/kg per day) increased ACh turnover. On PD 35, there were no effects of treatment on either ACh content or turnover; however a statistically nonsignificant increase in ACh turnover was observed in males exposed prenatally to buprenorphine, 0.3mg/kg per day. Unlike methadone, buprenorphine acts at δ, κ, as well as μ, opioid receptors, and is an antagonist at higher doses which may explain its different effect on cholinergic neurons.

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found between the patients. Similarly, the two groups of methadone maintenance patients obtained significantly higher impulsivity scores ($F = 6.84; df = 2; P < 0.01$) compared to the control group (both $P < 0.05$), but no difference in impulsivity was found between the two groups of methadone patients. Thus, while these results support previous reports of higher delay discounting rates and impulsivity in methadone patients than in non drug-dependent controls, they suggest that these measures do not covary with several frequently used indicators of addiction severity.

557 THE EFFECTIVENESS OF AN INTERVENTION MODEL WITH DUAL STRATEGIES TO REDUCE DRUG USE AND HIV RISK BEHAVIORS AMONG DRUG INJECTORS IN PUERTO RICO

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Introduction. This longitudinal study examined the effectiveness of an intervention model that aimed to retain community-recruited drug injectors in treatment in order to reduce drug use and HIV risk behaviors in Puerto Rico. The nine-session intervention was delivered by trained counselors using motivational interviewing strategies and outreach workers using case management strategies. Methods. About 536 drug injectors recruited in rural communities were randomized to an experimental group (49.7%) or to a control group (50.3%). This paper reports findings of 440 drug injectors (82.1%) at follow-up, 6 months after baseline. The sample was comprised mainly of males (90.2%); 12.4% were HIV positive, 31.5% were diagnosed with severe depression; and 37.7% entered drug treatment. Results. Controlling for age, gender, HIV status and depressive symptomatology, three regression models were used to explain effects of the dependent variables: reduced drug use and reduced HIV risk behaviors. The first regression model showed that participation in drug treatment reduced heroin and cocaine use (measured by urinalysis). The second regression model showed that the intervention model was effective in reducing cocaine use but not heroin use. The last model demonstrated that the intervention was effective in reducing needle sharing in all types of drugs used. The model was effective in reducing needle sharing after controlling for depressive symptomatology. Conclusion. This study proved the effectiveness of a dual-strategy intervention model that reduces drug use and HIV risk behaviors. The fact that, contrary to previous findings, drug treatment did not reduce HIV risk behaviors may mean that residential services in Puerto Rico are not addressing these behaviors. The effectiveness of the intervention on reducing cocaine use is worth pursuing further.

558 NALTREXONE COMBINED WITH NICOTINE REPLACEMENT: EFFECTS ON SMOKING CUE REACTIVITY

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Naltrexone (NAL) might affect urges to smoke because of its effects on meso-limbic pathways associated with drug reinforcement, and the combination with nicotine replacement (NRT) might be particularly effective by targeting different mechanisms of action concurrently. Smokers underwent 10 h of tobacco deprivation while randomized to one of six conditions. Each received a transdermal nicotine or placebo patch (1, 20 or 42 mg) after smoking their last cigarette on arising, then took a capsule with 0 or 50 mg of NAL at 1 p.m. At 5 p.m., all were exposure to neutral cues then smoking cues, following which a smoking ‘taste-rating task’ provided an unobtrusive measure of smoking behavior. Prior to smoking cues, a main effect for NRT was found but urge was reduced only with 42 mg NRT ($P < 0.05$). Similarly, the small cue-elicited changes in urge and withdrawal were affected ($P < 0.05$) only by 42 mg of NRT. NAL had a significant effect ($P < 0.05$) on reducing cue-elicited negative affect. For amount of tobacco smoked, NAL reduced smoking only when combined with 21 mg NRT, increased smoking with 0 mg NRT, and had no effect with 42 mg NRT. After the taste test, urge was lower for women than men when on NAL and the reverse when on placebo ($P < 0.05$). Otherwise no gender interactions were seen in any analysis. Conclusions: NRT may only be beneficial at 42 mg, and NAL may not be beneficial in combating tobacco deprivation effects.

559 CONTINGENCY MANAGEMENT FOR TREATING ADOLESCENT CIGARETTE SMOKERS

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Cigarette smoking by adolescents is a dangerous behavior. Estimates of adolescent smoking indicate at least two thirds of all adolescents have smoked one cigarette by age 18, 15% smoke every day and 11% of high school seniors smoke at least ten cigarettes per day (Johnston, O’Malley, & Bachman 1998; Stanton, Lowe & Gillespie, 1996). Among adolescents aged 12–17, 4.1 million, or 18.3%, are current smokers (SAMHSA, 1996). Despite these alarming statistics effective treatment strategies for this population have not been developed. This report describes the early phase of a clinical trial examining the efficacy of contingency management in helping adolescent cigarette smokers to stop this potentially fatal behavior. Early results are quite promising with the majority of individuals in the contingency management group initiating abstinence and maintaining it for approximately 4 weeks. Individuals in an educational control group have not routinely initiated significant periods of abstinence. While these are early results and must be considered tentative, they do point towards the efficacy of using contingency management in the treatment of adolescent cigarette smoking.

560 EFFECTS OF ACUTE COCAINE AND HYDROCORTISONE ADMINISTRATION ON COGNITIVE FUNCTION IN INDIVIDUALS WITH COCAINE DEPENDENCE

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Chronic use of both cocaine and glucocorticoids has been demonstrated to produce cognitive deficits. This study sought to explore whether: (1) acute cocaine administration also produces cognitive deficits and (2) these deficits can be modeled using exogenous hydrocortisone. Double-blind placebo-controlled cocaine (0.2 mg/kg) and hydrocortisone (0.5 mg/kg) were administered as an IV bolus to five individuals with cocaine dependence (mean age ± SD: 43.6 ± 5.2 years; two females and three males; four African American and one Caucasian; ASI Drug Score = 0.14 ± 0.13). Blood cortisol assays were obtained immediately prior and 5, 10, 15, 30, 60, 90 and 120 min following the bolus administrations. Cognitive testing included tasks that assessed attention, free recall and recognition for categorically related words before the boluses and 20 min thereafter. These tasks have been standardized and validated in studies on the effects of different classes of drugs in a number of patients’ populations. Both
cocaine and hydrocortisone, but not placebo administration resulted in significant elevations (P < 0.01; Friedman ANOVA test) in plasma cortisol levels (also reported in an other abstract) and produced a trend in significant decreases in free recall and recognition memory (P < 0.067; Wilcoxon matched pairs test). These results suggest that cocaine causes a similar pattern of cognitive impairment as hydrocortisone. More experiments using varying doses of hydrocortisone are underway in our laboratory to explore whether the HPA axis activation produced by cocaine may be involved in the acute cognitive impairment resulting from cocaine administration. The data generated by those experiments will be presented.

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561 ORGANIZATIONAL AND ATTITUINAL FACTORS ASSOCIATED WITH THE ADOPTION OF ACUPUNCTURE IN PRIVATE SUBSTANCE ABUSE TREATMENT ORGANIZATIONS

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The adoption of acupuncture in substance abuse treatment provides the opportunity to examine a practice that is neither pharmaceutical or behavioral, and which in some definitions represents ‘complementary and alternative medicine.’ Data were collected in 2001 regarding acupuncture adoption in a nationally representative sample of 400 privately funded substance abuse treatment organizations. Within the sample, about 9% have adopted acupuncture, 44% report their staffs are familiar with but do not use acupuncture, and 47% report their staffs are unfamiliar with acupuncture. The most strongly supported reason for adoption is acupuncture’s minimal side effects. The principal barriers to adoption include inadequate access to medical personnel and inadequate information about the treatment. A multivariate logistic regression model indicated significant effects on the adoption of acupuncture of the following organizational variables: size, proportion of counselors in recovery availability of outpatient detox, emphasis on the use of medications, and use of spiritual therapy. Centers that emphasized confrontational group therapy were less likely to adopt acupuncture. In examining organizational predictors of treatment center staff familiarity with acupuncture, for-profit centers showed significantly lower familiarity, a higher level of organizational efficiency was a positive predictor, and the proportion of counselors in recovery positively predicted staff familiarity with acupuncture.

562 PERCEIVED VALUE OF VOUCHER VERSUS CASH INCENTIVES

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Rationale: Contingency management in the form of vouchers has proven to be effective in promoting abstinence in drug abusers. However, not all participants respond favorably to the voucher incentives possibly due to the perceived cash value or worth placed on the voucher by the individual participant. Factors such as the delay in receipt of the exchange items, and restrictions on what can be purchased may account for some of the variability found among responders. Purpose: This study will examine perceived value of voucher reinforcers comparing them with receipt of cash in a hypothetical choice task. Hypothesis: The perceived value of the voucher will be less than its cash equivalent, particularly when money is presented as an immediate reinforcer, and the voucher exchange item is delayed. Methods: Using a randomized, within group, 2 × 3 design we will examine choice behavior among drug dependent pregnant women (N = 50), in one session with six choice conditions. Two instructional sets (immediate and delayed) will be counterbalanced, while three voucher amounts ($10, $50, and $100), will be presented in random order within each instructional set. Results: Primary outcome is the cross over point from voucher to money choice (Six data points per subject). Data collection is on going; results will be available at the meeting. Implications: These findings will be important for understanding the relative potency of vouchers versus money reinforcers and for further refining methods for implementing voucher reinforcement programs.

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563 SUBSTANCE ABUSE AND THE NEED FOR MONEY MANAGEMENT ASSISTANCE

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Background: The use of disability payments by dually diagnosed beneficiaries to pay for drugs and alcohol harms beneficiaries and undermines public support for the payment of benefits. Multivariate analysis of data from a survey of psychiatric inpatients was used to evaluate the relationship between both substance abuse and psychopathology and clinician-rated need for money management assistance. Methods: Altogether, 236 subjects were drawn from 570 consecutively admitted psychiatric inpatients approached. Subjects were those veterans who did not have a payee, agreed to complete a money-management-focused questionnaire, and had inpatient clinicians who also agreed to complete a questionnaire. RESULTS: Subjects were predominantly male (95%), older (mean = 49), receiving Social Security or Veterans Benefits (55%) and had a DSM substance abuse diagnosis (71%). Multivariate analyses revealed significant positive, albeit modest; relationships between need for assistance and both drug and alcohol composite scores on the ASI. There was no relationship between need for assistance and presence of a major mental illness (Schiz, Bipolar, Psychosis-NOS) or number of psychiatric symptoms endorsed from the ASI mental health module. Substance use severity significantly increased the risk of needing money management assistance among patients with severe mental illness. Clinicians indicated that they would assign a payee to 11% of the patients, and drug use severity predicted clinician-rated need for a payee. Conclusions: Substance abuse contributes to funds being misspent, an effect that is especially pronounced in patients with severe psychopathology. A substantial proportion of patients need money management interventions that specifically address problems related to substance use.

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564 PREDICTORS OF SUBSTANCE USE AND PSYCHOSOCIAL ADJUSTMENT AMONG HIV-AFFECTED YOUNG ADOLESCENTS


The objective of the study was to determine the association of family functioning and peer networks with substance use and psychosocial adjustment among a sample of at-risk young adolescents. Method: Study subjects were 73 adolescents between 9–15 years old with a HIV-ill parent. Most of the parents had a history of drug abuse. Study
constructs were four measures of family functioning (family conflict, parental permissiveness, parental detachment, and parental child abuse and neglect), peer networks (extent of anti-social behavior-including drug use-among peers), lifetime substance use, and psychosocial adjustment (the composite measure of the Child Behavioral Checklist). Results: Subjects were 51% male, 59% African-American, 29% Hispanic; mean age was 11.9. About 21 subjects (29%) had a history of substance use (20% cigarettes, 22% alcohol, 8% other psychoactive drugs). Analysis was conducted by logistic and ordinary least squares regression; age was used as a covariate. Substance use was significantly (P < 0.05) associated with parental detachment and peer networks. These data underscore the importance of developing and evaluating family and peer interventions for preventing poor developmental outcomes for this at-risk population.

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**565 A MONKEY MODEL OF COCAINE CRAVING AND THE ROLE OF DOPAMINE RECEPTORS**

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Cocaine craving is a phenomenon that is difficult to model in animals. In this study, separate groups of rhesus monkeys were trained to self-administer cocaine (0.03 mg/kg per injection, n = 4 or 0.3 mg/kg per injection, n = 8) under a fixed-interval (FI) 3-min schedule. Approximately every 2 weeks, monkeys were subjected to probe sessions consisting of a period of abstinence (1-3 days) followed by a single FI 2-h. After the final cocaine session, animals were euthanized and brains analyzed for the acquisition portion of the experiment. During probe sessions, there were significant differences between groups (P < 0.001), with monkeys from the 0.3 mg/kg injection cocaine group responding at the highest rates compared to baseline. For this group, response rates during probe sessions were positively correlated with D1 but not with D2 receptor densities in the caudate (r = 0.94) and putamen (r = 0.85). In the 0.03 mg/kg per injection cocaine group, the only significant effect was a positive correlation between probe session response rates and D1 receptor density in the putamen (r = 0.92). No significant correlations were observed within the n. accumbens in either group. These data suggest that this procedure may have validity as an animal model of craving and suggest possible neural correlates associated with this behavior.

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**566 CHRONIC TREATMENT WITH THE 5HT2A AGONIST DOI MODULATES THE BEHAVIORAL AND CELLULAR RESPONSE TO (+)-MDMA**

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MDMA (ecstasy) has a complex mechanism of action that includes affinity for the serotonin (5-HT) transporter and 5-HT2 receptors. In fact, the 5-HT2A receptor (5-HT2AR) antagonist M100907 has been shown to partially block (+)-MDMA-evoked locomotor hyperactivity. Therefore, we hypothesized that down regulation of 5-HT2AR would reduce the degree of locomotor activation by (+)-MDMA. Male Sprague-Dawley rats (n = 80) were treated with a regimen of the 5-HT2R agonist DOI (2,5-dimethoxy-4-iodoamphetamine; 1 mg/kg, s.c., 8d) which has been shown to down-regulate 5-HT2AR but not 5-HT2CR. On day 9, the animals were challenged with (+)-MDMA (3, 6, or 12 mg/kg, s.c.), and locomotor activity was assessed for 90 min in photobeam monitors. Contrary to our hypothesis, the DOI-treated rats showed significantly higher (+)-MDMA-induced motoric activation than the saline-pretreated controls (P < 0.05). However, down-regulation of 5-HT2AR in DOI-treated animals was confirmed via immunohistochemical staining. In addition, immunohistochemical analysis of c-Fos immunoreactivity, as a marker of neuronal activation, indicated that DOI pretreatment decreased the number of (+)-MDMA-induced c-Fos immunopositive nuclei in the striatum, nucleus accumbens, and prefrontal cortex, while increasing the number in the ventral pallidum (P < 0.05). We postulate that the DOI regimen may have down-regulated 5-HT2CR along with 5-HT2AR. The 5-HT2CR appears to play an inhibitory role in locomotion, and 5-HT2CR antagonists potentiate (+)-MDMA-evoked hyperactivity. If chronic DOI results in down-regulation of both 5-HT2AR and 5-HT2CR, the loss of normal inhibitory control by 5-HT2CR may predominate resulting in the observed increase in (+)-MDMA-evoked hyperactivity in DOI-treated relative to saline-treated rats.

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**567 SEX DIFFERENCES IN THE ACQUISITION AND MAINTENANCE OF INTRAVENOUSLY SELF-ADMINISTERED METHAMPHETAMINE IN RATS**

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Previous work indicates that female and male rats differ on several aspects of psychostimulant self-administration. Specifically, female rats initiate cocaine use sooner than male rats and reach significantly higher breaking points (BPs) for a single injection of cocaine under a progressive ratio (PR) schedule than male rats. The present study extends previous work examining sex differences in the acquisition and maintenance of cocaine self-administration to methamphetamine (METH) self-administration. An automated autoshaping procedure that has previously been shown to be sensitive to detecting sex differences in the acquisition of drug self-administration was used for the acquisition portion of the experiment. Additionally, a PR schedule that has been previously used to detect sex differences in maintenance levels of cocaine and heroin self-administration was used for the maintenance portion of the experiment. Preliminary results indicate that a greater percentage of female rats met the acquisition criteria for METH (0.02 mg/kg) self-administration compared to male rats (50% vs. 14.5%, respectively), and they did so in significantly fewer days compared to males (7.3 ± 1.4 vs. 20.0 ± 6.0 days, respectively). Dose-response curves using BPs obtained under a PR schedule as the response measure indicate that female rats have increased motivation to self-administer low doses of METH (0.01 and 0.02 mg/kg) compared to male rats, as indicated by a vertical shift upward in the dose-response function of female rats at the 0.01 and 0.02 mg/kg doses of METH compared to males. These data suggest that female rats are more vulnerable to the acquisition of METH self-administration compared to male rats. The data also indicate that female rats are more sensitive to the reinforcing effects of low doses of METH, and they have increased motivation to self-administer low doses of METH compared to male rats.
This work was supported by NIDA grants R01 DA03240 (M.E.C.) and F31 DA14161 (M.E.R.).

568 Behavioral naltrexone therapy (BNT): efficacy of a new behavioral treatment for heroin dependence and future directions

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The goal of this ongoing Stage I project has been to develop a behavioral therapy to improve the efficacy of naltrexone maintenance and promote abstinence from heroin. Behavioral Naltrexone Therapy (BNT) is a 6-month therapy approach combining elements of several empirically tested treatments for opiate dependence, including Network Therapy, the Community Reinforcement Approach, voucher-based contingency management, cognitive-behavioral Relapse Prevention Therapy, and Motivational Enhancement techniques. A Stage I pilot trial showed encouraging results in a sample of 47 heroin-dependent outpatients. A Stage II pilot-controlled trial has been conducted, comparing BNT to Compliance Enhancement Therapy (CE), a control condition intended to simulate the standard practice of naltrexone maintenance by a physician in an office or clinic. To date, 73 subjects have entered the controlled trial, with 32 participants randomized to BNT, 31 to CE. The principal outcome measure is retention in treatment. The following analyses were performed on 63 cases; ten participants were de-randomized after failing to complete the inpatient detoxification. Results indicate that at 4 weeks, although not statistically significant, retention is higher in BNT (22/32; 68.7%) than in CE (15/31; 48.4%).

570 Reduced frontal white matter integrity in chronic cocaine users

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Chronic cocaine use is associated with persistent changes in brain metabolism, structure and neurotransmission. Cocaine and its metabolites may adversely affect cerebral white matter (WM). In vivo magnetic resonance studies have identified WM T2 signal hyperintensities and biochemical abnormalities, and functional neuroimaging and neuropsychological studies suggest that cocaine may impair frontal lobe functions dependent on white matter connectivity. Selective frontal lobe reductions in relative cerebral blood flow and brain glucose metabolism levels have also been associated with chronic cocaine use. The goal of the present study was to begin to assess frontal WM microstructure in long-term heavy cocaine users. Diffusion tensor imaging (DTI) was employed to examine the WM integrity of frontal brain regions in four consecutive 5 mm thick slices, e.g. 10, 5, 0, and 5 mm below the anterior commissure-posterior commissure (AC-PC) plane. Repeated measures analyses of variance and follow-up pairwise comparisons were performed to compare the fractional anisotropy (FA) and mean diffusivity (Trace/3) of 12 cocaine dependent patients and 13 age-similar healthy controls. The cocaine dependent patients were found to have significantly reduced FA in the frontal WM at the AC-PC plane and a trend toward reduced FA at 5 mm below the AC-PC plane, suggestive of reduced WM integrity in these regions. There were no significant group or interaction effects for mean diffusivity. In related studies using different patient populations reduced FA in frontal WM correlates with poor performance on tests of executive function. These findings are consistent with hypotheses that cocaine dependence involves alterations in thalamo-orbitofrontal cortical circuitry, which may play a role in the compulsive-repetitive behaviors contributing to maintenance of addictive behaviors.

571 Investigation of gender and treatment modality differences using the TCU Client Evaluation of Self and Treatment (CEST)

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Levels of motivational, psychological, and social functioning at admission to treatment are different for women and men. The TCU Client Evaluation of Self and Treatment (CEST) instrument, which includes 16 scales, was used to assess patient functioning and investigate gender differences. Subjects included 580 patients receiving treatment in outpatient and residential programs. Analysis of variance (ANOVA) was used in a 2 x 2 design (gender by treatment modality) to examine psychological and social functioning, treatment needs, services received, and treatment engagement. Gender differences were found in motivation, treatment engagement, psychological function-
ing, and services. Women had higher levels of motivation, poorer psychological functioning, were more engaged in their treatment, and received more services. Patients in residential treatment had greater motivation, lower psychological functioning, more treatment participation, and utilized more services. Interactions between gender and treatment modality were found in levels of anxiety and hostility, with no gender difference in hostility among outpatients, but significantly higher hostility among males in residential treatment compared with females. Treatment services also showed an interaction with women receiving more services in outpatient, but no gender differences in residential. Treatment implications include the need to assess patient functioning in order to adequately plan and adjust treatment regimens based on gender differences.

572 **DIFFERENTIAL PREDICTORS OF SUBSTANCE USE AMONG CLINICALLY REFERRED COMORBID YOUTH**

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Comorbidity of substance abuse and psychiatric disorders is regarded as one of the most important focal areas in the ‘new generation’ of drug abuse treatment research (Leshner, 1997). Although comorbidity has received significant attention in the adult substance abuse field, only recently have researchers begun to uncover important variations in adolescent substance abuse patterns in relation to psychiatric comorbidity. Specifically, researchers have suggested that the factors influencing substance use may vary in important ways for adolescent substance abusers with different comorbid conditions. A large body of research has established that the most significant predictors of adolescent substance use generally are family and peer factors, including poor parental monitoring and discipline practices, family conflict, parental substance use and psychopathology, and peer deviance. Yet little is known about the specificity of risk factors for substance use among different comorbid groups. Hypothesis: The investigators hypothesized that substance abusing teens with externalizing disorders only, compared to those with both internalizing and externalizing disorders, would evidence different predictors of substance use. Procedure: Data were collected from 120 youth and families upon intake to treatment as part of a clinical trial comparing family-based and residential substance abuse treatment for dually diagnosed youth. Comprehensive data on youth internalizing and externalizing symptoms, peer deviance, and family problems were collected from adolescents and their parents. Sample: The sample included mainly minority youth, all of whom were referred for residential treatment and met DSM-IV criteria for a comorbid psychiatric disorder as well as substance abuse or dependence. Analyses: Structural equation modeling was used to examine differential predictors of substance abuse among clinically referred adolescents with different types of comorbid disorders. The results of the study inform the design of effective treatment approaches for adolescent substance abusers with different comorbid problems by identifying critical targets of intervention.

573 **ROLE OF GABA-A/ALPHA-1 RECEPTORS IN THE HIGH-DOSE DISCRIMINATIVE STIMULUS EFFECTS OF ZOLPIDEM**


The discriminative stimulus (DS) effects of high doses of zolpidem differ from those of conventional benzodiazepines (BZs), but the extent to which these effects reflect the selectivity of zolpidem for GABA-A/alpha-1 receptors is not known. The present study investigated the ability of GABA-A/alpha-1-prefering agonists to substitute for a high training dose of zolpidem and the ability of GABA-A/alpha-1-prefering antagonists to block zolpidem’s DS effects. Squirrel monkeys were trained to discriminate intravenous injections of zolpidem (3.0 or 5.6 mg/kg) from saline and tested with BZ agonists differing in selectivity and efficacy at GABA-A/alpha-1 receptors. Antagonism of the DS effects of zolpidem was studied using the GABA-A/alpha-1-prefering antagonists beta-carboline-3-carboxylate-t-butyl ester (BCCT) and 3-propyloxy-beta-carboline (3-PBC). Zolpidem and quazepam (GABA-A/alpha-1-prefering agonist) engendered full substitution for the high training dose of zolpidem, whereas CL 218,872 (GABA-A/alpha-1-prefering partial agonist) and the non-selective BZ agonists alprazolam and flunitrazepam engendered low and variable levels of zolpidem-lever responding. Both BCCT and 3-PBC antagonized the DS effects of the high dose of zolpidem in a surmountable fashion, with in vivo apparent pA2 values consistent with the affinities of the antagonists at GABA-A/alpha-1 receptors. Our findings provide evidence for a key role of GABA-A/alpha-1 receptors in the DS effects of zolpidem at a high training dose and suggest that high selectivity and efficacy at GABA-A/alpha-1 receptors is required for BZ agonists to reproduce these DS effects. (Supported by DA11792, DA13591, RR00168, and MH46851).

574 **CEREBRAL METABOLISM IN COMORBID COCAINE Dependence and depression**

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Depression occurs with increased incidence among cocaine-dependent individuals. We are using FDG-PET in cocaine dependence (CD), major depressive disorder (MDD) and in the comorbid condition (CD+MDD) to assess neurobiological relationships among these disorders. Prior studies have shown decreased global cerebral metabolic rate for glucose (CMRglc) in both MDD and CD. We hypothesized that individuals with CD+MDD would show a global deficit greater than that in either disorder separately. Volunteers with CD-only (n = 6, no other drug dependence beyond nicotine), MDD-only (n = 3, all unipolar) and CD+MDD (n = 3, criteria as for the single disorders) were imaged medication-free. Those with CD and CD+MDD had abstinence monitored for 72 hrs as inpatients prior to PET, with stable interim mood ratings. Images were quantified by the Sokoloff autoradiographic method applied to whole-brain gray matter (GM) pixels. Mean GM CMRglc (±SD; mg/min/100gm) for CD was 7.12±0.44, for MDD, 8.26±0.87 and for CD+MDD, 6.44±0.35. CMRglc did not differ between CD and MDD (P = 0.12). One-tailed t-tests based on our hypothesis showed that CMRglc for CD+MDD was lower than for either CD (P < 0.03) or for MDD (P < 0.02). These preliminary results suggest that CD and MDD contribute additively to the global CMR deficit in CD+MDD. With larger samples, we will assess such additivity for specific brain regions involved in the two disorders.

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575 **DISCRIMINATIVE-STIMULUS EFFECTS OF SIBUTRAMINE IN COCAINE-TRAINED HUMANS**

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Sibutramine is a novel stimulant that is approved for the treatment of obesity. In vitro and in vivo neuropharmacological data suggest that the mechanism of action of sibutramine is distinct from that of prototypical abused stimulants like cocaine. The metabolites of sibutramine, which are thought to be responsible for its pharmacological actions, are potent serotonin and norepinephrine uptake blockers and inhibit dopamine uptake only at high doses. Our laboratory has conducted several experiments aimed at elucidating the behavioral neuropharmacological mechanisms of action of commonly abused stimulants in humans. In the present experiment, five human volunteers with recent histories of cocaine use learned to discriminate 150-mg oral cocaine HCL. After meeting a predetermined discrimination criteria (i.e., ≥80% correct responding on 4 consecutive days), a range of doses of oral cocaine (50, 100, and 150 mg), sibutramine (25, 50, and 75 mg), methylphenidate (30, 60, and 90 mg) and placebo were tested to determine if they shared discriminative-stimulus and subject-rated effects with 150-mg cocaine. Methylphenidate was included as a positive. All doses of cocaine and the highest dose of methylphenidate, but none of the doses of sibutramine, increased drug-appropriate responding significantly above placebo levels. Cocaine, methylphenidate, and sibutramine produced qualitatively and quantitatively similar cardiovascular effects (e.g. increased heart rate and blood pressure). The results of this study are consistent with in vitro and in vivo behavioral neuropharmacological data, and suggest that the behavioral effects of cocaine in humans are mediated by central dopamine systems.

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576 GENDER DIFFERENCES IN PLACE PREFERENCE FOR COCAINE AND HPA ACTIVITY IN RATS

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Although sex differences in the behavioral and neurochemical response to cocaine have been reported, it is not clear whether these differences exist in cocaine reward. To determine the role of sex in the development of conditioned place preference (CPP), intact male and female rats were conditioned with cocaine (10 mg/kg) and saline on alternating days for 4 or 8 days. Female rats demonstrated CPP after 4 days, which was extinguished following 8 days of conditioning. On the other hand, male rats developed a significant place preference following 8 days of conditioning only. Though, females had higher blood plasma levels of CORT, no effects of conditioning were observed for either sex. A second cohort was conditioned with saline, 5, 10, or 20 mg/kg of cocaine for 4 days. Female rats developed CPP at lower cocaine doses (5–10 mg/kg), while males required higher doses (20 mg/kg of cocaine). Saline/saline pairings did not produce a significant preference in any of the conditions. A dose-dependent induction of HPA activity was observed in female rats, where plasma CORT levels were significantly higher in rats given 20 than 5 mg/kg of cocaine. Collectively, these results suggest that females are more sensitive to the rewarding effects of cocaine, which may be influenced by increased HPA activity.

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577 FAMILY STUDIES OF SUBSTANCE DEPENDENCE AND ANTISOCIAL PERSONALITY DISORDER: A POTENTIAL SELECTION BIAS?


Substance use disorders (SD) and antisocial personality disorder (ASPD) cluster within families and well-designed family studies are needed to further investigate this phenomenon. Hypothesis: Studies requiring interviews of multiple family members may select for the healthiest families regarding SD and ASPD. Methods: We attempted to interview both parents of 418 adolescent patients in treatment for substance and behavior problems and both parents of 285 adolescent controls. Results: We successfully interviewed both parents in 36% of patient families and 72% of control families, mothers only in 56% and 21% respectively, and fathers only in 7% and 6%, respectively (χ² = 92.23; P < 0.001). About 24 mothers of adolescent patients met criteria for ASPD; in these 24 patient families, only 1 father was interviewed. In patient families where the mother did not have ASPD, it was 9.83 times more likely that both parents were interviewed, when compared to patient families where the mother did have ASPD. In patient families with mothers without SD, direct interviews of both parents were 1.18 times more likely, when compared with patient families with mothers with SD. Conclusions: In patient families with mothers with ASPD, few fathers were directly interviewed, suggesting that complete data on families with severe pathology is more difficult to obtain. Family history data collected from multiple informants may provide a correction to the bias of direct interviews. Additional analyses will be presented exploring the validity of family history data.

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578 CLINICAL PREDICTORS OF CHANGE IN TOBACCO USE AMONG BIPOLAR ALCOHOLICS

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Tobacco use is a significant problem in psychiatric population, especially those with severe comorbid psychiatric disorders and co-occurring alcohol use disorders. The aim of this study is to examine clinical predictors of change in tobacco use among bipolar alcoholics. About 43 patients with DSM-IV/SCID comorbid diagnoses of bipolar I disorder and alcohol dependence were prospectively examined over a 6-month period. Patients were assessed using the SCID-IV, the Hamilton Rating Scale for Depression-17, the Bech-Rafaelsen Mania Scale, the Addiction Severity Index, a 4-item self-report craving scale for alcohol, and tobacco use. Follow-up assessments were performed every 2 weeks for up to 24 weeks. The Mixed Model with restricted maximum likelihood procedure and unrestricted covariance matrix was used. We examined whether the severity of depressive symptoms, manic symptoms, craving, current alcohol use at each assessment, and age of onset of alcohol use predict change in tobacco use. The results of this study showed that depressive symptoms (t = -1.97, P = .05), craving measure (t = -2.14, P = 0.03), and alcohol use age of onset (t = -2.07, P = 0.03) predicted change in tobacco use over the study period. The results of this study suggest that depressive, not manic symptoms, along with craving, and early age of onset of alcohol use predict change in tobacco use. These findings may aid in implementing focused clinical interventions to address tobacco use among this population.

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579  SELF-REPORTED REASONS NOT TO INJECT AMONG HEROIN SNUFFERS: A FACTOR ANALYSIS

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Background: Preventing non-injection drug users from transitioning to injection is one of the most efficient ways for the containment of the AIDS epidemic because new injection drug users extend the risk of HIV-1 infection for themselves and their sexual partners. Therefore, a better understanding of non-injection drug users at high risk of injection and their reasons not to inject constitute a crucial component of any intervention aimed at preventing transition to injection and HIV-related high risk behaviors. Methods: As part of a structured interview, 300 heroin sniffers who had never injected a drug were given a list of 18 reasons for not initiating injection such as 'pressure from friends not to inject', 'fear of getting arrested,' and 'concerned about HIV/AIDS.' Each interviewee was asked to rank the importance of the reason on a five-point scale ranging from 'very important' to 'very unimportant'. Data on self-reported reasons not to inject provided by these heroin sniffers were employed to conduct a factor analysis using the promax rotation method as to determine underlying variables and identify the most parsimonious structure. Results: Two underlying factors were revealed which accounted for 66% of the variance among the original 18 variables. Factor 1 represents a psychosocial dimension which reflects social and mental constructs including negative attitudes of family and friends toward injection and fear of social consequences such as arrest and incarceration. Factor 2 represents a physical dimension including fear of HIV/AIDS, fear of other injection related diseases and fear of disfigurement. Conclusions: HIV Intervention programs that deal with non injecting drug users need to stress the psychosocial and physical consequences of injection drug use to deter initiation of injection.

580  SEXUAL DYSFUNCTION AMONG ADDICTED WOMEN WITH PRIOR SEXUAL ASSAULT

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Sexual assault triggers post traumatic stress disorder in women more often than any other traumatic event. Lifetime rates of sexual assault for women in treatment for substance use disorders vary from 20% to 70% (a wide range due to differences in measures). The characteristics of this population appear to include a higher incidence of depression, anxiety, suicidality, drug use disorders, severe alcohol problems; as well as an earlier onset of alcohol and other drug use. According to a small but growing body of research these women also frequently suffer from sexual dysfunction, leading a few investigators to suggest that self-medication of this condition may lead to substance use disorders. Building on these previous findings, this study involved examining the relationship between sexual dysfunction and sexual assault in a sample of 71 female patients receiving treatment for substance use disorders. Clinicians administered a multidimensional battery of tests at baseline and at 6 and 12 month follow-up intervals. Results from baseline data indicated that 34% of the women reported at least one previous sexual assault. These women scored significantly higher than non-assaulted women for sexual dysfunction overall on the Golombok Rust Inventory of Sexual Satisfaction, a discrepancy accounted for by high scores among assaulted women on the Avoidance and non-sensuality subscales. Sexual inhibition and a history of sexual assault each predicted the use of substances to increase sexual desire. The interaction between sexual inhibition and a history of sexual assault accounted for 2.6% of the variance in using substances to increase sexual desire, but the magnitude of this relationship did not reach levels of significance. These findings suggest that sexually abused women may follow a different course into substance-related problems than do non-abused women, possibly including self-medication to relieve sexual inhibition. Such patients may benefit from interventions tailored to their specific characteristics and needs, including the treatment of sexual inhibition. In addition, prevention efforts might focus on assessing and alleviating sexual dysfunction among survivors of sexual assault before the initiation of self-medication can occur.

581  PRIVILEGED ACCESS INTERVIEWING TO CHARACTERIZE COCAINE BASE PASTE (CBP) USERS

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Privileged Access Interviewing is one of the methods to study hidden populations. In Chile most CBP users do not reach our Health Care System. Objective: to characterize a sample of CBP users that have not received any substance abuse treatment recently. Methods: We designed a structured interview that covers socio-demographic information, patterns of substance use, risk behaviors, social functioning and Health Care System perceptions. We recruited and trained 9 interviewers who had access to CBP users. Privileged access interviews were conducted in two districts of Santiago with highly prevalent substance use. The inclusion criteria were: (1) at least 1 year of regular CBP use; (2) at least 10 CBP uses in the past year and (3) no substance abuse treatment in the past 12 months. Results: About 49 subjects were recruited (in progress). Gender distribution is 10 women (20.4%) and 39 men (79.6%). The mean age of the sample is 23 years (S.D. = 9.1). Forty two subjects were single (85.7%) and 35 were unemployed (71.4%). CBP was the primary substance in 39 subjects (79.5%) with a mean number of days of use in the previous 30 days of 22.4 (S.D. = 8.7). The mean amount consumed was 12.1 gr/day (S.D. = 14.6). The mean age of onset of CBP use was 16.8 years (S.D. = 5). The mean Severity of Dependence Scale score was 7 points (S.D. = 3). Thirty one subjects (63.2%) declared they were willing to receive treatment. Conclusion: these results, from the first Chilean Hidden Population Study, allow us to know the patterns of substance use of CBP users and their psychosocial needs.

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582  A VACCINE FOR NICOTINE DEPENDENCE: A TIME-COURSE STUDY OF NICOTINE TISSUE DISTRIBUTION IN VACCINATED RATS

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A nicotine vaccine has been developed which elicits nicotine-specific antibodies in rats which bind nicotine, reduce nicotine distribution to the brain, and decrease a variety of its centrally mediated effects. Vaccination reduces nicotine distribution to the brain even at nicotine doses greatly exceeding the antibody's binding capacity, suggesting a selective effect on nicotine distribution to the brain. The purpose of this study was to examine the effects of vaccination on nicotine distribution to brain and other tissues following a single nicotine dose. 60 male Sprague Dawley rats were vaccinated with either nicotine vaccine or carrier protein alone and nicotine (0.1 mg/kg) was infused via the jugular vein over 10s. Tissues were obtained at 1, 5, or 25 m. Nicotine levels in tissues were corrected for nicotine content due to residual blood in tissue. Vaccination significantly reduced nicotine distribution to the brain, with reductions of 64% at 1 min and 45% at 25 min. The effect of vaccination on nicotine distribution to tissues was not uniform. Some tissues showed reductions in vaccinated animals similar to those observed in brain, but of lesser extent (muscle 30%, testes 36%, and kidney 27% at 1 m). In each of these tissues, reductions were greatest at the earlier time points. Fat showed the opposite effect.
with increased nicotine concentrations in the vaccinated animals (increase of 32% at 1 min and 90% at 25 min). Lung and heart had a mixed pattern with initial reductions in nicotine concentrations in vaccinated animals followed by increases. Chronically infused nicotine (1.0 mg/kg per day) showed similar patterns of tissue distribution, but of lesser magnitude. These differences may in part explain the ability of modest amounts of antibody to reduce the distribution of large doses of nicotine to brain.

583 COMPARISON OF RAPID OPIATE DETOXIFICATION AND NALTREXONE WITH METHADONE MAINTENANCE IN THE TREATMENT OF OPIATE DEPENDENCE: A RANDOMIZED CONTROLLED TRIAL

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Despite the claims and counterclaims for the benefits of naltrexone treatment and agonist maintenance, there has not been a controlled trial that has directly compared these treatments with patients randomly assigned to one or other condition. We report the findings from two such trials. In the first trial, 79 heroin dependent individuals who were not currently in treatment were randomly assigned into one of three groups (1) rapid opiate detoxification under anaesthesia followed by naltrexone tablet treatment for 1 year, (2) rapid detoxification under sedation followed by naltrexone, and (3) advice to commence methadone maintenance. The second trial comprised 80 persons with a similar history but who had been on methadone maintenance for at least 1 year. They were randomly assigned to rapid detoxification under anaesthesia or continuation on methadone. Overall, 92% of those admitted for rapid detoxification completed it successfully and started on naltrexone. Of heroin users undergoing anaesthetized and sedated detoxification, 72 and 60% respectively were on naltrexone and were opiate-free 10 days later. In those who remained on naltrexone at 3 months, opiate use was suppressed by > 90% and more achieved total abstinence from heroin than those on methadone. However, only 40% of those assigned to naltrexone were on treatment at this time. Among those initially on methadone maintenance who underwent rapid detoxification, 74% were engaged in treatment at 10 days. Opiate use was suppressed by > 95% on naltrexone and 54% were in treatment at 3 months. In both trials the amount of clinical care and the effort required to support patients in naltrexone treatment was considerable. Rapid opiate detoxification is an effective way of ensuring detoxification from opiates and inducting patients on to naltrexone. Treatment with naltrexone suppresses heroin use effectively but it requires considerable commitment by patients and their carers. Rapid opiate detoxification and naltrexone treatment is a more satisfactory treatment for those who have been stabilized on methadone rather than as a primary treatment for active heroin users.

584 CENTER OF EXCELLENCE IN SUBSTANCE ABUSE TREATMENT AND EDUCATION AT VA PUGET SOUND HEALTH CARE SYSTEM AND UNIVERSITY OF WASHINGTON, SEATTLE, WA

A.J. Saxon, K.L. Sloan, P. Nichol, D.N. Howell, K.N. Bush, D.A. Calsyn, J.S. Baer, B.L. Felker, D.R. Kivlahan, Substance-Dependent Individuals Often Lack Awareness of Their Medical Conditions

Individuals with substance use disorders (SUDs) often have comorbid medical conditions. SUD treatment with simultaneous, routine medical care appears to decrease rates of hospitalizations for illicit drug users. Barriers to such patients obtaining routine medical care include poor understanding on their part of the seriousness of their medical problems and poor motivation to seek care. This investigation documents health conditions self-reported by individuals entering SUD treatment, to determine if these self-reported conditions influence primary care attendance, and compares the self-reported conditions to blood pressure and laboratory screening. This study was conducted as part of a clinical trial comparing integrated vs. referral models of primary care for veterans entering specialty SUD treatment. Subjects (n = 269) who reported having a chronic medical condition or screened positive for an asymptomatic condition were included. Self-reported conditions were tabulated, categorized, and compared to screening results. No self-reported health conditions were endorsed by 8 (3.0%) subjects, while 42 (15.7%) reported 1, 51 (19.0%) reported 2, 61 (22.8%) reported 3, and 106 (39.4) reported 4 or more. The number of self-reported health conditions did not influence the likelihood of patient attendance at a primary care appointment (Age adjusted OR: 1.01 95% CI.56-1.83, P = 0.97). Among 210 subjects (78.1%) who reported no history of hypertension, 83 (39.5%) had elevated blood pressure levels on screening sphygmanometry. Among 263 subjects (97.8%) who did not report a history of elevated cholesterol, 69 (26.2%) had non-fasting cholesterol levels > 200 mg/dl. Among 185 subjects (68.8%) who reported no history of hepatitis B or C, 40 (21.6%) had elevated ALT levels. Thus, no apparent relationship was found between self-perceived health burden and attendance at a primary care visit. Many SUD patients remain unaware of potentially serious, treatable asymptomatic conditions that they have incurred.

585 ‘WHO GETS IN?:’ RECRUITMENT AND SCREENING PROCESSES OF OUTPATIENT SUBSTANCE ABUSE TRIALS

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A brief telephone-screening interview was conducted with 1759 callers seeking treatment for substance abuse at the Treatment Research Clinic over a 16-month period. The purpose of this study was to examine the effectiveness of various recruitment methods in attracting eligible participants and to identify screening variables that characterized eligible and ineligible callers. Callers who were referred by friends and family were more likely to be eligible than callers from other referral sources. Callers seeking treatment for cocaine abuse reporting more severe alcohol/substance problems were more likely to be eligible for treatment protocols, while those with severe problems in other psychosocial areas (legal, medical, psychiatric) were more often excluded. Alcohol and nicotine dependent callers reporting more severe alcohol problems were more likely to be eligible, but otherwise were not different from callers who were ineligible. The effectiveness of recruitment methods is not the same for different types of substance abuse treatment programs. For cocaine, referrals from friends and family were more effective than other more costly recruitment methods. Finally, this study underscores the importance of having a sensitive screening assessment for recruiting a homogeneous yet representative sample for outpatient substance abuse clinical trials.

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586 PSYCHOSOCIAL CORRELATES OF PREGNANT WOMEN WITH AND WITHOUT PHYSIOLOGICAL SYMPTOMS OF COCAINE DEPENDENCE

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Debate continues over clinical and research utility of DSM-IV diagnostic criteria for substance dependence. In particular, the utility of distinguishing between dependence with and without physiological...
symptoms of tolerance and withdrawal remains controversial. For pregnant drug dependent women, physiological as compared to psychological symptoms of dependence may be related to maternal and fetal/infant outcomes. The present study compared demographic and psychosocial measures in pregnant drug dependent women with and without physiological symptoms of cocaine dependence. Participants were 136 pregnant drug dependent women admitted for treatment to a comprehensive program in East Baltimore. \( \chi^2 \) and \( t \)-tests were used to identify psychosocial measures that differed for women with both tolerance and withdrawal related to cocaine use \( (N = 43) \) as compared to women with no symptoms of physiological cocaine dependence \( (N = 93) \). As expected, participants with physiological symptoms of cocaine dependence reported higher frequencies of recent cocaine use \( (M = 21.45 \text{ days}; \ S.D. = 11.17) \) and more months of regular cocaine use \( (M = 30.17 \text{ vs. } M = 53.70 \text{ months}, \ P < 0.01) \). Interestingly, participants with physiological symptoms of cocaine dependence \( (M = 4.65, \ S.D. = 7.75) \) reported higher frequencies of recent alcohol use than those without \( (M = 1.51, \ S.D. = 4.27, \ P < 0.05) \) and were more likely to have a non-substance induced DSM-IV Axis I psychiatric disorder. Logistic regression identified two significant predictors of physiological symptoms of cocaine dependence, including the number of days of cocaine use in the past month and any lifetime DSM-IV Axis I psychiatric diagnosis. Women with a diagnosis were a more likely to experience physiological symptoms of cocaine dependence than those without a diagnosis \( (\text{Odds ratio} = 0.23) \). Study findings suggest recent heavy cocaine use and a psychiatric history are present in pregnant women with physiological symptoms of cocaine dependence. The nature of this relationship warrants further exploration and is likely to have important implications for treatment of this high risk group of women and their children.

587 Evaluation of the antinociceptive properties of 11-OH-D8-tetrahydrocannabinol-dimethylheptyl (HU-210)

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The effect of the potent exocannabinoid agonist HU-210 was investigated for antinociceptive, antihyperalgesic, and antiallodynic efficacy in the male Sprague-Dawley rat. Antinociception (i.e. analgesia) induction via intrathecally-administered (IT) HU-210 was assessed by the D’Amour and Smith (1941) tail-flick test. Thermal plantar hyperalgesia and tactile allodynia were determined by an Ugo Basile 7370 analgesia meter and a calibrated set of von Frey filaments, respectively. Whereas 20 ul IT saline or vehicle (DMSO) administration did not incur significant analgesic effects, a 10 ug IT HU-210 administration induced analgesia at 120 min in the tail-flick paradigm and a significant increase in paw-withdrawal latency at 1, 5 and 10 ug IT. Following induction of a 1\% type-IV lambda intraplantar carrageenan-induced hyperalgesia, HU-210 significantly reversed both hyperalgesia and allodynia at 5 ug IT. A complete blockade of each HU-210 analgesic paradigm was effected by a 1h preadministration of the CB1 antagonist SR141716A (SR; 1 mg/kg IP), constituting suggestive evidence that HU210, as a CB1-specific agonist, is capable of producing a significant antinociception in a mammalian model of chronic pain and, therefore, indicates further evidence as to the efficacy of synthetic cannabinoids in attenuating human pain states.

588 Dopaminergic mechanisms of MDMA (‘ecstasy’) self-administration in rats

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The pattern of use of 3,4-methylenedioxymethamphetamine (MDMA; ‘ecstasy’) is often characterized as intermittent and, until recently, it’s use has been restricted primarily to members of the dance club scene. There have been few documented reports of uncontrolled or excessive use, lending support to the widely held view that potential for abuse of MDMA is low. Whereas virtually all drugs that are abused by humans are self-administered by laboratory animals, only three published reports (two using non-human primate subjects and 1 using rat subjects) have documented MDMA self-administration in animals. In those studies, a low level of responding was produced in subjects with a history of self-administration of other drugs. We found that the racemic mixture of MDMA was self-administered by laboratory rats that were experienced with self-administration of amphetamine as well rats that were drug naive. Self-administration \( (0.25–2.0 \text{ mg/kg infusion}) \) was dose-dependent, extinguished when saline was substituted for MDMA and was reinstated when MDMA was reintroduced. Maximal response rates were comparable to or exceeded rates maintained by amphetamine \( (0.08 \text{ mg/kg per infusion}) \). Prior administration of the dopamine D-1 antagonist, SCH 23390 \( (0.005–0.02 \text{ mg/kg, SC}) \) decreased responding maintained by MDMA \( (0.5 \text{ mg/kg per infusion}) \). These results indicate that MDMA has abuse liability that compares favourably to amphetamine, and is dependent on dopaminergic mechanisms.

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589 Effects of SCH 23390 on acquisition and expression of conditioned suppression with cocaine as the unconditioned stimulus

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Most studies of the classically conditioned effects of abused drugs involve diffuse stimuli, such as the environment where a drug is given. Less effort has been directed at studying drug conditioning with discrete stimuli. We have previously used the conditioned suppression procedure to study conditioning with cocaine to discrete stimuli. The purpose of the current study was to determine the involvement of the dopamine D1 receptor system in that conditioned effect. Rats were trained to nose-poke on a food-reinforcement schedule. A 70-s tone-light compound stimulus was then presented approximately 30 min into the session. 1 min after the onset of the stimulus, cocaine \( (3.0 \text{ mg/kg, i.p.}) \) was administered. For three groups of rats, SCH 23390 \( (0.003–0.03 \text{ mg/kg, i.p.}) \) was given prior to each of 8 training sessions. For a fourth group of rats, no drug was given prior to the training sessions, however, animals were given saline or SCH 23390 at the same doses prior to each of four test sessions following training. Each test session was separated by two additional training sessions. During the test sessions, cocaine was not administered. Rats not given drug during training developed conditioned suppression, as evidenced by a reduction in responding during the tone-light stimulus. Preliminary data suggest that SCH 23 390 did not affect either the development of suppression when given prior to training sessions or the expression of suppression when given prior to testing. These results suggest that dopamine D1 receptors are not involved in this conditioned response to discrete stimuli.

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590 Effects of chronic 'binge' pattern cocaine administration on dopamine D1 receptor binding in C57Bl/6J and 129Sv mice

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Mice of the C57BL/6 (C57) and 129/J (129) strains differ in their behavioral response to 3 and 14 days of 'binge' pattern cocaine administration (Schlussman et al., Pharmacol. Biochem. Behav. 1998, NIDA Res. Monogr 180 1999). Over 14-day 'binge' pattern cocaine exposure, C57 mice develop tolerance to cocaine's locomotor stimulating effects, while 129 mice show no locomotor activating effects. Earlier, Unterwald et al. found that Fischer rats, with the same cocaine administration and experimental conditions, showed behavioral sensitization, and suggested that the development of sensitization was correlated with dopamine D1 receptor (D1R) density in the nucleus accumbens (NAc: Unterwald et al., JPET 1994). To test this hypothesis, we used quantitative receptor autoradiography to examine D1R density in the same C57 and 129 mice studied for behavioral response to chronic (14-day) 'binge' cocaine. Results: In the rostral pole of the NAc, the binding density of the D1R was greater in C57 mice than in 129 mice, although this just missed significance (P = 0.051) and no effect of cocaine was observed. In the ventral shell of the NAc, the D1R binding density was increased in C57 mice which received cocaine compared to drug naive littersmates (P = 0.0509). In the rostral dorsolateral striatum, the binding density of the D1R was significantly greater in 129 mice than in C57 mice (P < 0.005), but no drug effect was observed. Regression analysis showed no correlation between locomotor activity and D1R density in any region of the NAc. These data demonstrate the presence of subtle strain differences in NAc D1R density and, with the possible exception of the ventral shell in C57 mice, that chronic 'binge' cocaine does not affect NAc D1R density in either strain. These data are consistent with the hypothesis that upregulation of NAc D1R correlates with the sensitization of cocaine-induced locomotor activity, and not with the expression of cocaine-induced hyperlocomotion per se.

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591 OPIOID MAINTENANCE AND NEUROPSYCHOLOGIC PERFORMANCE

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Heroin use has been associated with neuroadaptive changes on molecular level and manifold neurological sequelae. Furthermore, neuronal injuries have been found in heroin users by neuroimaging and post-mortem examinations. Neuropsychological deficits in opioid users have also been reported. However, the evidence is somewhat less conclusive, and the effect of heroin maintenance on neuropsychological functions has not been investigated yet. To address the hypothesis that intravenous (IV) heroin maintenance, embedded in a comprehensive treatment program, may have an impact on cognitive functioning this study firstly aims at examining the neuropsychological function of 30 opioid-dependent subjects on admission to IV heroin maintenance treatment (baseline). Secondly, the study seeks to assess whether the neuro-psychological test performance will remain stable, improve or worsen after an initial period of 3 month on heroin maintenance treatment as compared to baseline assessment. We are presently comparing the test results with the test performance of an age- and sex-matched control group consisting of 30 opioid-dependent patients being on oral methadone maintenance. Preliminary results of 24 baseline examinations revealed visual and, less pronounced, verbal memory deficits among heroin-dependent patients entering opioid maintenance treatment. Moreover, cognitive flexibility was impaired in three out of four measures suggesting a functional impairment of the prefrontal cortex. Hitherto, follow-up tests of five heroin and three methadone patients showed improvements in figural memory and figural fluency, but deterioration in verbal fluency.
testing the efficacy of NTX at doses higher doses (> 50 mg/d) in this comorbid population.

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594 Behavioral Treatment for Cocaine-Dependent Women

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Aims: To compare the efficacy of Community Reinforcement Approach (CRA) and 12-Step Facilitation (TSF) counseling and of voucher based reward therapy (VBRT) and a yoked, non-contingent voucher control (VC) for the treatment of cocaine dependent pregnant women or women with young children. Methods: Subjects (N = 145) were randomly assigned to 1 of 4 treatment groups (CRA + VBRT, CRA + VC, TSF + VBRT, TSF + VC). VBRT voucher value increased for each successive cocaine-free urine sample obtained twice weekly during the 1st 12 weeks and was faded from the final earned value to $5 during the last 12 weeks (max. value $880). All subjects earned vouchers for attendance at scheduled twice weekly counseling sessions (max. value $120). Manual-guided CRA and TSF were provided by experienced clinicians who received extensive training in either CRA or TSF and weekly supervision. Results: The 4 groups were comparable on most baseline characteristics: 91.7% not working; 90.3% not living with a partner; 42.8% less than HS education; 43.3% pregnant at enrollment; 77.9% black; mean age 31.1 (5.6) years; 46.9% met SCID with a partner; 42.8% less than HS education; 43.3% pregnant at most baseline characteristics: 91.7% not working; 90.3% not living with a partner; 42.8% less than HS education; 43.3% pregnant at enrollment; 77.9% black; mean age 31.1 (5.6) years; 46.9% met SCID with a partner; 42.8% less than HS education; 43.3% pregnant at

596 Changes in Cocaine Use and Cocaine Craving Among Outpatients Receiving Cognitive Behavioral Therapy for Cocaine Dependence

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The relevance of craving to drug use during drug treatment remains unproven, due to difficulties in measuring craving and to the small number of studies designed to rigorously assess this relationship. In order to further evaluate the ability of craving to predict drug treatment outcome, a 12-week study of cognitive behavioral interpersonal therapy for cocaine dependence was conducted in 85 outpatients, in which craving for cocaine and other drugs was measured prospectively once per week using several instruments, and use of illicit drugs was verified by urine toxicology. Instruments used to measure drug craving included visual analog scales as well as a 45-item multidimensional cocaine craving questionnaire (Tiffany, et al., Drug and Alcohol Dependence 34 (1993) 19–28). Repeated-measures, within-subject statistical analysis using generalized linear mixed regression modeling was used to evaluate trends in drug use and drug craving over time, as well as the ability of craving to predict drug use. Patients enrolled in this study were cocaine-dependent, 64% African-American and 27% female. Approximately one third (28/85, 33%) completed all twelve weeks of the counseling program. Among patients who completed the program, there were significant decreases in both cocaine use (t = -4.55, P < 0.0001) and cocaine craving (t = -6.98, P < 0.0001) during the twelve-week course of therapy. During treatment, higher craving scores were significantly associated with current cocaine use (t = 3.68, P = 0.0003) as well as with cocaine use 1 week later (t = 2.51, P = 0.013). However, cocaine craving was not an independent predictor of subsequent cocaine use after controlling for current cocaine use. The implications of this study’s findings both for improving the measurement of craving and for addressing craving in treatment for cocaine dependence will be discussed.

597 Changes in Opioid Receptor-Stimulated G-Protein Activation and Inhibitory G-Protein mRNA Expression Following Cocaine Administration

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Cognitive behavioral relapse prevention is an important treatment modality for substance dependence. The primary goal of this treatment is to help drug dependent individuals develop new behavioral responses to cues associated with drug use. However, relapse rates remain high, suggesting drug dependent individuals have difficulty implementing the skills presented in this treatment modality. Thus, developing a procedure to assess the effect of drug cues on their behavioral response within the context of an outpatient treatment program may help identify individuals at greater risk of relapse. We developed a computerized Drug Stroop task, based on the Classic Stroop, to assess the effect of cocaine, heroin, marijuana, and neutral cues on a color-naming task administered to drug dependent patients. We present the results of two sets of analyses testing the discriminant validity of the drug stimuli presented on the Drug Stroop test. First, 67 individuals (31 cocaine dependent, 20 heroin dependent, and 16 marijuana dependent) rated the valence of the words used for each drugstimuli class. Preliminary data suggests that valence ratings are greater for word groups associated with participants’ drug of choice compared to other drug word groups. Second, to date, 25 participants (six African American, seven Hispanic, nine Caucasian, and three ‘other’) have completed the Stroop assessment prior to entering a drug treatment program. It is hypothesized that drug dependent participants will demonstrate greater mean reaction times and more errors on drug-related words than neutral words, and that participants will demonstrate greater mean reaction times and more errors on the words related to their drug of choice as compared to words related to other drugs. The findings may have implications for identifying those who are at greatest relapse risk, or may benefit less from cognitive-behavioral techniques.
Chronic cocaine administration produces alterations in mu and kappa opioid receptor density as well as striatal and accumens opioid regulated adenyl cyclase activity suggesting a psychostimulant responsive interaction between opioidergic and dopaminergic systems. Opioid receptors are coupled to G-proteins which inhibit adenyl cyclase production of cyclic AMP. The present study employed in situ [35S]GTP\(_\gamma\)S binding to measure opioid receptor stimulated activation of G-proteins and [35S]labeled G-protein mRNA expression in rats following acute and chronic binge pattern cocaine administration. Male Fischer rats were given three daily cocaine injections (15 mg/kg i.p.) spaced 1 h apart for 1, 3 or 14 days. DAMGO stimulation of mu opioid receptors resulted in increases in [35S]GTP\(_\gamma\)S binding in both the core and shell of the nucleus accumens, all regions of the caudate/putamen and the cingulate cortex in cocaine treated animals versus saline matched controls. The greatest increases in DAMGO-stimulated [35S]GTP\(_\gamma\)S binding were observed in the dorsal areas of the caudate/putamen in animals that received 14 days of cocaine. In situ hybridization revealed significant increases in Gialpha1 subunit gene expression in the dorsal caudate/putamen and cingulate cortex in response to 3 days but not 1 or 14 days of cocaine injections. An evaluation of delta and kappa opioid receptor stimulated [35S]GTP\(_\gamma\)S binding and Go alpha subunit gene expression in these animals is ongoing. In summary, alterations in brain levels of dopamine produced by binge pattern cocaine administration can induce changes in both mu opioid receptor-mediated G-protein activity and the gene expression of G-protein alpha subunits associated with opioid receptors. These results provide support for the hypothesis that the addictive properties of both psychostimulants and opiates may share common neurochemical signaling substrates.

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598 VALIDITY OF SELF-REPORT AND SCHEDULED URINALYSIS OF COCAINE USE AMONG HOMELESS IN TREATMENT


Research shows the concordance between self-reported drug use and biological assays vary as a function of anonymity, contingencies, and testing time. This study investigated the concordance between self-report and scheduled versus random urinalysis of cocaine abstinence among homeless persons in day treatment. It was hypothesized that more false reports of abstinence would be revealed by random as compared to scheduled urinalysis. 141 treatment outcome study subjects were administered the ASI (self-reported drug use) and scheduled urinalysis at 2, 6, and 12-month assessment points and weekly/monthly random urinalysis over 12 months. More false abstinence reports (negative self-report and positive urinalysis) were revealed by random than scheduled urinalysis (2-mo: 59.7% vs. 19.0%; 6-mo: 56.1 versus 26.5%; 12-month: 46.2 versus 19.4%). These results suggest that both self-report and scheduled urinalysis will underestimate recent cocaine use. Whereas urinalysis is considered the ‘gold standard’ in drug use monitoring, random urinalysis is less subject to manipulation, like ‘cleaning up for drug testing’, and represents a more valid measure of current drug use for clinical and research contexts.

599 BRAIN GLUCOSE METABOLISM AFTER DEXTROMETORPHAN CHALLENGE IN ALCOHOL-DEPENDENT MALES AND CONTROLS

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Introduction Pre-clinical studies indicate that acute and chronic effects of alcohol are mediated by NMDA receptor. NMDA receptors have been suggested to be the primary target of alcohol. We have demonstrated alcohol-like effects in healthy controls and blunted effects in recently detoxified alcoholics when challenged with 2.0 mg/kg Dextromethorphan a non-competitive NMDA antagonist. Induction of craving effect was recorded in patients only. MAIN OBJECTIVE is to compare brain glucose metabolism profiles of alcohol dependent males and healthy controls induced by blocking NMDA receptors with dextromethorphan. METHODS We compared regional metabolism using [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) in recently detoxified alcoholic patient and controls (double blind, double dummy, placebo controlled) after challenge with 2.0 mg/kg Dextromethorphan. Controls were additionally challenged with alcohol (0.6 g/kg). Subjects were being assessed with standard measurements. RESULTS based on preliminary statistical analyses (so far five patients and ten controls, aim 12/12): (1) Lower metabolism rate in all brain regions among recently detoxified alcohol dependent males under placebo condition. Alcohol globally reduces regional brain glucose metabolism in controls. (consistent with published findings) (2) In alcohol dependent males dextromethorphan challenge led to no changes, or small reduction in brain glucose metabolism, most pronounced in the cerebellum (−4.9%). (3) In controls dextromethorphan challenge was associated with a small, non-significant increases in metabolism, most pronounced in the frontal region (6.1%), and least pronounced in the cerebellum (2.2%). This finding of ‘hyperfrontality’ is consistent with reported findings from ketamine challenge.

600 INTERNET RESOURCES ON PROBLEMS OF DRUG DEPENDENCE AND ABUSE FOR HEALTH CARE PROFESSIONALS AND STUDENTS

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The Internet provides a wealth of information in support of health care education and clinical practice on issues of drug dependence and abuse. This poster/presentation will present quality Internet sites that are available to enhance the work of educators and clinicians that teach and practice in this important field. A portal to reliable, quality, valid Internet resources will be developed and presented in a format that is easy to locate and follow, while being transportable to a wide range of instructional and clinical practice sites. This project will focus on the presentation of mega, or large-scale web sites that collate and bring together the rich array of resources available in the broad and diverse field of drug dependence and abuse. The poster/presentation will insure access to a variety of Internet resources without regard to organization, institution or country of origin. The Internet resources selected will be international in scope. Among the criteria used for selecting Internet sites will be the quality, reliability and uniqueness of the information provided. An important focus will be to support the information needs of both educators and health care students in all related disciplines by presenting sites that support a problem-based learning format. Sites will be chosen for their ability to foster a multidisciplinary educational approach. A strong cautionary component also will be designed to inform participants of the sometimes unreliable and untrustworthy information that is available on the Internet. Attention will be given to teaching participants how to identify hallmarks and distinguishing features of these sites.

601 BALTIMORE'S TREATMENT-ON-DEMAND INITIATIVE: ESTIMATING THE IMPACTS OF DELAYING ONSET OF TREATMENT SERVICES

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The Internet provides a wealth of information in support of health care education and clinical practice on issues of drug dependence and abuse. This poster/presentation will present quality Internet sites that are available to enhance the work of educators and clinicians that teach and practice in this important field. A portal to reliable, quality, valid Internet resources will be developed and presented in a format that is easy to locate and follow, while being transportable to a wide range of instructional and clinical practice sites. This project will focus on the presentation of mega, or large-scale web sites that collate and bring together the rich array of resources available in the broad and diverse field of drug dependence and abuse. The poster/presentation will insure access to a variety of Internet resources without regard to organization, institution or country of origin. The Internet resources selected will be international in scope. Among the criteria used for selecting Internet sites will be the quality, reliability and uniqueness of the information provided. An important focus will be to support the information needs of both educators and health care students in all related disciplines by presenting sites that support a problem-based learning format. Sites will be chosen for their ability to foster a multidisciplinary educational approach. A strong cautionary component also will be designed to inform participants of the sometimes unreliable and untrustworthy information that is available on the Internet. Attention will be given to teaching participants how to identify hallmarks and distinguishing features of these sites.
Baltimore launched a major initiative in 1998 to increase the availability of drug abuse treatment. The ultimate goal of this ongoing effort is to provide ‘treatment-on-demand’. A key component of this initiative was a 12-month multi-site evaluation of the effectiveness of treatment and of the impact of delays in the onset of services in 800 new slots created across 16 community programs (eight ‘drug-free and eight methadone’). Rapid onset of treatment services was defined as treatment entry within 2 days of study intake. The present study reports on a subset of 991 participants who completed the study intake evaluation and began treatment; 482 in drug-free and 509 in methadone settings. Drug use, HIV risk behavior, crime and other clinical measures included self-report (e.g. ASI, RAB) and objective indices (e.g. urine specimens, criminal justice data). Two major findings were observed. Delays in the onset of treatment did not diminish clinical effectiveness. Subjects who received rapid and those who received delayed treatment entry had quick and comparable reductions from intake across multiple indices of drug use, HIV-risk behavior and crime. The second major finding was determined by comparing the differences in ASI responses at intake and 30-days following onset of treatment. These change data were used to estimate the impact of delaying treatment for 30-days per 1000 drug abusers in the community. Each 30-day delay in treatment is associated with 13 700 days of heroin use, 3800 days of cocaine use, 5300 days of crime and $267 850 in illegal income. Data will be presented comparing the intake versus 30-day, 6 and 12-month evaluation of drug use, HIV risk behavior and crime. These data will be used to illustrate each of the major findings described above.

**602 ALTERATIONS IN SIGNAL TRANSDUCTION SYSTEMS AT VARIOUS LEVELS OF MORPHINE TOLERANCE**

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The opioid literature contains a considerable number of inconsistencies concerning cellular or molecular alterations in tolerant versus acutely treated animals. Many factors such as species differences, route of administration, opioid used, rate of administration of the drug to produce tolerance and others have been recognized as the cause of the variability from one study to another. In the present study we have kept all the other variables constant and altered the amount of morphine given to the mice to produce an 8.7 and a 50.2 fold antinociception tolerance. We compared DAMGO’s ability to stimulate mu receptor-mediated G-proteins in membranes prepared from spinal cord and various brain areas of mice from each of the tolerant groups and placebo-pelleted animals. The results of these studies showed a significant (~25%) decrease in the tolerant animals of basal GTP-gamma-S binding in the pons/midbrain, with no change in any other brain region examined or spinal cord. Interestingly, the magnitude of this decrease in basal G-protein activity was not different between mice exhibiting high and low levels of tolerance. There was also a modest (20%) desensitization of DAMGO-stimulated GTP-gamma-S binding observed in the spinal cords from both groups of tolerant mice, measured as a decrease in percent stimulation by DAMGO. These results agree with previous studies on the effect of chronic morphine on GTP-gamma-S binding in brain membrane preparations, but extend those findings to show that decreased local G-protein activity in pons/midbrain does not correlate with level of morphine tolerance. In total, these results demonstrate that the magnitude of morphine tolerance does not correlate with the effect of chronic morphine on G-protein activity in the CNS, when measured in isolated membrane homogenates.

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**603 PRELIMINARY FINDINGS FROM THE EARLY RE-INTERVENTION (ERI) EXPERIMENT WITH CHRONIC SUBSTANCE ABUSERS**

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The majority of people presenting for publicly funded substance abuse treatment relapse and receive multiple episodes of care before achieving long-term recovery. This experiment evaluates the impact of an Early Re-Intervention (ERI) protocol involving motivational interviewing, case management, and organizational linkages to facilitate treatment re-entry. It is hypothesized that ERI would reduce the length of time to readmission and increase the amount of treatment received. Data are from 448 adults recruited from Haymarket’s Chicago Central Intake who were randomly assigned to either quarterly outcome monitoring (OM) or quarterly OM plus ERI. The participants were 59% Female, 85% African American, and 75% aged 30–49. Over 90% met criteria for dependence (mostly cocaine, alcohol, heroin, and marijuana), 68% had been in treatment before and 67% were referred to inpatient treatment. While almost 4/5ths of the participants in both groups returned to treatment during months 3–15, those assigned to ERI returned to treatment sooner and had more total (subsequent) days in substance abuse treatment (57 vs. 51 days, z = −16.5, P < 0.0001). ERI participants were also significantly less likely to be in need of treatment during the four subsequent interviews at months 6, 9, 12 and 15 (mean of 40% vs. 42% of four times, z = −12.9, P < 0.0001). Providing transportation assistance and escorting people to the admissions increased the size of the effect. This demonstrates the feasibility of altering treatment careers and the promise of using ERI type protocols to accelerate treatment re-entry. We are continuing to track these clients to look at the impact of these changes on outcomes in subsequent years.

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**604 DISCRIMINATIVE STIMULUS EFFECTS OF BUPRENORPHINE AND NALBUPHINE IN OPIOID-DEPENDENT RHESUS MONKEYS**

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The discriminative stimulus effects of buprenorphine and nalbuphine were tested in four rhesus monkeys that were treated twice daily with LAAM (1 mg/kg), and in three monkeys that received morphine (3.2 mg/kg) once daily. Both groups were trained to discriminate a withdrawal-precipitating dose of naltrexone (0.0178 mg/kg) from saline. Buprenorphine (0.032–3.2 mg/kg) substituted for naltrexone in just one LAAM-treated monkey (OP). Up to a dose of 32 mg/kg, nalbuphine occasioned predominantly saline-lever responding in all four monkeys. When administered prior to naltrexone both buprenorphine and nalbuphine dose-dependently shifted the naltrexone dose-effect curve to the right (3.5–100 and 3.5–35 fold, respectively), with the exception of monkey OP in which buprenorphine shifted the naltrexone dose-effect curve 4–20 fold to the left. Buprenorphine substituted fully for naltrexone (≥80% naltrexone-lever responding) in two morphine-treated monkeys and partially in a third monkey. Nalbuphine did not substitute for naltrexone in any morphine-treated monkey. In morphine-deprived (withdrawn) monkeys, buprenorphine and nalbuphine each partially reversed naltrexone-lever responding. These behavioral assays are sensitive to efficacy differences between buprenorphine and nalbuphine that are consistent with previously reported in vitro data. Collectively, these data show clear differences between low-efficacy opioids in their ability to mimic or modify the naltrexone discriminative stimulus. The relative ability of these opioids to substitute for, or to attenuate, the naltrexone stimulus in these two groups of monkeys...
Nicotine replacement therapy (NRT) typically replaces only 50% of the nicotine concentrations achieved while smoking. Incomplete replacement may contribute to NRT limited success. We determined whether inhibition by methoxsalen of CYP2A6, the primary enzyme responsible for nicotine’s metabolism, could increase the systemic concentration of nicotine after NRT (21 mg/day nicotine patch or 4 mg nicotine gum). The study was a randomized, double-blind crossover comparison of nicotine and cotinine concentrations with and without methoxsalen treatment in 12 dependent smokers (DSM-IV; Fagerström > 3) using the patch, and 11 using the gum. Subjects in the patch study received patch for 4 days while taking 10 mg methoxsalen or placebo t.i.d. On Day 5, the final patch was removed. Nicotine kinetics were determined on Days 4 and 5. On Day 4 of patch, mean nicotine concentrations were increased by 24% during methoxsalen compared to placebo (P < 0.05). Cotinine concentrations were unchanged. Subjects in the gum study received 10 mg methoxsalen or placebo t.i.d. for 3 days. On these days, they chewed one piece of nicotine gum for 30 min every h x 5 and nicotine levels were determined. Mean plasma nicotine concentrations were increased by 52% on Day 3 of methoxsalen compared to placebo (P < 0.05). The larger effect seen with oral than patch likely reflects a combined effect on systemic clearance and hepatic metabolism of swallowed nicotine. CYP2A6 inhibition should increase the efficacy of NRT by providing greater nicotine replacement than with the use of NRT alone.

**606 Behavior and technology: advancing to reduce HIV risk due to injection drug abuse**


Drug Abuse and AIDS are intersecting epidemics that have not gone away in spite of several decades of well-planned extensive work. On the one hand, the 9000 base-pair HIV is very difficult to defeat and on the other hand human beings have great difficulty in desisting from practices and behaviors that result in the spread of HIV and lead to drug addiction. The purpose of our study is to demonstrate the impact of an intervention in which the materials and skills needed to clean needle/syringes (n/s) are delivered directly to sites where IDUs gather to inject (risk locales). We previously showed that exposure to bleach will inactivate HIV in short intervals, that HIV DNA are present in n/s and also in the paraphernalia (cottons, cookers) and wash waters shared at shooting galleries. We found HIV RNA in n/s. Thus, there is a secondary risk for HIV spread. Through networks of informal social relations among IDUs, the research team has identified risk locales to implement n/s cleansing interventions. Two interventions are implemented in selected risk locales: (1) regular delivery of needle cleansing wherewithal and (2) delivery plus training of personnel. We established rapport to non-participant-observation of injection drug use (heroin and cocaine) and associated social interactions in the risk locales (male and female African Americans, Puerto Ricans, and whites, ages 20–50’s). We utilized Applied Biosystems TaqMan real time PCR to detect and quantify HIV RNA across a wider order of magnitude range of concentrations than hitherto accomplished. We used human 18S rRNA (25–25 fg) to normalize for total RNA in each specimen and as an initial standard curve for relative quantification of HIV. Using this new technology, we detected HIV RNA not only in n/s but also in cottons, cookers, and wash-waters. We are currently extending the study for absolute virus load determination using purified monodisperse HIV gag vector for the standard curve.

**607 Pilot randomized-double-blind-placebo-controlled study of dexamphetamine for cocaine dependence**

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Cocaine use has been identified as a serious public health concern in Sydney, Australia particularly among more marginalised and vulnerable injecting drug users where cocaine use has been associated with criminal involvement, violent behaviour, HIV risk taking and psychosis. The objective of this trial was to establish the feasibility of conducting a controlled clinical trial of dexamphetamine replacement for cocaine dependence and to obtain preliminary data on the safety and efficacy of this treatment. Thirty dependent injecting cocaine users were randomly assigned to receiving 60 mg/day dexamphetamine or placebo for 14 weeks. Treatment retention was equivalent between groups however outcomes favoured the treatment group with no improvements observed in the placebo group. The proportion of cocaine positive urine samples detected in the treatment group declined from 94 to 50% (P = 0.01) compared to no change in the placebo group (79% positive). The treatment group also reported reduced cocaine use (P = 0.02), reduced criminal activity (P = 0.04), reduced cravings (P < 0.01), reduced severity of cocaine dependence (P < 0.01) and improved health (P = 0.03) based on the Opiate Treatment Index, visual analogue scales and the Severity of Dependence Scale. The incidence of adverse events was equivalent between groups. A definitive evaluation of the utility of dexamphetamine in the stabilisation of cocaine dependence is warranted.

**608 Behavioral effects of volatile solvents on C57BL/6J and D2AJ mice**

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Indbred mouse strains often have radically different responses to drugs of abuse. In particular, the C57BL/6J (B6) and DBA/2J (D2) mouse strains have been used extensively to explore the genetic loci of several behavioral effects of ethanol. The behavioral effects volatile anesthetics and solvents are in many respects similar to those of ethanol and may involve common neurochemical systems. In order to determine if B6 and D2 mouse strains would be good candidates for similar behavioral genetics studies with volatile anesthetics and solvents, the locomotor activity altering and incoordinating effects of methoxyflurane were examined in eight B6 and eight D2 mice. Vapor exposure/locomotor activity monitoring chambers consisted of a 26 l sealed bell jars bisection by pairs of photo beams. Internal fans volatilized test compounds injected onto a filter paper disc suspended in the chamber. Locomotor activity/vapor exposure test session were 20 min in duration. On Mon a habituation test was administered. On Tues–Fri, methoxyflurane concentrations of 0, 500, 2000 and 6000 PPM were tested using a random latin square presentation order. Following the vapor exposure, the mice were removed from the test chamber and loss of righting reflex, forelimb grip strength, inverted screen climbing
time and landing foot splay were rapidly assessed by a technician blind to test concentration. Methoxyflurane had a biphasic effect on activity in both strains. Under control conditions, there was no significant difference between strains in locomotor activity. Both the B6 and D2 mice showed increases in motor activity at the 2000 ppm concentration. However at the 6000 ppm concentration, the B6 mice showed decreases in locomotor activity whereas activity in the D2 mice was not significantly different from the control condition. Methoxyflurane did not have a significantly different effect between strains on any of the other measures tested. The locomotor data suggest that B6 and D2 mice may be useful for further exploration of the genetic basis of volatile anesthetic effects.

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609 Investigating the actions of bupropion on dependence-related effects of nicotine in rats

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The clinical success of the antidepressant bupropion, marketed as Zyban, in smoking cessation represents a major discovery with regards to understanding factors fundamental to nicotine dependence. The present experiments utilise bupropion as a reference compound to examine putative interactions with stimulus properties of nicotine in rats. In male hooded Lister rats, bupropion (10 and 30 mg/kg IP) administered 30 min prior to each intravenous nicotine (0.03 mg/kg per inf) self-administration session failed to attenuate rates of nicotine intake. Moreover, following the large dose of bupropion, nicotine intake was enhanced 3-fold and response rates remained elevated throughout the 28-day course of treatment. To examine interactions with subjective effects of nicotine, rats trained to discriminate nicotine (0.2 mg/kg SC) from vehicle were tested with bupropion (10 and 30 mg/kg IP). At both doses, bupropion pre-treatment failed to exert a ‘nicotine-like’ action and also failed to modify the orderly dose-related discrimination function of nicotine (0.05–0.4 mg/kg SC) in rats. Using the conditioned taste aversion procedure to assess the aversive stimulus properties of nicotine, a function implicated in the regulation of nicotine intake, bupropion (3, 10 and 30 mg/kg IP) pre-treatment failed to modify the aversive effects produced by a sub-maximal dose of nicotine (0.2 mg/kg SC). The results obtained with bupropion in these animal models of dependence suggest this antidepressant may not modify the clinical efficacy may be exposed in animal models that are based upon chronic exposure to nicotine and upon abstinence effects.

610 Behavioral differences between d-methamphetamine and d-amphetamine: locomotor activity and working memory

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Previously, we showed that d-amphetamine (AMPH; 2 mg/kg) produced greater locomotor activity than d-methamphetamine (METH; 2 mg/kg). While METH and AMPH were found to release dopamine (DA) equally in the nucleus accumbens (NAC), only AMPH released glutamate (GLU) in the NAC. Here we test the hypothesis that, in female Sprague–Dawley rats, AMPH produces more locomotor activity than METH due to NAC GLU release. Locomotor activity was assessed after intra-NAC pretreatment with the competitive GLU antagonists AP5 or DNQX, or vehicle (VEH), followed by systemic METH or AMPH. VEH-AMPH produced greater locomotor activity than VEH-METH due to a longer duration of effect. Pretreatment with either AP5 or DNQX decreased the duration of activity produced by AMPH without affecting the duration of activity produced by METH. Thus, in the presence of GLU antagonists, the difference between METH and AMPH was abolished. GLU, therefore, appears to enhance the duration of locomotor activity produced by AMPH. We have also previously shown that AMPH is more effective than METH at releasing DA in the prefrontal cortex (PFC). Since an optimal level of DA in the PFC is required for intact working memory, we hypothesized that AMPH would affect working memory more than METH. Working memory performance was assessed, in female Sprague–Dawley rats, using a delayed-alternation T-maze task. Both METH and AMPH produced dose related biphasic effects on working memory; however, AMPH was more potent than METH. Thus, based on our previous microdialysis data, we have predicted and demonstrated several behavioral differences between METH and AMPH.

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611 A snapshot of HIV/AIDS-related services in clinical treatment providers for NIDA’s Clinical Trials Network


In January 2001, the HIV/AIDS Workgroup for NIDA’s Clinical Trials Network (CTN) initiated the task of developing a ‘snapshot’ of the type of HIV- and hepatitis-related services delivered at the participating Clinical Treatment Providers (CTP) sites. A total of 65 CTPs representing 12 of the 14 CTN nodes responded to our survey representing the New England, Eastern, Southeast, Midwest, and Western U.S. regions. This report details the responses of the CTPs based on settings delivering these treatment modalities: drug-free outpatient (84.6%), intensive outpatient, day hospital, or partial hospital (70.8%), inpatient (43.1%) and opiate substitution (41.5%). These assessments included on-site HIV counseling and testing to referral to community testing sites for counseling and testing. Formal assessments are conducted by program counselors (35.6%), intake workers (35.6%), nursing/medical staff (35.6%), HIV counselors (5.1%) or self (3.4%). The vast majority of CTPs also reportedly provide HIV/AIDS education to their clients (82.8%) upon admission, although there is a broad range of the format, content, and timing of the education sessions. Only 28.3% of the CTPs conduct outreach to drug using groups at high-risk for HIV transmission. Corresponding to this, over one-half of CTPs estimated HIV infection rates in their client population below 5% (33.8%), one-quarter (25%) between 5 and 10%, and the remainder (21.1%) above 10%. Estimates of Hepatitis C in the patient population ranged form 38.3% of CTPs estimating infection rates at 10% or lower, 31.9% of CTPs estimating rates above 50%, and the remainder between 10 and 50%. This report indicates a wide variation in services specific to HIV and Hepatitis C within the CTN. Findings provide direction for mounting nation-wide trials of interventions that target behavioral risk reduction in treatment-seeking drug users.

612 Can stopping cannabis use result in withdrawal symptoms?

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Cannabis withdrawal has been a subject of debate during revisions of Diagnostic and Statistical Manual of Mental Disorders (DSM). In DSM-IV, the withdrawal symptoms have been stated to be of ‘uncertain clinical significance.’ This paper attempts to test the hypothesis that stopping cannabis use can result in withdrawal symptoms. Method: Data collected from DSM-IV field trial using CIDI: Substance Abuse Model (SAM) was analyzed (N = 1225). 823 subjects were cannabis users, of whom 812 had cut down on cannabis at some time. Preliminary analyses were done on the 812 individuals, who were further grouped into (a) cannabis only users (b) cannabis and opioid users and (c) cannabis and other drug users. Analyses were repeated for the following categories (a) withdrawal from cannabis only (b) withdrawal from cannabis and opioids (c) withdrawal from cannabis and other drugs. Results: After stopping use, of those who used cannabis only, 4.1% reported feeling depressed, 2.7% reported being anxious, restless or irritable, 2.7% had trouble concentrating, 7.4% reported feeling tired, sleepy or weak and 8.1% reported a change in appetite. Similarly, amongst those who reported withdrawal only from cannabis (2 or more withdrawal symptoms), 49.1% reported being depressed, 37.7% were anxious, restless or irritable, 26.4% had trouble concentrating, 47.2% were tired, sleepy or weak, 26.4% had trouble sleeping, 45.3% had a change in appetite and 20.8% had yawning symptoms. Withdrawal from cannabis with opioids and other drugs increased the rate of reporting of only two of the symptoms: feeling anxious and trouble concentrating. Conclusion: Stopping drugs increased the rate of reporting of only two of the symptoms: yawning symptoms. Withdrawal from cannabis with opioids and other drugs. Results: After stopping use, of those who used cannabis only, 4.1% reported feeling depressed, 2.7% reported being anxious, restless or irritable, 2.7% had trouble concentrating, 7.4% reported feeling tired, sleepy or weak and 8.1% reported a change in appetite. Similarly, amongst those who reported withdrawal only from cannabis (2 or more withdrawal symptoms), 49.1% reported being depressed, 37.7% were anxious, restless or irritable, 26.4% had trouble concentrating, 47.2% were tired, sleepy or weak, 26.4% had trouble sleeping, 45.3% had a change in appetite and 20.8% had yawning symptoms. Withdrawal from cannabis with opioids and other drugs increased the rate of reporting of only two of the symptoms: feeling anxious and trouble concentrating. Conclusion: Stopping drugs increased the rate of reporting of only two of the symptoms: yawning symptoms.

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613 COMPARISON OF NEUROENDOCRINE STRESS RESPONSE AFTER MARATHON RUNNING AND INTRAVENOUS COCAINE

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The purpose of this study was to compare the neuroendocrine stress response in trained marathon runners after competition to previously reported effects of intravenous cocaine in drug-free subjects with cocaine abuse, including stimulation of the hypothalamic-pituitary-adrenal (HPA) axis with secretion of prolactin (PRL) and luteinizing hormone (LH). Subjects were ten trained runners with a mean age of 48±9 years who provided blood samples the day before and within 24 h after completing the 2001 Boston Marathon. Comparing pre- to 2 h post-race values, there were 2.4-fold increases in cortisol (801±8 from 342.5±28 nmol/l, P = 0.0001) and PRL (26.6±2.6 from 11.7±1.0 ng/ml, P = 0.0001), with decreases in LH (trend) and testosterone (340±24 from 440±28 ng/dl, P = 0.02). Marathon running stimulated the HPA axis with secretion of PRL similar to the effects of cocaine but differed in suppressing the pituitary-gonadal axis.

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614 EFFECTS OF THE KAPPA AGONIST U69593 ON LOCOMOTOR ACTIVITY, CONDITIONED ACTIVITY AND CONDITIONED PLACE PREFERENCE INDUCED BY COCAINE IN RATS


Neuronal substrates that mediate the conditioned stimulant and reinforcing effects of cocaine are not well characterized. To examine opioid mechanisms, we tested the kappa agonist U69593 for its capacity to alter the expression of conditioned locomotor activity (CLA) and conditioned place preference (CPP) in male Sprague–Dawley rats. For CLA, six conditioning sessions were conducted over a 10-day period. Paired rats received 10 mg/kg ip cocaine prior to activity sessions and saline prior; unpaired controls received saline prior and cocaine after. For CPP, eight conditioning sessions were conducted over a 13-day period; rats received 10 mg/kg ip cocaine while restricted to one of two distinct chambers and, on alternate days, they received saline in the other. U69593 was also assessed on cocaine-stimulated locomotor activity for comparison; rats were injected with escalating doses of cocaine (5, 10, 20, 40 mg/kg ip) over a 2-h activity session. U69593 (0.1–1.0 mg/kg s, 20-min pretreatment) did not affect the direct stimulatory effect of cocaine on locomotor activity. U69593 significantly blocked the expression of CLA at both doses tested, 0.3 and 1.0 mg/kg, but only partially attenuated the expression of CPP at the dose of 1.0 mg/kg. These data are consistent with findings that U69593 also blocks the expression of sensitization to the effects of cocaine (Heidbreder et al., 1995). In addition, direct and conditioned effects of cocaine were shown to be differentially sensitive to kappa opioid agonists. (VA and NIDA support.)

615 COCAINE-DEPENDENT PATIENTS’ PERCEPTIONS OF HOW THEIR COCAINE USE INFLUENCES THE REINFORCING EFFECTS OF CIGARETTES AND MONEY

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Cocaine users report smoking more cigarettes when using cocaine than while sober, the veracity of which was supported in a previous study by our group using cotinine levels as an objective measure of smoking (Roll et al., 1997). One possible explanation for cocaine’s ability to increase cigarette smoking is that it increases the reinforcing effects of smoking. Given that patients’ self-reports appear to accurately reflect their smoking under conditions of cocaine use and nonuse, the present study uses a self-report instrument to examine how acute and chronic cocaine use may influence the reinforcing effects of cigarettes as well as that of another reinforcer, money. Fifty cocaine-dependent patients were asked how much they would pay or work (press a space bar on a computer keyboard) for two puffs on a cigarette after using varying amounts of cocaine. Patients were then asked how much they would work for $1.00 following the same amount of cocaine use. Finally, these questions were repeated for varying durations of cocaine use (i.e., chronic use). The amount patients were willing to pay and work for smoking increased with both acute and chronic cocaine use (P < 0.001). The amount patients were willing to work for money increased to a comparable extent as smoking with acute dosing and to a lesser extent with chronic dosing (P < 0.001). The ability of acute and chronic cocaine use to increase the reinforcing effects of smoking supports a possible behavioral explanation for the cocaine-produced increases in cigarette smoking. The cocaine-produced increases in the reinforcing effects of money are a novel observation and to our knowledge represent a first look at the effects of cocaine use on this nondrug reinforcer.

616 CEREBRAL BIOENERGETIC CHANGES AT ONSET OF METHADONE MAINTENANCE TREATMENT IN HEROIN-DEPENDENT POLYDRUG ABUSERS

Bioenergetic and phospholipid abnormalities have been reported in polydrug abusers, suggestive of compromised cerebral metabolism. This study evaluated cerebral phosphorous metabolites and transverse relaxation times (T2RT) in opiate-dependent subjects after beginning methadone maintenance treatment (MM), to characterize early neurochemical events occurring with treatment onset. Phosphorous magnetic resonance spectroscopy (31P-MRS) and T2RT data, which reflect steady state cerebral metabolism, were acquired from 50 and 1.5-mm axial brain slices, respectively, through the orbitofrontal and occipital cortices, at 1.5 Tesla. About 43 MM subjects (treatment duration: 0–1, 2–7, 8–14, or 15–28 days prior to scan) and 15 age-matched healthy controls were examined. When compared to controls, %PME levels were elevated in the group with longest MM duration (F1, 30 = 4.35, P < 0.05), while elevated % PDE levels were observed in subjects with 2–7 days MM (F4, 53 = 2.79, P < 0.05). In addition, % PCR levels were decreased (F4, 53 = 7.31, P < 0.005) and T2RT values were elevated with prolonged MM treatment (F4, 42 = 6.48, P < 0.001). When all groups were considered together, these measures were negatively associated (r2 = –0.08, P < 0.005). These data provide evidence that changes in cerebral metabolic status begin to appear shortly after initiation of MM treatment in poly-drug abusers.

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617 THE THERAPEUTIC WORKPLACE BUSINESS: A LONG-TERM TREATMENT FOR DRUG ADDICTION AND CHRONIC UNEMPLOYMENT

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The Therapeutic Workplace is a long-term treatment for drug addiction and chronic unemployment. In the Therapeutic Workplace, patients are hired and paid to perform data entry jobs. To promote abstinence, patients are required to provide drug-free urine samples to gain daily access to the workplace. Initially, each participant’s "job" is to work in a job skills training program. Successful participants then are hired as employees of a Therapeutic Workplace data entry business. The Therapeutic Workplace was evaluated in patients (N = 40) enrolled in a methadone treatment program for pregnant women. Patients were randomly assigned to a Therapeutic Workplace (N = 20) or a usual care control (N = 20) group. Therapeutic Workplace participants were invited to work in the workplace every weekday for over 4 years. Eight participants entered the business at about 3 years after intake. This presentation will describe the results of the 4th year after intake when participants served as data entry operators in the Therapeutic Workplace data entry business. Preliminary analyses of monthly assessments conducted during that 4th year showed that relative to the Usual Care Controls, Therapeutic Workplace participants had more urine samples negative for cocaine (25 vs. 55%; P = 0.019), opiates (31 vs. 60%; P = 0.019), and both cocaine and opiates (18 vs. 47%; P = 0.021); more days employed per month (means of 2.1 vs. 9.4 days; P = 0.003); and higher monthly employment income (means of $61.00 vs. $472.00; P = 0.003). During the 1st year of operation of the business, participants entered over 15 million characters at an average rate of 2498 per h, and an accuracy of 99.6% correct. During that year, the business completed 19 data entry jobs for 11 customers, and received $43,000 in revenues. This study suggests that the Therapeutic Workplace business can maintain long-term drug abstinence and employment and might become self-sustaining.

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618 ASSESSMENT OF RELIGIOSITY AND SPIRITUALITY IN SUBSTANCE ABUSE TREATMENT

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More attention has been given to the role of religion and spirituality in substance abuse treatment. Consideration of religion and spirituality as factors in behavior change require reliable measures of these factors. In this regard, this review addresses the role of religion and spirituality in recovery; also included will be discussions of the associations between religiosity/spiritual beliefs, ethnic and gender differences, and the role of religiosity and spirituality in the process of recovery from substance abuse disorders. Additionally, this review describes the development of the Religion and Spirituality in Recovery inventory (RSR); Religion and Spirituality in Recovery (RSR) is a 21-item inventory that assesses participants’ current use of spiritual and religious practices as well as their desire/motivation to have religious or spiritual components become a part of their substance abuse treatment programs; the RSR assesses the above mentioned domains for all drugs of abuse; the processes to obtain test-retest reliability and internal consistency are described.

619 RELAPSE: DOES IT AFFECT COGNITION IN METHAMPHETAMINE ABUSERS?

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Data from 75 methamphetamine (MA) abusers enrolled in a longitudinal cognitive study were used to examine the effect of relapse on cognition. About 25 of the MA abusers remained abstinent, 25 relapsed, and 25 never stopped using. All MA abusers gave weekly random urine samples to verify status. The mean time that participants were monitored before testing was 99.3 days. There was no difference between groups on age, education, ethnicity, gender, or time monitored. In general the using group had the highest scores. Participants in the relapse group were significantly better (t = 44 = –2.6, P = 0.01) than those in the abstinent group on a backward span test but did not reliably differ from the abstinent group on any of the other 26 outcome measures. The relapse group was significantly worse than the using group on all four measures of episodic memory (word recognition t = 48 = –2.02, P = 0.03; picture recognition t = 48 = –2.2, P = 0.03; word recall t = 48 = –2.02, P = 0.05; picture recall t = 48 = –2.14, P = 0.04). On the discrimination learning task the performance of the relapse group fell between that of the other two groups. Although the relapse group was not significantly different from either of the other groups with respect to learning, those groups differed significantly on five of the seven outcome measures. With the exception of measures of episodic memory, relapse seems to be associated with performance that is worse than that of abusers who are currently using and better than that of those who have remained abstinent. However, for measures of episodic memory, scores of the relapse groups were significantly lower than those of the using group and lower than those of the abstinent group.

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620 DRINKING GAME PARTICIPATION AND OTHER PREDICTORS FOR ALCOHOL, SMOKING, AND SUBSTANCE ABUSE AMONG YOUNG ADULTS

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The study evaluated risk factors for drinking, smoking, and substance abuse among 61 young adults in college. A survey research design was used to assess drinking game participation and patterns of substance abuse. A stepwise regression analysis determined the order of predictors for alcohol use. The results support that lifetime alcohol use is a primary predictor and drinking game participation is a secondary predictor for alcohol use. Another stepwise regression analysis showed that lifetime alcohol use is also a direct predictor for smoking cigarettes and substance abuse. These findings suggest that lifetime alcohol use may serve as a risk factor for heavy drinking and substance abuse among young adults. Prevention programs should assess and address lifetime alcohol use and the social context of drinking to deter alcohol and substance abuse.

**621 IN VIVO AND IN VITRO MEASURES OF IMMUNE FUNCTION AFTER PRENATAL COCAINE EXPOSURE**

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Recently, we reported that prenatal cocaine exposure (PCE) suppressed immune reactivity in offspring (post-natal day (PND) 50) and this suppression was uninfluenced by gender, maternal behavior or nutrition (Randall et al., Soc. Neurosci. 26:1097;2000). We subsequently reported the temporal relationship of these effects (CPDD, 2001), demonstrating that PCE dramatically suppressed immune reactivity at PND25, an effect that was reduced at PND50 and no longer evident at PND100. The present study further characterized the effects of PCE at PND25, the time-point showing the greatest suppression of immune reactivity. Specifically, this experiment examined the consequences of long-term (pre- and gestational) PCE on both in vitro and in vivo immune parameters in the offspring of Long–Evans rats. Dams in group COC (Cocaine) received exposure to cocaine for 30 days prior to, and 12 days during (days 7–19), gestation. Subjects in group PF (Pair-fed) received the drug’s vehicle and were matched on food consumption to those animals in COC. Animals in group SUR (Surrogate) received no manipulation and half of the litters from COC and PF were reared by dams from SUR to examine any effects of maternal behavior. At PND 25, half of the male and female pups from every litter were sacrificed and blood samples were collected to assess mitogen-induced lymphocyte proliferation (in vitro). The other animals underwent the in vivo delayed-type hypersensitivity (DTH) assessment. As previously reported, PCE significantly suppressed immune reactivity at PND 25 in the in vitro measure of immune function. There was no influence of gender, nutrition or maternal behavior. Although evident within the in vitro measure, there were no significant differences between groups in the DTH response, suggesting a differential effect of PCE on measures of in vitro versus in vivo immune function. However, the in vivo assessment followed a similar pattern to that of the in vitro measure, suggesting that further investigation of the effects of PCE on in vitro immune reactivity and in vivo response correlates is warranted.

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**623 EMPLOYED WOMEN AND DRUG DEPENDENCE: CHARACTERISTICS, CONSEQUENCES, AND TREATMENT OUTCOMES**

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Contrary to the image of the ‘skid row’ drug user, 77% of drug users are gainfully employed (SAMHSA, 2002). Yet, little research exists on employed people with drug addiction, specifically, and most women included in addiction studies do not work outside the home. For the first time, this study explores characteristics, consequences of use, and treatment outcomes of employed women compared to male peers. Patients (N = 210) entering a 28-day treatment program completed the Addiction Severity Index (ASI; McLellan et al., 1980) at intake and 6 and 12 months follow-up. Women and men were similar in terms of employment (95% full-time), marital status (42% married), and family status (67% with children). Similar to men, most women reported their employer knew of their treatment entry (93%) and that their jobs were not contingent upon treatment completion (89%). However, in the year prior to treatment entry, women were more likely than men to have been disciplined on the job (x² = 4.94, P < 0.05) or fired (x² = 4.56, P < 0.05), yet less likely than men to have been sent to treatment by their employer (x² = 5.39, P < 0.05) despite similar absenteeism rates (overall M = 9.15 days) and drug use severity. No differences were noted between women and men on baseline ASI composite scores across medical, employment, alcohol, drug, legal, family/social, or psychiatric domains. Problem drug use days in the month prior to treatment entry were similar among men and women (overall M = 7.86). Women were just as likely as men to be living with someone using drugs or alcohol (x² = 0.48, P > 0.05) and reported a similar amount of family conflict days, F(1, 209) = 0.16, P > 0.05. Overall, these data suggest the severity of chemical dependency problems for women is similar to men at treatment entry, yet women appear to experience a greater degree of job-related problems. ASI data at 6 and 12-months have been collected and are currently being compiled. Follow-up analyses, including comparisons of the course of recovery and treatment outcomes among women and men, will be completed by spring.

Objective: To examine changes in cerebellar blood volume and urinary cannabinoid concentration after a 7-day washout period. Method: We acquired dynamic susceptibility contrast (DSC) MRI data on twelve current, long-term marijuana users before and after a supervised 7-day abstinence period. Resting state cerebellar blood volume (CBV) data was also acquired in 12 comparison subjects. Imaging of heavy smokers was completed on days 1 and 7 of the study. Data was acquired with a 1.5-T GE Signa scanner. DSC sequences were completed in the axial plane following a bolus of gadoteridol. Results: Compared to control subjects, smokers displayed significantly increased cerebellar blood volumes at Day 7 of the washout period (P = 0.006). Age was not a significant predictive factor for CBV values (P = 0.317), nor was the total number of lifetime smokes for cannabinoid users (P = 0.935). However, a significant gender effect was present (P = 0.011), and within the marijuana user groups, urinary THC concentrations on Day 7 were highly predictive of cerebellar CBV values (r = −0.75, P = 0.005). Conclusion: These results suggest that cerebellar blood volume is associated with the degree of recent marijuana use, rather than cumulative lifetime use. The significant inverse relationship between urinary cannabinoid levels and cerebellar CBV at Day 7 invites the hypothesis that alterations in blood volume may be related to alterations in cognitive function and behavior.

Supported by NIDA grants DA12483 and DA10346.

**622 CEREBELLAR BLOOD VOLUME CHANGES AFTER A 7-DAY WASH-OUT PERIOD IN CHRONIC MARIJUANA SMOKERS: A DSC-MRI STUDY**

N.S. Simpson, S.A. Gruber, H.G. Pope Jr., D.A. Yurgelun-Todd, Cognitive Neuroimaging Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Objective: To examine changes in cerebellar blood volume and urinary cannabinoid concentration after a 7-day washout period. Method: We acquired dynamic susceptibility contrast (DSC) MRI data on twelve current, long-term marijuana users before and after a supervised 7-day abstinence period. Resting state cerebellar blood volume (CBV) data was also acquired in 12 comparison subjects. Imaging of heavy smokers was completed on days 1 and 7 of the study. Data was acquired with a 1.5-T GE Signa scanner. DSC sequences were completed in the axial plane following a bolus of gadoteridol. Results: Compared to control subjects, smokers displayed significantly increased cerebellar blood volumes at Day 7 of the washout period (P = 0.006). Age was not a significant predictive factor for CBV values (P = 0.317), nor was the total number of lifetime smokes for cannabinoid users (P = 0.935). However, a significant gender effect was present (P = 0.011), and within the marijuana user groups, urinary THC concentrations on Day 7 were highly predictive of cerebellar CBV values (r = −0.75, P = 0.005). Conclusion: These results suggest that cerebellar blood volume is associated with the degree of recent marijuana use, rather than cumulative lifetime use. The significant inverse relationship between urinary cannabinoid levels and cerebellar CBV at Day 7 invites the hypothesis that alterations in blood volume may be related to alterations in cognitive function and behavior.

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624 Risperidone for the treatment of individuals with schizophrenia and cocaine dependence

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Objective: To evaluate the efficacy of risperidone for the treatment of craving and for preventing substance abuse relapse in cocaine-dependent schizophrenics. Procedures: We conducted a preliminary open-label trial comparing risperidone with conventional neuroleptics for reducing cocaine craving and improving symptoms associated with schizophrenia. Symptom severity was rated weekly, and each patient completed a cocaine-craving questionnaire before and after a cue-exposure procedure. Results: Patients receiving risperidone (N = 8) had significantly less cue-elicted craving on the intensity (P = 0.05) and depression (P = 0.03) dimensions of craving, and tended to have reduced Positive and Negative Syndrome Scale negative (P = 0.07), and global (P = 0.08), scores compared with patients receiving a conventional neuroleptic (N = 10). Conclusions: Risperidone may prove to be more effective than conventional neuroleptics in decreasing cocaine craving and substance abuse relapse in cocaine-dependent patients with schizophrenia. Future research should include a double-blind trial comparing risperidone with a conventional neuroleptic in this population.

625 Effects of D2-receptor alkylation in the ventral pallidum on speedball self-administration in rats

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Receptor alkylation antagonists have proven to be useful research tools for determining functional involvement of receptor systems in complex behaviors. The role of D2-receptors in the VP was investigated using NIPS, a selective irreversible inhibitor of D2 receptors. Rats were trained to self-administer cocaine/heroin combinations on an FR2 schedule of reinforcement and given vehicle (20% DMSO) or 0.3 or 1.0 nmol of NIPS into each side of the VP. NIPS (1.0 nmol) decreased self-administration of 0.170.015, 0.330.030 and 0.670.060 mg infusion of cocaine/heroin by 50% for up to 4 days after administration, with a gradual return to baseline values thereafter. Administration of either vehicle or 0.3 nmol of NIPS into the VP had no significant effect on cocaine self-administration. The effects of administration of NIPS into the VP on speedball self-administration were much less than the effects previously found on cocaine self-administration, in which 1.0 nmol of NIPS completely abolished responding for up to 2 weeks. Similar, administration of 0.3 nmol of NIPS into the VP decreases cocaine self-administration by 50% over a similar range of doses that were used for the speedball studies and this dose of NIPS is ineffective at decreasing speedball self-administration. These data support previous microdialysis studies demonstrating a potentiation of cocaine’s effects on dopaminergic systems by heroin.

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626 Drug interactions between cocaine and mixed-action opioids on locomotor activity

M.A. Smith, K.A. Gordon, C.K. Craig, M.E. Ferguson, A.M. French, J.D. Gray and J.M. McClean, Davidson College, Davidson, NC

The purpose of the present investigation was to examine the effects of mixed-action opioids on the locomotor-activating effects of cocaine. Male, Long–Evans rats were habituated to an open-field, locomotor-activity chamber, and the effects of cocaine and various mixed-action opioids were tested under a cumulative dosing procedure. In this procedure, a selected dose of an opioid was administered during the first component of a session, with increasing doses of cocaine administered during subsequent components. When administered alone, cocaine produced dose-dependent increases in locomotor activity. The mu agonist levorphanol, as well as the mixed-action opioids buprenorphine, butorphanol and nalbuphine, dose-dependently enhanced the effects of cocaine at doses that did not alter locomotor activity when administered alone. In contrast, the kappa agonist spiradoline, and the opioid antagonist naloxone, dose-dependently attenuated the effects of cocaine at doses that did not alter locomotor activity when administered alone. Across an extensive dose range, the mixed-action opioid nalorphine failed to alter cocaine’s locomotor-activating effects. These data suggest that mixed-action opioids possessing significant mu-agonist activity (e.g. buprenorphine, butorphanol, nalbuphine) may potentiate the effects of cocaine in a manner similar to that typically observed with full mu agonists.

Supported by DA13461.

627 Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification

B.-F.X. Sobel, J.A. Liebson, D.H. Ginn, G.E. Bigelow, Johns Hopkins University School of Medicine, Baltimore, MD

We describe a first-in-man evaluation of a polymer micro-capsule depot formulation of buprenorphine designed to have a 1-month duration of action. Five physically dependent volunteer opioid abusers participated. Patients initially received oral hydromorphone on an as-needed basis for withdrawal relief (range 30–60 mg over 5–12 h). Opioid treatment was then abruptly discontinued overnight and each patient received a single s.c. depot injection of 58 mg buprenorphine. Patients were assessed periodically before and for 6 weeks after for signs and symptoms of opioid agonist effects and/or of opioid withdrawal. Blood samples were collected for pharmacokinetic analysis. Opioid response was assessed in weekly challenge tests (hydromorphone 0 vs. 3 mg, s.c.; double-blind, random order). Patient acceptability and staff global impression were very favorable. No appreciable opioid withdrawal or opioid intoxication were observed in the 6 weeks after depot administration. No patient required further medication. Opioid response remained attenuated throughout the 6 weeks. Mean plasma levels declined from approximately 1.7 ng/ml on Day 2 to approximately 0.3 ng/ml on Day 28. Depot buprenorphine appears safe and effective, and has the potential to deliver effective opioid dependence treatment while minimizing both the burdens of patient compliance and the risks of illicit diversion.

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628 Weight change during treatment for methamphetamine abuse

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This report presents data on weight change gathered during the course of treatment for methamphetamine dependence. Data were collected in several clinical trials utilizing one or more of the following treatment strategies; relapse prevention, contingency management, and placebo controlled medication trials. The results from these studies were pooled for analyses. Data were grouped by treatment outcome, which was defined as being successful (i.e. provided a urine sample which was methamphetamine negative at the first follow up interview) or unsuccessful (i.e. provided a urine sample which was methamphetame-
mine positive at the first follow up interview). Differences between genders were also examined. Our findings suggest that weight gain in men correlates with successful treatment. Men who were successful gained approximately 10 pounds, while those who were unsuccessful gained about 50% less. For women, regardless of treatment outcome, the results indicated that a weight gain of approximately 10 pounds was typical. These results suggest that for women, weight gain is a likely outcome of treatment participation. These data have clinical implications for those considering methamphetamine treatment.

629 THE ABUSED INHALANT, ISOBUTYL NITRITE, IS CYTOTOXIC BY MEANS OTHER THAN PEROXYNITRITE FORMATION

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Nitrite inhalant abuse has been correlated with HIV and HHV-8 infection and with Kaposi’s sarcoma. Using a mouse model, we have found that inhalation of isobutyl nitrite suppressed immune responses critical during resistance to infection and tumor growth. Using the macrophage cell line, RAW 264.7, isobutyl nitrite caused a dose-dependent loss of viability. While isobutyl nitrite reacted with hydrogen peroxide to form peroxynitrite, assays of mitochondrial respiration and nitration, which detect peroxynitrite, indicated that very little peroxynitrite was present in cultures exposed to the inhalants. Isobutyl, isooamyl, and butyl nitrates inhibited mitochondrial respiration, but only at high concentrations. Similarly, the nitrating activity of isobutyl nitrite occurred only at high concentrations and was not affected by the presence of hydrogen peroxide. Western blots employing antibody to nitrotyrosine showed that the inhalant did not increase nitrotyrosine formation in RAW cells or in peritoneal exudate macrophages from exposed mice. Thus, the toxicity induced by isobutyl nitrite was probably not due to peroxynitrite formation.

630 SUBJECTIVE EFFECTS OF AN ACUTE HIGH DOSE OF PROGESTERONE IN MEN AND WOMEN

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The goal of this study was to investigate the effects of an acute intramuscular dose of progesterone in men and women. Although endogenous progesterone levels are very low in men, compared to women, there is evidence that metabolites of progesterone have central actions on GABA receptors in men just as they do in women. Allopregnanolone and pregnanolone are highly potent ligands at the GABA receptor complex, and in preclinical models produce sedative-like effects. These effects have been observed in both male and female animals. Relatively few studies have examined these neuroactive effects of steroids in humans, and only one previous study has examined the behavioral effects of progesterone in men. We hypothesized that progesterone would produce increases in self-reported sedation and sedative-like impairments in cognitive performance. Method: Women (N = 8) in their early follicular phase and men (N = 10) received intramuscular injections of progesterone (200 mg) or placebo. Plasma levels of progesterone, pregnanalone and allopregnanolone were obtained at regular intervals, and subjects completed self-report measures of mood and subjective effects and performed behavioral tests. Results: The results are complex and only partly support our hypothesis. In men, significant subjective ratings of sedation were found after progesterone administration, however, accompanied with increased feelings of discomfort. In women, both significant increases and decreases in sedation accompanied with increased feelings of restlessness were found after progesterone administration. The plasma assays of progesterone, pregnanalone and allopregnanolone are under analyzes. They may further shed light on the complexity of the result. Conclusions: This study is the first to investigate the effects of an intramuscular injection of 200 mg progesterone in both men and women. The results suggest that progesterone and its metabolites, can produce sedative-like effects in both men and women.

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631 COCAINE WITHDRAWAL SYMPTOMS ARE ASSOCIATED WITH ENHANCED SUBJECTIVE RESPONSE TO COCAINE

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In a previous study, we observed that cocaine users reporting cocaine withdrawal symptoms, compared to those who did not, had more frequent medical, mental health and psychosocial problems. To extend these findings, we examined differences in the subjective response to smoked cocaine in 25 male and 19 female cocaine users with and without withdrawal symptoms. Participants received a single dose of 0.4 mg/kg of smoked cocaine during the adaptation session of impatient experimental protocols. The main analysis compared two groups for subjective and physiological responses to cocaine with repeated measures ANOVA. We hypothesized that the presence of withdrawal symptoms would alter the subjective response to cocaine. Cocaine users with withdrawal symptoms (N = 34), compared to those without (N = 10), had enhanced subjective ratings of ‘high’ and ‘feel the effect of last dose’ in response to a single delivery of smoked cocaine. Change in heart rate, systolic and diastolic blood pressure in response to cocaine did not show significant group differences. These results suggest that the enhanced cocaine effects may contribute to the greater cocaine use in cocaine users with withdrawal symptoms.

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632 EVALUATION OF TREATMENT ON DEMAND IN SAN FRANCISCO: QUALITATIVE METHODS ILLUMINATE WAITING LIST DATA

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Purpose: One goal of implementing demand (TOD) in San Francisco is to improve access to treatment. As a measure of treatment access we examined monthly program-level reports of waiting lists for treatment admission. Method: Data were gathered from the 75 programs reporting in San Francisco 2 years before through 2 years after implementation of a TOD policy that increased treatment budgets by over 30%. We measured: (1) Number of patients waiting monthly and (2) time patients waited before entering treatment. Using a procedure augmenting linear regression with an autoregressive model to account for random error (accounting for autocorrelation of error), data were analyzed to detect changes in waiting lists associated with implementation of TOD. These quantitative data were supplemented by program perspectives, obtained from structured interviews with administrative staff in 13 programs that received allocations to implement TOD. Results: County-wide waiting lists averaged about 1000 applicants monthly; there was not a decrease in number of patients waiting or days waiting before entering treatment, but some treatment modalities experienced significant decreases. Administrative interviews revealed variability in program reporting methods, which illuminated the meaning of the observed data and will yield county-wide recommendations to improve data collection. Conclusions: Qualitative information can reveal variegations in the quantitative data that policy-makers depend upon to evaluate changes in policy.
633 Vasocostriction in the chick embryo milieu caused by cocaine is enhanced by pretreatment with salicylate

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There is interactive toxicity from a combination of NaSalicylate (NaSal) and cocaine (Coc) on incubation day 12 (E12) or E18. NSl, at nontoxic doses used for quantifying hydroxyl free radicals in hearts and brains of embryos caused hemorrhages and greatly reduced hatchability when combined with Coc (1,2). The diameters of membrane-bound blood vessels (BV) were measured after pretreatment with NSal (10 mg/kg egg), followed by infusion of Coc HCl (67.5 mg/kg egg) during 15 min. Baseline BV diameters (E15, N = 8 per group) were unaffected by NaSal (100 mg/kg egg). Coc caused significant vasocostriction after 15 min (i.e. after 67.5 mg/kg egg) and 5 min post-infusion. Vasocostriction was significant in the NaSal + Coc group vs the controls and the Coc only group within 5 min (i.e. after 22.5 Coc mg/kg egg). The data suggest NaSal enhances the distribution of Coc or interferes with the vasculature’s capacity to mount a compensatory vasodilatory response, perhaps via inhibition of prostaglandin synthesis. Experiments are underway to test these possibilities.

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634 Is the gender gap closing? Gender differences in substance use prevalence between white and lakota 7th grade students in South Dakota

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Despite evidence that American Indian youth tend to start using drugs at an earlier age compared to other ethnic groups, few studies have targeted samples of younger American Indian adolescents to closely examine substance abuse patterns and risk factors. Baseline data collected from students participating in a randomized field trial to evaluate the effectiveness of Project ALERT, a substance use prevention curriculum designed for middle-school students, provide a window into substance use behavior among Lakota (Sioux) girls and boys. The sample is comprised of White (N = 4289) and Lakota (N = 400) 7th grade students enrolled in 55 middle schools in South Dakota in 1997–1998. Preliminary results showed higher rates of use among Lakota youth compared to White youth, for cigarettes, alcohol, marijuana and inhalants. Lakota girls showed higher rates of past month tobacco use as compared with Lakota boys, White boys, and White girls (43.0, 30.2, 9.7, 8.9%, respectively); alcohol use (26.7, 19.6, 14.5, 11.1% respectively); marijuana use (17.6, 14.9, 2.6, 1.5 respectively); and inhalant use (15.0, 7.7, 6.9, 4.3% respectively). Additional analysis will be performed to identify risk factors for both White and Lakota boys and girls. The high rates of use among Lakota girls suggest that the period of risk for these girls may occur sooner than what is generally expected for American Indian girls.

635 Polydruk use and behavioral economics: methadone and Valium interactions

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Most methadone-maintained (MM) patients abuse benzodiazepines. Methadone and diazepam self-administration in MM patients who abused benzodiazepines was examined. Utilizing a unique human drug self-administration procedure this study examined the effect of increasing the price of methadone when diazepam was and was not concurrently available as well as increasing the price of diazepam when methadone was and was not available. Increasing price decreased methadone consumption. When diazepam was concurrently available the amount of methadone consumed at low prices was less than the amount consumed at the same prices when only methadone was available. At higher prices the amount of methadone consumed when diazepam was concurrently available was more than the amount of methadone consumed when methadone alone was available. Consumption of diazepam increased as the price of methadone increased and methadone consumption decreased. Diazepam functioned as an economic substitute. Behavioral economic analysis was used to characterize the methadone-valium interaction. Methadone consumption was less elastic when diazepam was concurrently available than when methadone alone was available. Implications of these findings are discussed.

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636 Cognitive effects of polysubstance abuse

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Cocaine and heroin are two very addictive drugs that cause serious health problems. There is extensive literature on cocaine and heroin co-dependence. In this present study, we compared cocaine abusers, cocaine and alcohol abusers, and polysubstance abusers with controls and heroin abusers to determine whether heroin use together with cocaine use, produced greater cognitive deficits. Neuropsychological tests were administered to 148 substance abusers and 53 controls. All of the subjects were matched for age, education, and intelligence. In this investigation, neuropsychological deficits were observed in attention, planning, mental flexibility, executive functioning, and psychomotor functioning. The present study suggests that moderate to heavy cocaine use alone or in combination with alcohol use or polysubstance use (cocaine, alcohol, and heroin) might cause neurocognitive deficits.

637 Suggestive evidence of an association between gabaa-gamma2 subunit gene and heroin dependence in a Chinese population


Previous case/control association studies have suggested that the GABAA-beta2, GABAA-alpha6, GABAA-alpha1 and GABAA-gamma2 subunit genes clustered on 5q33 are associated with the development of alcohol dependence. The current study aims to examine whether these subunit genes are associated with the development of heroin dependence. 193 unrelated Hong Kong Chinese heroin-dependent subjects (178 males, 15 females) satisfying the DSM-IV diagnostic criteria of opiate dependence and without a history of alcohol or other substance abuse were recruited. 202 healthy blood donors with no history of substance abuse were used as controls. Six single nucleotide polymorphisms (SNPs) across the four GABAA subunit genes clustered on 5q33 that were reported previously (Loh et al. 2000,
A project was designed to de
treated with a residential treatment facility especially designed for
women (N = 42) who had prior treatment, and
12 months later were examined to assess the relationship of prior
treatment episodes to client characteristics and outcomes. Clients with
prior treatment episodes were found to base their
employment problems, greater recent and lifetime drug use, greater
criminal involvement, more suicide attempts, more depression, and a
less stable living situation. However, there were few differences
between the two groups in terms of treatment outcomes at follow-
up. It is concluded that the number of prior treatment outcomes may
in fact reflect greater problem severity at admission, but that this may
not necessarily result in poorer treatment outcomes.

639 INNOVATIVE JOB PLACEMENT: ADAPTING THE INDIVIDUAL PLACEMENT AND SUPPORT (IPS) MODEL OF VOCATIONAL REHABILITATION TO METHADONE-MAINTENANCE CLIENTS

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The Individual Placement and Support (IPS) model of vocational rehabilitation (VR) was developed for and shown to be effective with seriously mentally ill patients. Unlike earlier ‘train-and-place’ approaches, the IPS model stresses a rapid job search for competitive employment and emphasizes intense, sustained counselor support to help patients find and keep jobs. A modified IPS model was developed for substance users (IPS-SU). An efficacy trial of the adapted IPS model is underway to compare its outcomes with those of standard VR for methadone maintenance patients. Unemployed patients currently abstinent from opiates and cocaine were eligible to participate in the study. Subjects voluntarily accepted random assignment to either the experimental (IPS-SU) or control (standard VR) condition, participated in a baseline interview covering work history, substance use and related topics, and agreed to remain in the study for 18 months and be re-interviewed every 6 months. Employment (e.g. hours worked, dollars earned) is the primary outcome measure. The 5-year clinical trial is being conducted at two methadone clinics in New York City operated by Greenwich House and a hospital-affiliated clinic Each site was assigned one IPS-SU vocational counselor, and had at least one standard VR counselor. The IPS-SU model will be described in detail and ten case vignettes will be presented as preliminary data-half with positive outcomes (e.g. the female patient who quit her cannabis habit almost as soon as she entered the IPS program, and who then promptly found a job) and half with negative outcomes (e.g. the male patient addicted to Xanax who ignored a job interview when a mental health clinic persuaded him to apply for disability). These early cases have suggested additional modifications to improve the model.

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640 A GENOME-WIDE SEARCH FOR QUANTITATIVE TRAIT LOCI INFLUENCING SUBSTANCE DEPENDENCE VULNERABILITY


Psychoactive substance dependence is a multifactorial, complex disorder, likely to be influenced by multiple genetic and environmental factors. We conducted a genome-wide scan for quantitative trait loci (QTL) that contribute to the risk for substance dependence in adolescence. Subjects were 180 patient probands (14–18 years of age) and 221 full-siblings (14–25 years of age). Substance dependence data were collected using structured psychiatric interviews. An index of substance dependence vulnerability was defined as the sum of DSM-IV dependence symptoms endorsed for tobacco, alcohol and eight categories of illicit substances, scaled by the number of substances used repeatedly. Scores were then standardized within gender and corrected for normative age effects using standard regression methods. DNA (extracted from buccal cells) was collected from all adolescent participants and their biological parents. All subjects were genotyped for 400 highly polymorphic micro-satellite markers (average inter-marker distance = 10 cm). Single-point and multipoint sibpair linkage analyses were conducted using a regression approach developed for selected samples. Results indicated suggestive linkage to a region near the telomere of chromosome 9 (LOD > 2.0 near marker D9S1826). Follow-up affected sib pair analyses at marker D9S1826 showed significant allele sharing (63%). Regions with LOD scores greater than 1.0 were detected on chromosome 13 and 17. These findings demonstrate the feasibility of detecting QTLs for substance dependence vulnerability. Funded in part by DA-12845, DA-11015, and DA-05131

641 PARENTAL MONITORING PREDICTS ABSTINENCE IN A CONTINUITY-MANAGEMENT TREATMENT OF ADOLESCENT MARIJUANA ABUSE

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Contingency-management (CM) interventions can enhance therapeutic outcomes across a wide range of adult substance abuse treatment populations. CM approaches have not yet been studied in adolescent marijuana-abusing populations. We are in the process of developing and testing a developmentally appropriate CM intervention for adolescent marijuana abusers. This intervention combines individual, cognitive behavioral counseling with two CM-based treatment components. An abstinence-based reinforcement program provides monetary-based vouchers contingent on drug-negative urine specimens. Second, a behavioral parent training program is used to teach parents CM skills that can increase drug abstinence and other prosocial behavior. Parents are taught to increase monitoring of their teen’s behavior and to provide more consistent consequences following drug use or abstinence and other related negative or positive behaviors. Pilot data from a four-session version of this intervention will be presented. About 28 adolescents who met criteria for marijuana abuse or dependence have participated to date. At intake, 86% provided a marijuana-positive urine specimen. About 75% completed treatment. At discharge, 50% provided a marijuana-negative urine specimen. We tested several predictors of 4-week outcome (positive vs. negative urine drug test for marijuana) in a logistic regression. Candidate predictors included parent and teen ratings of family functioning, parent ratings of monitoring their adolescent, and parent and teen ratings of internalizing and externalizing symptoms. Only parental monitoring was a significant predictor of marijuana use at outcome. Using intake monitoring scores alone, 80% were correctly classified as marijuana negative at outcome, and 90% were correctly classified as marijuana positive (Wald $X^2(1) = 5.50, P < 0.02$). Consistent with previous research on predictors and prevention of adolescent substance abuse, these findings highlight the importance of targeting parent behavior in the treatment of adolescent substance abuse.

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**642 Gender differences in drug use and drug problems among offenders**

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A growing body of research has focused attention on differences in substance use between men and women (i.e. Wallen, 1992; Westermeyer, and Boedicker, 2000). Specifically, there are differences in drugs of choice, age of drug use initiation, treatment barriers for drug use problems, and the health/mental health consequences of drug use. While the literature has explored gender differences of clients in treatment, literature focusing on gender differences among offenders is limited. The purpose of this presentation is to describe drug use, drug problems, and drug treatment utilization among male and female offenders. It was hypothesized that women would report increased severity of substance abuse problems and increased service utilization. Face–face interviews were completed with 350 Drug Court participants (249 males and 101 females). Analyses indicate that males were significantly younger than females at first alcohol use and multiple substance use. Compared to females, males reported increased use of alcohol and marijuana use 30 days before Drug Court, as well as significantly more years of regular use. In contrast, there were no significant differences in years of regular cocaine use and multiple substance use, or in the 30 days before Drug Court. Females were slightly more likely to report being extremely concerned by drug problems during the 30 days before Drug Court (33 vs. 24%). Females reported significantly more admissions to drug treatment (1.9 vs. 1.4), ever being admitted to a short-term inpatient program (56 vs. 40%), and a long-term residential program (14 vs. 5%). Findings suggest that women, as hypothesized, reported more substance abuse problems and more service utilization than men. Implications to reduce relapse will be discussed.

**643 Gender differences and risk factors for AOD disorders among California arreestees**

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Research has shown that both female and male arrestees have high rates of alcohol and drug (AOD) disorders, yet less is known about whether there are gender differences associated with risk factors that contribute to AOD disorders among arrestees. This study examined associations between: (1) family trauma (sexual, physical or emotional abuse, parental AOD disorders, incarceration), (2) partner factors (partner AOD disorders, incarceration) and (3) crime history (length of time offending, types of crimes committed) and severity of alcohol and drug use in male and female arrestees using data from the California Drug Use Forecasting Project (CAL-DUF). Between 1994–1996, structured interviews were conducted with 1321 males and 396 females in jails located in 13 counties throughout California. Urinalysis was also performed to validate self-reported drug use. 64.3% of males and 71.2% of females tested positive for one or more drugs. Separate logistic regression models were run to assess different predictors of AOD severity for males and females. Preliminary analyses suggest that there is a gender effect for familial abuse and addiction severity. For males who report prior abuse, crime is more closely associated with drug use severity, whereas for females who report prior abuse, mental health problems are more closely associated with drug use severity. Clinical and policy implications are discussed.

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**644 Attachment style as a mediator of treatment response in marijuana-dependent adults**

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Adult attachment style has been invoked as a partial explanation not only for social/relational functioning but also as potential contributor to other domains or areas of life functioning and adaptation, including healthcare utilization and compliance, treatment engagement, and occupational/academic functioning. Capacities for attachment formation should impact the degree to which an individual may be able to engage in and benefit from psychotherapies which rely on the establishment of a therapeutic bond for carrying out their work. A multi-site, Randomized Controlled Trial of treatment for marijuana was conducted with 450 adults evidencing chronic use and problems associated with marijuana. Participants were assessed on attachment style (categories included: secure, insecure-anxious/ambivalent, insecure-avoidant) which is believed to be a stable and persisting trait. In the larger study, treatment was found to be more effective than no treatment (waitlist control) in reducing number of days of marijuana use and associated problems. The relatively longer intervention (a 9-session integrative approach including MET, CBT, and case management components) was more effective than a 2-session MET-focused treatment. Attachment style was examined as a potential mediator of treatment efficacy. Adults with secure attachment styles benefited more in both treatment conditions than those who were insecure in their relational functioning. Secure adults who received the longer treatment benefited more than any of the other groups, suggesting attachment working models (internalized templates guiding relational functioning) may mediate the effects of treatment for substance abuse.
645 EFFECTS OF DEXTROMETHORPHAN ON DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS: INTERACTIONS WITH ACUTE AND CHRONIC MORPHINE TREATMENT

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Dextromethorphan (DM), the active ingredient in most over-the-counter cough medicines, has been shown to have a variety of effects related to its ability to interact with multiple receptor types. DM has little or no opioid activity, but binds to sigma receptors, the PCP site of the NMDA receptor, and acts as a non-competitive antagonist at the alpha3beta4 nicotinic receptor. DM has been reported to decrease the self-administration of many drugs of abuse, including morphine (MS), methamphetamine, cocaine, and nicotine. Thus, DM may be useful in treating a variety of forms of drug abuse. The mesolimbic pathway is often thought of as the ‘reward pathway’ and most drugs of abuse increase extracellular levels of dopamine (DA) in the nucleus accumbens (NAC). Thus, the effects of DM on DA release in the NAC of naïve rats and of rats treated acutely and chronically with MS were studied using in vivo microdialysis. Female Sprague–Dawley rats, weighing approximately 240 g, were surgically implanted with guide cannulae in the shell of the NAC, and microdialysis was conducted 3–10 days later. Acute MS (20 mg/kg, iP) treatment increased the levels of DA in the NAC to approximately 175% of basal levels. Chronic MS (20 mg/kg, iP; twice daily for 5 days) increased DA release by the NAC to 250% of basal levels. Acute treatment of DM (20 or 30 mg/kg, SC) alone did not alter NAC DA. Pretreatment with DM (20 mg/kg, SC, 20 min prior) did not alter the effects of either acute or chronic MS on NAC DA. The ability of DM to decrease self-administration of abused drugs, but to not alter the levels of DA in the NAC, either alone or following acute or chronic MS administration, suggests that the mechanism mediating the effects of DM on drug self-administration is not via the dopaminergic mesolimbic pathway. Further research is necessary to evaluate the involvement of other pathways mediating reward, especially those having high densities of nicotinic alpha3beta4 receptors (e.g. the habenulointerpeduncular pathway).

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646 DELETION OF THE GluR1 SUBUNIT OF AMPA RECEPTORS FAILS TO BLOCK BEHAVIOURAL SENSITIZATION TO COCAINE, BUT BLOCKS CONDITIONED PLACE PREFERENCE

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Behavioural sensitisation to cocaine is influenced by the formation of associations between the unconditioned drug stimulus and environmental conditioned stimuli. Behavioural sensitisation, and conditioned events have been associated with adaptations in glutamatergic systems leading to facilitation of excitatory transmission mediated by AMPA receptors. GluR1 knockout (KO) mice were generated and backcrossed to a C57Bl/6J strain. For the current experiments, heterozygous pairs were mated, and homozygous KO and wildtype (WT) offspring identified by PCR. KO mice showed heightened activity, which only partly attenuated following extensive habituation. Cocaine (10 mg/kg, i.p.) or saline vehicle was administered to adult offspring of each genotype at 48h intervals, before placing them in locomotor runways for six trials. Although KOs showed heightened activity, there was no evidence that the stimulant effect of cocaine was altered in these mice. When saline was injected on trial seven, mice previously treated with cocaine showed heightened activity relative to mice previously treated with saline, when tested in the locomotor runways, but not in an alternative apparatus, suggesting the locomotor runways had acquired conditioned activating properties. GluR1 KO mice also showed this conditioned behaviour. Thus GluR1 subunits of the AMPA receptor do not appear to be essential for cocaine behavioural sensitisation, or conditioned activity. In place preference experiments, food restricted mice were conditioned by placing them in one outer compartment of a three compartment apparatus, and given either food (Noyes pellets) or nothing: compartments were counterbalanced. WT, but not GluR1 KO mice showed a preference for the compartment paired with food when subsequently given the opportunity to explore the apparatus freely, suggesting that the GluR1 subunit plays a role in this form of conditioning. GluR1 KO mice differentiate between different forms of conditioning relevant to drug abuse.

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647 CTAP AND NALTREXONE ANTAGONISM OF ETORPHINE ADMINISTERED PERIPHERALLY AND CENTRALLY

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Etorphine is a potent, lipophilic, thebaine-oripavine derivative with high affinity for μ, κ and δ opioid receptors and unusual properties in electrophysiological studies. In the present series of experiments, the role of etorphine route of administration was examined and compared to morphine in the rat tail-withdrawal assay. In addition, the nonselective opioid antagonist, naltrexone, and the selective mu opioid antagonist, CTAP [D-Phe-Cys-Tyr-d-Trp-Lys-Thr-Pen-Thr-NH2], were compared for their ability to block the antinociceptive effects of etorphine. Male, Sprague–Dawley rats (N = 72) were loosely restrained and the latency for tail withdrawal from 55 °C water was measured. A multiple-trial, cumulative-dosing procedure was used. Etorphine (0.0003–0.0032 mg/kg; 0.01 – 1.0 μg) and morphine (1.0–10 mg/kg; 1.0–32 μg) produced full antinociceptive effects whether administered by the s.c. or i.c.v. routes of administration although morphine was significantly more potent by the i.c.v. route of administration as opposed to the s.c. route of administration. Naltrexone (0.032–0.32 mg/kg), administered either s.c. or i.c.v., was approximately equipotent as an antagonist of the antinociceptive effect of either s.c. or i.c.v. etorphine as revealed by apparent pA2 analyses. CTAP (0.1–1.0 μg) was more potent as an antagonist of etorphine i.c.v. than naltrexone administered either s.c. or i.c.v. All slopes of the Schild regressions included unity in these analyses. These data suggest that etorphine, whether administered centrally or peripherally, produces antinociceptive effects through the mu opioid receptor. Furthermore, CTAP is a potent mu opioid antagonist of etorphine in the rat wram-water tail-withdrawal procedure.

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648 CLONING OF AN μ OPIOID-LIKE RECEPTOR IN AN AMPHIBIAN, RANA PIPINNS

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Opioid receptors are integral membrane proteins found on neurons that bind morphine and other opioid analgesics. This drug-or ligand binding is the initial step in activating the receptor. The ligand induces conformational change and activates the receptor. In humans and other mammals, there are three distinct types of opioid receptors from three distinct genes. These receptors are known as mu, kappa, and delta opioid receptors. While most clinical opioids act at mu opioid receptors, there are selective opioid agonists and antagonists for each
type of mammalian opioid receptor. However, it is not known what specific sequences or domains of opioid receptors determine the type selectivity of opioid agents. Understanding the differences in the primary sequences of the three opioid receptor proteins and how those differences determine the structure-activity of the mu, kappa, and delta opioids is essential for designing better analgesics. The present studies took a comparative approach to understanding the mechanisms of opioid receptor selectivity and opioid analgesia. To date, the type of opioid receptor mediating analgesia in non-mammalian species is not known. Much data exists on the analgesic effects of μ, κ, and δ opioids and on the radioligand binding of selective opioids in an amphibian model. The present studies complement previous data by cloning and sequencing Rana pipiens opioid-like receptors; expressing the opioid-like receptors in cell lines, and performing receptor antisense experiments in whole animals. Additionally, the use of an earlier-evolved vertebrate model provides an opportunity for examining the molecular evolution of mu, kappa, and delta opioid receptor types. Using a PCR-based strategy and degenerate primers based on mammalian opioid receptors, we have cloned the complete coding sequence of a mu opioid-like receptor, termed RPMOR. The RPMOR shows 75–85% homology to existing mu opioid receptors. A phylogenetic analysis using CLUSTAL-W and MEGAlign programs produced a nearest-neighbor dendrogram consistent with RPMOR arising from common ancestors of non-mammalian species.

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649 MK-801 AND THE AVERSIVE PROPERTIES OF CHRONIC MORPHINE

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With chronic opioid administration, it has been reported that the rewarding effects of the drug increase (i.e. sensitization) and its aversive effects decrease (i.e. tolerance), properties that are known to affect a drug’s acceptability and use. Consequently, abuse potential increases with repeated drug exposure. Although the prototypical non-competitive NMDA receptor antagonist MK-801 is reported to block the development of tolerance to morphine-induced antinociception and locomotion, reports examining the effects of MK-801 on the affective properties of morphine are few in number and limited to acute preparations. The goal of the present research was to determine if MK-801 can block tolerance to morphine’s aversive effects. To that end, the effects of MK-801 on tolerance to the aversive effects of morphine following repeated morphine exposure were examined within a chronic preexposure preparation of the conditioned taste aversion design. Following habituation to water deprivation, male Spargue-Dawley rats were preexposed to 5 mg/kg morphine, 0.10 mg/kg MK-801 (a dose that does not produce aversions, but does inhibit tolerance to morphine analgesia) or a combination of morphine and MK-801 every fourth day for a total of five drug exposures. Following preexposure, all subjects were given 20-min access to a novel saccharin solution and given an intraperitoneal injection of 10 mg/kg morphine or distilled water (for a total of five conditioning trials). All subjects injected with vehicle during conditioning drank saccharin at high levels, independent of the drug given during preexposure. As expected, vehicle-preexposed, conditioned subjects acquired robust aversions, while morphine-preexposed, conditioned animals displayed attenuated aversions to morphine, indicative of tolerance to morphine’s aversive effects. Animals preexposed to the combination of MK-801 and morphine acquired robust aversions, similar to those in vehicle-preexposed subjects, i.e. MK-801 had no effect on morphine tolerance within this preparation. These data suggest that at these doses, MK-801 does not block tolerance to the aversive effects of chronic morphine.

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650 AMERICAN INDIAN YOUTH’S ADDICTIONS ISSUES AND NATURAL HELPING NETWORKS


American Indian youth must access services within a context of high need, low service availability, and convoluted financing. We examine the addictions services of 403 American Indian youth, using data from the Diagnostic Interview Schedule, the WHO-DAS, and the Service Assessment for Children and Adolescents (SACA). 79% of the youth had mental health or addiction problems: 53% had symptoms of alcohol or drug addiction, 27% met criteria for drug abuse/dependence, and 13% for alcohol abuse/dependence. Only 13% with addictions symptoms had an addiction or psychiatric specialist helper. One out of four youth used configurations with informal adults or peers; one in eight with nonspecialist professionals; and 1 in 20 with specialists or traditional healers. Youth who met criteria for alcohol dependence or abuse were more likely to use only the configurations with specialist or nonspecialist professionals. Youth who met criteria for drug abuse and dependence were more likely to use configurations with informal adults (48 vs. 62%), and specialists (5 vs. 19%). Youth who used nonspecialist professionals had higher functional impairment scores (19 vs. 13), and more addictions symptoms (39 vs. 23). Youths who used specialists had more symptoms (33 vs. 16), but not more impairment. Youth who used informal adults, peers or traditional healers had neither more impairment nor symptoms, but those who used traditional healers or informal adults had higher ethnic identity (16 vs. 9, and 11 vs. 9). Knowing the complex natural service configurations can direct funding and policies.

651 TYPOLOGIES OF ADOLESCENT DRUG ABUSERS SEEKING TREATMENT

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Relative to the adult addictions literature, there is a paucity of research examining adolescent substance abuse treatment outcome (Williams et al., 2000; Winters, 1999). Kazdin (2001) recently observed that one of the key questions that needs to be addressed if the field is to expand meaningfully beyond its current boundaries is to elucidate client characteristics that mediate or moderate treatment outcomes for drug-abusing youth. Out of the many possible client characteristics that might be examined as outcome predictors, a focus on personality dimensions related to externalizing and internalizing traits is supported on empirical and clinical grounds. The paper will address the validity of a typology for adolescent drug abusers based on data from our NIDA-funded treatment outcome and long-term functioning research project of 245 youth. Each adolescent participant sought treatment for a substance use disorder at a local treatment facility. The client descriptor data identified three groups that accounted for nearly 90% of the sample: internalizers, externalizers, and combined internalizers and externalizers. Treatment outcome was defined in several ways, including treatment completion status, drug use at 3- and 6-months post-treatment, and psychosocial functioning at 3- and 6-months post-treatment. The findings indicate that the internalizers had consistently better outcomes than the other two groups on the outcome measures. Additional analyses indicated that the former group participated more in aftercare and reported less problems with the law at intake and at follow-up. Treatment implications of the findings will be discussed.
The ability of the opioid antagonist naloxone (NLX) to precipitate abstinence symptoms in opioid-dependent patients is well known. However, no studies have been reported in humans demonstrating a quantitative, linear relationship between methadone dose and severity of NLX-precipitated withdrawal using low antagonist doses. The purpose of this study was to develop a technique that causes minimal discomfort to the research participant but enables quantitative assessment of the degree of physiological dependence to be used as possible predictor of outcome in future clinical studies. Male and female volunteers between ages 20 and 50 were recruited from clinically stable (at least 2 weeks on current methadone [METH] dose) and abstinent from street drugs) patients in our METH clinic and research volunteers on METH from other protocols. Women had negative pregnancy tests before participating. Volunteers with active psychiatric disorders (by DSM IV) other than opioid or nicotine dependence or with significant medical disorders or taking prescribed medication other than METH were excluded. A small fixed dose of NLX (0.1 mg, i.m.) or saline placebo (PLA, i.m.) was administered on two challenge days under double blind, counterbalanced conditions separated by at least 1 day. Subjects were challenged at near trough METH levels (20 h after last dose) at the same time every morning (9 AM) and were excluded from testing that day if urine toxicology was positive for substances other than METH. Subjects were given their daily METH at the end of the challenge. Established scales were used for assessing the magnitude of subjective and observer rated withdrawal responses. Physiological measures and pupil diameter were also determined. This is an interim analysis of seven subjects (five men and two women), with METH dose ranging from 30 to 95 mg. Correlation coefficients were calculated for peak difference scores (NLX − PLA) and METH dose for antagonist symptoms, observer ratings, pupil diameter difference and heroin craving. Results so far were statistically significant only for antagonist symptoms (r = 0.76, F = 7.13, P < 0.04). These preliminary results suggest that it is feasible to give 0.1 mg NLX i.m. to patients maintained on a range of METH doses and that withdrawal symptoms are correlated with dose.

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**653 EFFECTS OF GONADAL STEROID HORMONES ON μ, κ AND δ OPIOID ANTAGONICITY**

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Sex differences in opioid antinociception have been described in humans and rodents. This study was designed to examine the role of gonadal hormones in basal nociception and buprenorphine, U50,488 and SNC 80 antinociception in adult Sprague–Dawley rats. About 81 male and 168 female rats were gonadectomized (GDX) or sham-gonadectomized (sham). In GDX male rats, Silastic capsules containing testosterone (T) or nothing (0) were implanted s.c. immediately after surgery. GDX female rats received estradiol (E2)-filled or empty (0) capsules immediately after surgery, and vehicle (V) or progesterone (P) injections at 4-day intervals. Basal nociception and opioid antinociception were tested 28 days after surgery on 50 °C hotplate (HP) and tail withdrawal (TW) assays. Estrous cycle effects on basal nociception and opioid antinociception were assessed by testing sham females in diestrus I, estrus or proestrus. There were no significant differences in baseline latencies among the male groups on the HP or TW assays. Among the females, GDX + E2 and GDX + E2 + P females had significantly higher HP baseline latencies than GDX + 0 females. On the TW assay, diestrus I, GDX + E2 and GDX + E2 + P females had significantly higher baseline latencies than GDX + 0 females. The effects of gonadal hormones on opioid antinociception varied across the different drugs and assays. On the HP assay, U50,488 was more potent in sham and GDX + T males than in GDX + 0 males. U50,488 was more potent in diestrus and estrus females than in proestrus females, and more potent in GDX + E2 and GDX + E2 + P females than in GDX + 0 females. In contrast, on the TW assay, the efficacy of U50, 488 was significantly decreased in GDX + P females relative to other GDX females. The effects of gonadal hormones on buprenorphine and SNC 80 antinociception were not significant. These results suggest that gonadal hormones modulate thermal pain thresholds in female but not male rats. In addition, gonadal hormones appear to modulate kappa opioid antinociception in rats of both sexes.

**654 ADOLESCENT SUBSTANCE USE ASSESSMENT: CONCORDANCE BETWEEN QUESTIONNAIRE AND INTERVIEW FORMATS**

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This presentation focuses on evaluating the agreement between adolescent self-report of substance use frequencies obtained from questionnaire versus interview formats. A sample of 135 adolescents (101 males, 34 females), aged 12 to 19 (mean = 15.74, S.D. = 1.17), predominantly white (83%), completed a 4-h assessment to ascertain chemical dependency status as part of an adolescent treatment outcome study (Latimer et al., in press). A urine sample was collected to validate self-report of recent substance use. The battery included instruments to measure substance use frequency in both questionnaire and interview formats. The primary substance use questionnaire utilized during the assessment was the Personal Experience Inventory (PEI) for adolescents. Considerable psychometric data is available on the PEI that supports its reliability and validity when used with both school-based and clinical samples (Winters and Henley, 1988). The interview was developed based on the Adolescent Diagnostic Interview (Winters and Henly, 1989) and was designed to assess the frequency, quantity, and duration of substance use. Correlations between adolescent self-report of alcohol (r = 0.76) and marijuana (r = 0.80) use frequencies for the 3-months preceding the baseline assessment were strong suggesting good agreement between questionnaire and interview formats. However, initial analyses also suggest a trend where adolescents were more likely to report greater use frequencies for alcohol and marijuana during the face–face interview when compared to the questionnaire format. The significance of the findings to the evaluation of treatment outcome studies will be discussed.

**655 SEVERE PERSONALITY DISORDERS: IMPACT OF SUBSTANCE DEPENDENCE IN HIV+ WOMEN**

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There is a dearth of literature on drug-dependent women living with HIV, particularly with respect to co-occurring psychiatric disorders. As the proportion of HIV patients is increasingly female, it is important to understand how substance-dependence and psychiatric problems may affect the healthcare needs of these women. The current study sample consisted of 74 HIV + women seeking ambulatory psychiatric care in an HIV-mental health clinic. About 28% were substance-dependent based on the UM-CIDI (20% drug, 8% both EtOH and drug, 0% EtOH only). The majority were African–American (85%), unmarried (61%), and unemployed (76%). In
addition, 43% were single mothers. The average participant earned less than $10,000 per year and had less than a high school education. In terms of health status, the mean T-cell count was 347.71 (S.D. = 341.38). (Healthy T-cell counts range from 1000–1500, and counts below 200 are considered to be AIDS-defining.) Key findings of the study were: (1) almost 30% of the women were substance-dependent, (2) none were alcohol-dependent only, and (3) substance-dependence status was significantly related to Axis II but not Axis I disorders. 

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656 INDIVIDUAL DIFFERENCES IN ALCOHOL CHOICE AND AMPHETAMINE EFFECTS IN HUMANS

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Individuals differ in their responses to the effects of commonly abused drugs. The purpose of this experiment was to determine if light (N = 8) and moderate (N = 8) drinkers responded differentially to the effects of ethanol and d-amphetamine. In the first phase of this experiment, volunteers sampled one dose each of 0.5 mg/kg ethanol and placebo. The order of administration was randomized across volunteers. Following the sampling sessions, volunteers completed three sessions in which they chose either ethanol or placebo. In the second phase, volunteers received 0, 5, 10, and 15 mg t-amphetamine. Each dose was administered twice. Following drug administration in both phases, volunteers completed a battery of physiological, subject-rated, and performance measures periodically for 5 h. Ethanol produced prototypical effects (e.g. increased ratings on the Alcohol Sensation Scale). Ethanol was chosen over placebo infrequently. Light and moderate drinkers did not differ in terms of the self-reported or reinforcing effects of ethanol. d-Amphetamine produced prototypical stimulant-like effects (e.g. dose-dependent increases in ratings of Rush and High). Moderate drinkers reported significantly greater drug effects than light drinkers. These results suggest that light and moderate drinkers do not differ in their sensitivity to ethanol which is concordant with previous studies. By contrast, moderate drinkers may be more vulnerable to the behavioral effects of d-amphetamine.

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657 PERSONALITY SUBTYPE AND OPPORTUNITY TO TRY CLUB DRUGS

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In this project, we seek to understand whether the personality facet openness to experience or sensation-seeking might promote opportu-
659 Predictors of treatment outcome in ambulatory cocaine-dependent patients

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Outcomes reported from cocaine dependence treatment research tend to be variable. Knowledge regarding individual differences among patients and their relation to treatment success is lacking. This study sought to identify baseline predictors of cocaine use across a 12-week outpatient, clinical trial for cocaine dependence. It was hypothesized that factors related to three assessment domains: (1) sociodemographic status (age, race, gender, education, employment, marital status); (2) substance use (previous treatment, inpatient/outpatient referral source, years of cocaine use, use in the last 30 days, cocaine craving, and alcohol dependence); and (3) psychosocial variables (self-efficacy, social support, depression, social functioning, and readiness to change) would predict cocaine use across treatment. Multivariate linear regression models for each domain were used to identify and examine potential predictors of outcome (percent cocaine-negative urine screens) for 165 treatment-seeking, cocaine-dependent patients. Results indicated that, in addition to treatment condition, significant predictors were found within each assessment domain, specifically race, education, use in the last 30 days, cocaine craving, inpatient/outpatient referral source, and self-efficacy. However, a final regression model using these six predictors found that only race and craving were predictive of cocaine use across treatment. African-Americans and those reporting higher cocaine craving at baseline used more cocaine across the 12-week clinical trial. Post-hoc analyses exploring racial differences are presented and treatment implications are discussed.

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660 Bioavailability of buprenorphine solution versus tablets during chronic dosing in opioid-dependent subjects

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Many clinical trials testing buprenorphine (B) for the treatment of opioid dependence have used a sublingual solution. Subsequent development has focused on B and buprenorphine/naloxone (B/N) tablets. The purpose of this study was to compare the relative bioavailability of daily sublingual 8 mg B solution, 8 mg B tablets, or 8/2 mg B/N tablets under chronic dosing conditions. Opioid dependent outpatient volunteers (n = 12; 9 males; average age 32.9 years) were twice maintained for 7-day intervals on each formulation. After 7 days stabilization on each, subjects had plasma samples collected before and at 0.5–6 h after the daily dose. Specimens were analyzed for B using LC-tandem MS. Results showed considerable variability between subjects in B blood levels for each formulation. The mean maximum B plasma concentrations (Cmax; ng/ml) for each formulation were: 3.11 (B solution); 2.08 (B tablets); and 2.65 (B/N tablets), with a significantly lower Cmax for the B tablet versus the other formulations (but no significant difference between solution and B/N tablets). Area under the curve analyses for the 6 h showed significant differences between all pairs of formulations (mg/ml/h): 9.44 (B solution); 6.33 (B tablets); and 8.01 (B/N tablets). While there is considerable variability between subjects in buprenorphine serum levels, these results suggest B/N may have better B bioavailability than B monotherapy tablets.

661 Hepatitis C (HCV) prevalence and provision of HCV services in a nationwide sample of methadone maintenance treatment programs

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This paper reports the results of a nationwide survey of a random sample of MMTPs (N = 159) in the United States, which showed that 48.4% of the programs had an HCV patient prevalence of 75% or greater. A logistic regression analysis revealed that MMTPs having a predominance of HCV+ patients (i.e. 75% or more) were those with a majority of drug injectors and a lower patient prevalence of HIV. Programs with a predominance of HCV+ patients were significantly more likely than programs with a lower proportion of HCV+ patients to educate all of their patients about HCV (77.9 and 63.4%, respectively), and most or all of their staff (83.1 and 64.6%, respectively). HCV antibody testing was more limited, however. Of the 119 programs (74.8%) that could provide an estimate of the percent of their patients tested for HCV antibodies while at their programs, 41 programs (34.5%) tested all of their patients. This was about twice as likely to be the case, however, among the MMTPs with a predominance of HCV+ patients (44.8%) than among the other MMTPs (21.2%). All but one program assisted HCV+ patients in some way to deal with their infection. MMTPs need to effectively focus the HCV services they provide according to their patients’ needs, which may be different from the focus of their HIV service provision.

662 Correlation of T2 deep frontal lesions with cocaine use and executive function


Hypothesis: Prior cocaine use or decreased performance on tests of executive function will be correlated with increased T2 deep white matter frontal lesions.

Methods: Of the 32 cocaine dependent (CD) subjects, 16 had deep frontal involvement. In addition to the demographic variables of age and gender, two domains of measures were used to predict presence or absence of deep frontal involvement: cocaine usage and performance on neuropsychological tests. There were four indices of cocaine usage: greater or less than $500/month; greater or less than $1500/month; and greater or less than $2500/month. There were four indices of performance on neuropsychological tests: Trails A, and Trails B. Separate logistic regression analyses were carried out for each domain. Results: The combination of Dollars/Week earning, time since last use, and Stroop was not statistically significant (P = 0.38). Trails A was of borderline significance (P = 0.08), and Trails B was not statistically significant (P = 0.6). Conclusion: In this sample of CD subjects, higher levels of cocaine use and poor performance on the Trails B task were
each predictive of the presence of T2 deep white matter frontal lesions. This suggests that cocaine use may be a causal factor in the development of deep white matter frontal lesions, which in turn may result in observable decreases in executive function.

**663 EFFECTS OF CANNABINOID PRETREATMENT ON AMPHETAMINE-INDUCED DOPAMINE LEVELS IN NUCLEUS ACCUMBENS AND BEHAVIOR**

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**BACKGROUND:** Cannabis use may lead to enhanced vulnerability to the addictive effects of other drugs and may thereby provide a ‘gateway’ leading users to even more highly addictive drugs such as amphetamine. In the present study, it was assessed whether subchronic pretreatment with the cannabinoid agonist WIN 55,212-2 (WIN) causes sensitization and/or cross-sensitization with amphetamine in terms of dopamine (DA) levels in nucleus accumbens and stereotypes and whether WIN, or the psychoactive constituent of cannabis δ9-tetrahydrocannabinol (THC), cause sensitization to amphetamine-induced locomotor activity. **METHODS:** Adolescent Sprague–Dawley rats (28 days old) were treated with WIN (1.25 mg/kg) once a day for 5 days. Following a 7-day drug-free period, an acute injection of amphetamine (0.5 mg/kg) or a challenge WIN (1.25 mg/kg) injection were given. DA levels in nucleus accumbens were analyzed using in vivo microdialysis in combination with high performance liquid chromatography with electrochemical detection and stereotypies were monitored. In the locomotor activity tests, the drug administration design was the same except that the rats were pretreated with three different doses of WIN (0.625, 1.25 and 2.5 mg/kg) or THC (0.75, 1.5 and 3.0 mg/kg). Locomotor activity was measured for 2 h after the amphetamine (0.5 mg/kg) challenge. **RESULTS:** Acute or subchronic WIN treatment did not increase DA levels in the nucleus accumbens. DA levels in the nucleus accumbens following amphetamine were not sensitized as a consequence of subchronic WIN pretreatment. However, WIN pretreatment did appear to affect the behavioral response to amphetamine, tending to enhance stereotypy and attenuate locomotor activity response. THC pretreatment also tended to attenuate the amphetamine-induced locomotor activity response. Taken together, the current data in adolescent animals do not support the gateway hypothesis since WIN pretreatment had no effect on amphetamine-induced DA eflux and pretreatment with WIN or THC had only subtle effects on the behavioral responses.

**664 AMERICAN INDIAN ADOLESCENTS, TRAUMA, AND HIV RISK**


There is little published research on HIV and addictions risk behaviors on American Indian (AI) adults, and none on adolescents. Adult AI use less condoms, more IV drugs, have higher rates of alcoholism, suicidality, domestic violence, and physical or sexual assault, all associated with their increased HIV risk behaviors. We examine the addictions services of 403 American Indian youth, using data from the Diagnostic Interview Schedule, and the Service Assessment for Children and Adolescents (SACA). The youth had high rates of all those adult AI predictors of HIV risk behavior: one in eight were alcohol dependent or abusing; 1 in 4 drug dependent or abusing (7% used IV drugs), experienced community violence; and one in five suicidal, experienced domestic violence, sexually abused or raped. As in the few adult AI studies, these problems were related to higher rates of HIV risk behaviors. If they were alcoholic or drug abusing or dependent, or suicidal they were twice as likely to have had sex, and to not use condoms or any birth control. If they experienced community violence, were beaten, or had any form of abuse they were also about twice as likely to have had sex, and to not use condoms or birth control. Talking with parents about HIV was associated with higher rates of condom use but not other risk behaviors. Classroom HIV education was unrelated to risk behaviors. Use of professionals (teachers, youth leaders, social workers, and physicians) for their addictions or social risk factors was associated with higher rates of condom use.

**665 USING ITEM-RESPONSE THEORY TO EXAMINE GAMBLING AFFINITY AS AN UNDERLYING VULNERABILITY ACROSS A CONTINUUM OF GAMBLING INVOLVEMENT**

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Although most current gambling assessment instruments are useful for the identification of gambling consequences and the sorting of individuals into pathological and nonpathological categories, these measures do not assess the attitudes and beliefs underlying gambling activity and therefore are less useful for assessing individual differences that precede the onset of gambling disorders. The Gambling Attitudes and Beliefs Scale (GABS: Breen and Zuckerman, 1999) was designed to assess a latent affinity for gambling ranging from non-problem through pathological levels of gambling involvement. Although scores on the GABS has been shown to be related several aspects of gambling problems (e.g. gambling frequency), the psychometrics of the measure, especially across the continuum of gambling has yet to be established. Using a sample of recreational gamblers (n = 861) and pathological gamblers entering treatment (n = 234), we provide evidence of the reliability and validity of the measure in both samples. Additionally, we utilize modern test theory techniques (e.g. item-response theory) to improve the measure by identifying biased items and isolating a subset of items that discriminated among levels of gambling affinity uniformly across these disparate samples.

**666 ENVIRONMENTAL FACTORS AND ADOLESCENT SUBSTANCE USE TREATMENT OUTCOMES**

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Background: Negative environmental factors are significantly associated with the progression of substance use to regular use in adolescents. The objectives of this study were to examine in adolescents receiving multi-modal residential treatment for substance use disorders (SUD) whether (a) environmental risk factors improve following residential treatment, (b) high risk environmental factors at intake are associated with post-treatment substance use severity, and (c) environmental risk factors are different between adolescents diagnosed with substance dependence versus abuse. Method: Subjects (n = 153) were adolescents in residential SUD treatment at Mountain Manor Treatment Center, Baltimore, Maryland. Treatment focused on interventions to improve home and peer environments, and school performance, in addition to 12-step The Global Appraisal of Individual Need (GAIN), a structured interview instrument, on admission and at 6, and 12 months post-intake was administered to obtain data for the three environmental indices (family, academic/vocational and the social/peer), substance use severity, and for a diagnosis of substance dependence. Results: Scores on the social/peer environmental index were notably higher (severe range) than scores on the other two indices; scores on all three environment risk indices declined significantly from intake to 6, and 12 months post-intake (P < 0.05). Neither substance dependence diagnosis (n = 140), nor demographic
factors such as age, gender or race was significantly associated with any of the environmental indices. Although substance use severity declined significantly at 6, and 12 months following treatment ($P = 0.00$), post-treatment severity of use was not significantly different for those with high or low (pre-treatment) environmental indices. (3) Conclusions: It is unusual that environmental factors are examined pre- and post-SUD treatment. Findings show that negative environmental factors improve along with reduction in substance use following treatment. This warrants future studies to determine the mechanisms of change and to establish a causal relationship between multimodal treatment interventions for substance abuse among adolescents and environmental factor and substance use outcomes.

667  EFFECTS OF DETOXIFICATION MODIFICATIONS TO RETENTION IN BEHAVIORAL NALTREXONE THERAPY

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Methods for rapid transition from heroin to naltrexone with buprenorphine and clonidine can precipitate substantial withdrawal symptoms, contributing to dropout. About 20 subjects seeking treatment for heroin dependence in a 24-week behavioral naltrexone treatment program were compared on withdrawal severity and outcome measures prior to, and after, revisions intended to improve prognosis and reduce withdrawal severity were implemented in the inpatient opioid detoxification. Revisions included: addition of standing doses to prn regimen of clonazepam and clonidine, flexibility in buprenorphine dosage and schedule, use of a greater variety of ancillary medications, increased flexibility in length of detoxification (more days between last dose of buprenorphine and first naltrexone dose). Ten patients entering detox, prior to these revisions and ten patients participating in the revised detox, were compared along several parameters measuring difficulty of detoxification. Mean SOWS scores during detoxification for Group 1 were 53.8 and for Group 2 were 38.1 ($t$ (18) = 2.01; $P = 0.075$). Mean total frequency of prn medication doses (clonazepam, clonidine, toradol, compazine, trazodone) required for Group one was 34.22 (S.D. 20.5) and for Group 2 was 16.22 (S.D. 13.35) ($t$ (16) = 2.21; $P = 0.04$). Percentage of premature discharges was higher for Group 2 (50%) than for Group one (0%) ($x^2$ = 21.32; $P < 0.01$). Post-detoxification outcome variables examined included mean Week 1 Ham-21 scores for Group 1 (15.00, S.D.3.91) and Group 2 (12.00, S.D.2.21; $P = 0.04$). Mean length of retention in treatment was 16.20 weeks for Group 1 and 4.11 weeks for Group 2 ($t$ (17) = 3.18; $P = 0.005$). These findings indicate that while the revisions implemented were associated with greater comfort during detoxification, these improvements did not lead to better retention during initial abstinence. Implications for inpatient opioid detoxification and naltrexone maintenance therapy will be considered.

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668  HEPATITIS C SEROPREVALENCE AND RISK BEHAVIORS AMONG DRUG-INVOLVED FEMALE SEX WORKERS IN MIAMI

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Hypothesis: Unprotected sex is a significant risk factor for Hepatitis C (HCV) infection among drug-involved female sex workers. Species: Human females. Number of Subjects: 300 Procedures: Participants are recruited from the streets of Miami by active sex workers trained in outreach techniques. Following informed consent, clients complete a baseline interview regarding risk behaviors, are urine tested for drug use, and participate in HIV/Hepatitis prevention education. Pre-test counseling and blood testing for hepatitis and HIV are then conducted. Test results, post-test counseling, and additional prevention education are provided 2 weeks later. Results: To date, the sample has a median age of 40 years, is 49% African-American, 43% white-Anglo, and 8% Latina; 81.1% used alcohol in the past 30 days, 56.8% used marijuana, 91.9% used crack-cocaine, and 13.5% used heroin. Drug use was confirmed by urine testing, and 35.1% of the participants reported a history of IDU. The participants had been sex workers for a mean of 18.1 years, with an average of 29.6 sex partners in the past month. Of those who results have been received, 41% tested HCV-positive and 17% tested HIV-positive. All of the women reporting a history of IDU tested positive for HCV, as did 23.1% of those who denied a history of IDU. Statistical Analysis: Descriptive statistics were compiled on demographic data, drug use and sexual behaviors of the clients. Pearson’s $x^2$ tests were used to examine relationships among categorical variables, and t-tests were used to examine continuous variables. Multi-variate logistic regression analyses will examine the relationship between HCV seropositivity and its predictors. Importance of Findings: Among persons with evidence of high-risk sexual practices who deny a history of IDU, HCV prevalence averages 6%. However, few studies have specifically targeted commercial sex workers for HCV testing. Rates of HCV infection are elevated in this sample (41% overall), and reach 23% among non-injecting women. This study suggests that HCV is sexually transmitted, and that HCV and HIV risk reduction programs for women sex workers are a priority.

669  ROLE OF GABAB RECEPTOR IN THE MAINTENANCE OF COCAINE-INDUCED REWARDING IN MICE

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Repeated exposure to drugs of abuse, including cocaine, has been shown to produce adaptive changes in the mesocorticolimbic neurons relevant to the rewarding effect in experimental animals. The present study was then designed to investigate the maintenance of the rewarding effect induced by cocaine in mice using the CPP paradigm. The cocaine-induced rewarding effects lasted for more than a week after the termination of the place conditioning session by cocaine in mice. These findings raise the possibility that the maintenance of cocaine-induced rewarding effect may reflect the craving for cocaine in mice. A GABAB receptor agonist baclofen produced a concentration-dependent G-protein activation in membranes of the limbic forebrain, lower midbrain and prefrontal cortex obtained from saline-conditioned mice using [35SGTPgammaS binding assay, whereas the stimulation of G-protein induced by baclofen was significantly decreased in these brain regions obtained from cocaine-conditioned mice. It is of interest to note that the maintenance of the cocaine-induced rewarding effect was inhibited by baclofen once a day for 6 consecutive days after every conditioning test. These findings suggest the possibility that the attenuation of GABAB receptor function caused by chronic treatment with cocaine may trigger to induce psychological dependence on cocaine. Furthermore, GABAB receptor agonists including baclofen may be useful for the treatment of cocaine addiction.

670  THE IMPACT OF DRUG AND ALCOHOL USE ON HEPATITIS C TREATMENT OUTCOMES

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Background: Although injection drug use accounts for the majority of cases of hepatitis C (HCV), little is known about how intervening drug and alcohol use impact upon HCV treatment outcomes. Current guidelines recommending 6 months of pre-treatment drug sobriety are based on medical opinion rather than clinical data. Methods: About 57
methadone maintenance patients were treated with interferon/ribavirin combination therapy, and intervening drug and alcohol use were assessed by monthly questionnaire. End-of-treatment response (ETR) was defined as undetectable HCV virus by PCR (< 550 IU/ml). Results: Patients using alcohol showed a small but not significantly reduced ETR (42% vs. 67%, P = 0.13). Patients with brief drug sobriety maintained treatment outcomes similar to those with lengthy sobriety (Fig. 1) (P = 0.15). Any drug use during treatment led to a mild, non-significant decrement in virologic outcome (45% vs 62%, P = 0.11). However, those who used drugs rarely or intermittently maintained a virologic response (Fig. 2), whereas those who used regularly showed no virologic suppression (P = 0.02). Conclusion: Although substance use during HCV treatment leads to reduced treatment responses, a significant proportion of patients still benefit. Although strategies that help patients maintain complete sobriety are important, emphasis should be placed on minimizing regular drug use rather than excluding patients with occasional drug use.

671 A GLUTAMERGIC BASIS FOR BLUNTED COCAINE CONDITIONED REWARD IN HOMER2 GENE KNOCK-OUT MICE

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Molecular candidates mediating drug-induced neuroadaptations and their behavioural manifestations are likely those regulating excitatory synaptic activity. We reported previously that mice homozygous for a deletion of the homer2 gene (homer2 KO) do not place condition to cocaine (COC) and display enhanced COC-induced motor sensitization. To determine whether the alterations in COC-induced behaviours were related to the dopamine (DA) and glutamate neurotransmission, wild type (WT) and homer2 KO mice were injected repeatedly with COC (8 × 15 mg/kg, IP) and in vivo microdialysis sessions were conducted on injection 1 of repeated treatment and then again on a test for sensitization after 3 weeks withdrawal. Consistent with previous observations that food reward is intact in homer2 KO mice, no genotypic differences in the basal levels of striatal DA were observed. Also, no genotypic differences were observed regarding the COC-induced increase in extracellular concentrations of DA in the striatum, indicating that the genotypic differences in COC-related behaviours are not related to differences in striatal DA transmission. In contrast to DA, basal glutamate levels were elevated in homo2 KO versus WT mice and, consistent with the data for COC place conditioning, the COC-induced increase in glutamate was completely absent in homo2 KO mice. Interestingly, a parallel experiment revealed that homer2 KO mice showed enhanced sensitivity to the behavioural-activating effects of MK-801 (0–1.0 mg/kg, SC). In combination, these data indicate that the constitutive expression of Homer2 protein regulates basal glutamate neurotransmission and NMDA receptor function. As NMDA receptor activation is required for the acquisition of COC place conditioning, it is suggested that the failure to observe COC conditioned reward in homo2 KO mice is related to an attenuated glutamatergic response to COC and likely, to reduced NMDA receptor stimulation.

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672 IMPLICATION OF RHO-ASSOCIATED PROTEIN KINASE (ROK) IN METHAMPHETAMINE-INDUCED DOPAMINE RELEASE

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It is widely recognized that either methamphetamine or morphine can enhance the release of dopamine at dopaminergic neuron terminals of mesolimbic system, which induces dopamine-related behaviors. The Rho family of small GTP-binding proteins, which includes Rho, Rac and Cdc42 subfamilies, modulates many functions such as the cell morphology, neuronal development, cell cycle and gene transcription. It has become apparent in recent studies that the reorganization of actin filaments plays a major role in the mechanisms of Ca2+/-dependent exocytosis at the synaptic nerve terminals. It has been also documented that Ca2+-dependent exocytosis is regulated by the Rho/ROCK-dependent pathway. The present study was then designed to investigate the role of ROCK in the expression of the methamphetamine- and morphine-induced dopamine release in the nucleus accumbens and dopamine-related behaviors in rats. Both the stimulation of dopamine release and the induction of dopamine-related behaviors by methamphetamine (1 mg/kg, s.c.) were significantly suppressed by pretreatment with an intra- nucleus accumbens injection of a selective Rho kinase inhibitor Y-27632. In contrast, the release of dopamine induced by morphine (10 mg/kg, s.c.) was not affected by microinjection of Y-27632 into the nucleus accumbens. These findings provide evidence that the activation of Rho/ROCK following methamphetamine treatment may be, at least in part, implicated in the release of dopamine and the induction of dopamine-related behaviors by methamphetamine. Futhermore, the present study suggests the differential mechanism underlying the methamphetamine- and morphine-induced elevations of the extracellular dopamine levels in the rat nucleus accumbens.

673 AN OVERVIEW OF SCHOOL AND COMMUNITY-BASED INDICATED PREVENTION PROGRAMS FOR ADOLESCENTS

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Comprehensive substance abuse indicated prevention programs targeting adolescents in the juvenile justice system may require assessment and intervention of learning needs, co-occurring mental health disorders and HIV-risk behaviors to be maximally effective. This comprehensive approach may also be critical in being able to effect change in their drug use behaviors. Although no controlled indicated drug abuse prevention programs for adjudicated adolescents in school- and community-based settings currently exists in the literature, indicated programs for youth who demonstrated multiple problem behaviors such as poor school achievement, substance abuse, depression, and suicidal ideation have been shown to be effective. Research suggests that intervention for this population should be based on a comprehensive theoretical framework grounded in a social network support perspective. This perspective emphasizes that behavior is a function of the individual within a network of social relationships. The review of research, drawing from work on drug involvement, truancy, and school failure, identified the school setting as the logical context for intervention with this population. The authors provide a research-driven model for indicated prevention programs for adjudicated youth that is school- and community-based; in addition to the theoretical components, this model includes sections on cost-effectiveness and the feasibility of interactive computer data entry by participants.

674 THE EEG OF COCAINE AND HEROIN ABUSERS

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EEG alterations in chronic cocaine abusers have been reported by a number of researchers. Less is known about the EEG of individuals abusing both cocaine and heroin. About 21 cocaine and heroin abusers

were tested after less than 24 h of abstinence. About 21 control subjects
were tested as comparison group. 3 min resting eyes closed EEG was
recorded from eight electrodes (F3, F5, P1, P3, O1, F4, C4, P1, and T2).
The artifactual EEG was converted to six frequency bands (delta, theta,
alpha and beta) using a fast Fourier Transform. Absolute power
was significantly lower ($P < 0.05$) for the cocaine and heroin abusers
than the control subjects for theta, alpha1 and beta1 bands. Relative power
in the cocaine and heroin abusers was significantly ($P < 0.05$) lower for
alpha and beta1 than in control subjects. These findings
suggest that prolonged use of cocaine and heroin produced EEG
deficits similar to those obtained in individuals who only abuse
cocaine.

**675 SIMULTANEOUS DETERMINATION OF BUPRENORPHINE AND NORBUPRENORPHINE IN HUMAN PLASMA BY LC/MS/MS**

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To date, there has been a paucity of reliable methods with an intact
product ion mass to quantitate buprenorphine (BN) and norbupre-
norphine (NBN) levels in biological fluids. We developed a sensitive and
highly specific method employing a liquid chromatography tandem
ion spray mass spectrometry (LC-TIS-MS-MS) for measuring buprenorphine and norbuprenorphine levels. This method
was fully validated for the simultaneous determination of BN and
NBN in human plasma. The detection was carried out with a MDS-
SCIEX-API-4000 triple-quadrupole mass spectrometer using turbo
spray ionization in the positive ion mode. Multiple reaction monitor-
ing mode was used to monitor the ion transitions (precursor Æ fragment ions), of m/z 468.4 Æ 396.4 for BN, m/z 414.4 Æ 187.2 for
NBN and m/z 472.2 Æ 400.3 for the internal standard (BNd4). Sample
preparation and cleanup procedures were performed using solid phase
extraction. Analyte separation was carried out by gradient RP-LC
using a Zorbax SB-C18 column (50 ¥ 4.6 mm i.d., 5 microns). The method showed excellent linearity and reproducibility in the range of
0.025–20.0 ng/ml ($r^2 = 0.999$) with a limit of quantitation of 0.025 ng/
ml for both analytes. Extraction recovery was 86% for BN and 101.1%
for NBN. The coefficients of variance (CV%) for the interday and
intraday precision and accuracy were within 8% for BN and NBN. No
discernable degradation was observed in the freeze-thaw cycle or
freezer storage (–20 °C) in short and long-term stability tests. The complete mass fragmentation patterns and structures with an intact
product ion for BN, NBN and BNd4 were addressed and confirmed
the sensitivity and specificity of the LC-TIS-MS-MS method. This procedure will be applied to bioequivalence, bioavailability and
pharmacokinet/pharmacodynamic studies of BN and NBN in hu-
mans.

**676 SUB-LINGUAL OPIOIDS TO ENHANCE PAIN RELIEF AND REDUCE THEIR ABUSE POTENTIAL**

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Opioid treatment of severe, intractable pain is emerging as acceptable
and necessary, but the increased use of opioids is accompanied by
potential for opioid diversion and abuse. Additionally, oral opioid
treatment is often impeded by malabsorption, side effects, and high cost.
To help deal with these problems sub-lingual dosages of methadone,
meperidine, fentanyl, and hydromorphone were formulated. Fruit
juice was used as the carrier, and the opioid formulation was delivered
in 1cc dosages by a dropper placed under the tongue. Fifty, severe,
intractable pain patients who were maintained on a long-acting opioid
have received one or more sub-lingual opioid formulations for
treatment of breakthrough pain. All subjects reported pain relief,
without sedation, with one or more of the formulations. Pain relief
occurred within 5 min and lasted 1–4 h. The required sub-lingual
dosage for pain relief was extremely low compared to the usual oral
dosage. Minimal, sub-lingual effective dosages have been: meperidine 4
mg; methadone 0.5 mg; hydromorphone 0.3 mg; and fentanyl 4 mg.
These preliminary results indicate that sub-lingual, liquid opioid
formulations may reduce abuse potential, enhance pain relief, and
reduce costs.

**677 EFFECTS OF CIGARETTE SMOKING ON ATTENTIONAL PROCESSES IN SCHIZOPHRENIA**

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Attentional deficits are well-known in patients with schizophrenia and
smoking may improve attentional processes. The purpose of this study
was to determine the effects of cigarette smoking and acute smoking
abstinence on measures of attention in patients with schizophrenia as
compared to controls subjects. Using an on-going study of acute
smoking abstinence and smoking reinstatement, we have studied the
effects of smoking on attention in schizophrenic and control smokers
using: (1) a computerized version of the Conner’s Continues Perform-
ance Test (CPT); (2) pre-pulse inhibition (PPI) of the acoustic startle
response, a measure of sensorimotor gating and attentional processing.
There were no significant differences between schizophrenic and
control smokers on daily cigarette consumption, expired breath carbon
monoxide levels, plasma cotinine and Fagerstrom dependence scores at
baseline assessment. Overnight smoking abstinence lead to undetect-
able plasma nicotine levels and an increase in tobacco withdrawal and
cravings; smoking reinstatement reduced tobacco craving and elevated
plasma nicotine levels. Acute smoking abstinence produced a deter-
rioration in CPT performance as assessed by an increase in reaction
time, omission errors and attentional variability, and a decrease in
CPT hit rate. The deficits in CPT performance in schizophrenic
patients appeared to be more robustly effected by smoking as
compared to controls. Smoking reinstatement reversed these absti-
nence-induced changes in CPT performance. PPI was deficient in
schizophrenics as compared to controls. In both patients and controls,
acute smoking abstinence significantly reduced PPI, and smoking
reinstatement reversed abstinence-induced decrements in sensorimotor
gating in both groups. Our preliminary data suggest that smoking can
improve attentional deficits in schizophrenic patients, and that reversal of
tobacco withdrawal-induced deficits in attentional function by
habitual smoking may be a factor contributing to the high rates of
cigarette smoking in patients with schizophrenia.

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**678 INFLUENCE OF GONADAL HORMONE DEPLETION ON THE ANTINOCEPTIVE EFFECTS OF OPIOIDS IN MALE AND FEMALE RATS**

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Sex differences in the antinociceptive effects of opioids have been
reported in a variety of nociceptive assays, and it has been postulated
that these differences are mediated by gonadal hormones. The present
study examined the influence of gonadal hormone depletion on opioid
antinociception in male and female rats. In a warm-water tail-
withdrawal procedure, the antinociceptive effects of the high-efficacy
mu opioids etorphine and morphine, the low-efficacy mu opioids
buprenorphine and dezocine, and the low-efficacy mixed-action
opioids butorphanol and nalbuphine, were examined in sham operated (intact) and gonadectomized rats of the F344 and Sprague Dawley (SD) strains. The opioids examined were generally more potent in producing an antinociceptive effect in intact males than intact females, with larger sex differences obtained with the less effective opioids. In F344 males, gonadectomy decreased the potency of morphine and etorphine, and decreased both the potency and maximal effectiveness of buprenorphine, dezocine, butorphanol, and nalbuphine. Similarly, in SD males gonadectomy decreased the potency of etorphine, buprenorphine, and butorphanol. In contrast, in F344 females gonadectomy increased the potency and maximal effectiveness of buprenorphine, butorphanol, and nalbuphine as well as the maximal effectiveness of dezocine. Gonadectomy did not, however, consistently alter the potency or effectiveness of the opioid in SD females. The present findings suggest that deleting gonadal hormones decreases antinociception in male rats and increases opioid antinociception in female rats. Additionally, utilization of less effective opioids may represent a sensitive pharmacological tool to study the mechanisms underlying sex differences in opioid antinociception.

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679  FACTORS AFFECTING THE IMPLEMENTATION OF RESEARCH IN CLINICAL SETTINGS: PERSPECTIVES OF TREATMENT PROVIDER STAFF

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Integrating research into practice requires a better understanding than currently exists of the factors that impede and support the implementation of research in clinical settings. The differing priorities, perspectives, and experiences of researchers, state administrators, and treatment provider staff, have the potential to create synergism as well as tension that can ultimately determine the quantity and the quality of the data collected. This qualitative study examines the implementation of an automated treatment outcome monitoring system (OMS, involving standardized assessments and follow-up interviews) during its pilot stage through the experiences and perceptions of the treatment provider staff involved. About 28 focus groups were conducted with 230 participants, (representing 13 counties and 43 provider sites) across the state, over a 6-month period. About 64% of the participants was female, 56% identified as White, 17% as African-American, 16% as Latino, 5% as Multi-racial, 3% as Native American, 2% as Asian/Pacific Islander, and 1% as other ethnicity/race. The focus group discussions lasted approximately 2 h, and were audiotaped and transcribed verbatim. The major findings emerging from the data include the factors that influence the implementation of research in clinical settings: (1) the treatment provider ethos; (2) the time-consuming nature of the OMS; (3) staff buy-in; (4) training; (5) the organization of staffing and staff responsibilities; (6) key people; (7) automation and computer issues; (8) regular and timely feedback; (9) use of standardized instruments and procedures; (10) tensions between research and practice; and (11) staff perceptions of benefits of the OMS. The focus group findings are useful in better understanding the barriers to conducting research in clinical settings and ways to avoid or overcome them.

681  MOTHERS’ PRENATAL AND CURRENT COCAINE USE, AND THEIR PARENTING OF CHILDREN AGE 9

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As part of ongoing research examining maternal prenatal cocaine use, data on current cocaine use, maternal psychopathology symptoms, environmental factors and parenting were gathered from two cohorts of children age 9. Data on prenatal cocaine exposure was obtained at delivery from maternal and infant hair samples, maternal urine metabolites and maternal self-report for the exposed cohort (n = 42). A contrast cohort (n = 39) born in the same hospitals and living in the same neighborhoods was recruited retrospectively. Mothers’ current cocaine use was assessed through hair assays taken at the time of delivery. Environmental risk was determined through maternal report of negative neighborhood events, stressful life events, and financial stress. Mothers also completed the Raising Children Checklist, which yields scores indicating endorsement of firm, harsh, and lax parenting behaviors. Independent samples t-tests were conducted to describe differences between the groups. Mothers of the exposed cohort scored significantly higher on a Milion Depression factor and Cluster C personality disorder factor than did contrast mothers. Additionally, mothers in the exposed cohort reported more environmental risk factors (negative neighborhood events and stressful life events) and endorsed more lax parenting. Hierarchical regressions were conducted to explore the relative contributions of prenatal cocaine exposure, maternal current cocaine use, maternal psychopathological symptoms (depression and Cluster C personality disorders), and environmental risk to lax parenting. Prenatal cocaine exposure did not relate to lax parenting. Mothers’ current cocaine use did predict more lax parenting, and predicted lax parenting more strongly than maternal psychopathology symptoms. However, environmental fac-
682 TOWARDS STABLE MORPHINAN DERIVATIVES OF NALTRINDOLE

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As part of our studies aimed at preparing analogs of naltrindole with increased delta opioid selectivity, we recently reported that morphinan-based 3-methoxy-4-hydroxy analogs possess very different SAR to the parent 4,5-epoxyindolomorphnans (J. Med. Chem. 1999, 42, 1673). Interestingly, one analog (AC673) was shown to be one of the most selective morphinan-based delta opioid ligands yet reported in vitro assays, whereas other analogs displayed much lower selectivity. To further investigate this intriguing class of ligands, novel ring opening methodology was developed (Tetrahedron, 2000, 56, 7399) in order to be able to prepare a range of diverse ligands. As 3-phenols tend to display higher affinity than 3-methyl ethers, key targets of the current research were the corresponding 3,4-dihydroxy and 3-hydroxy-4-methoxy derivatives. The 3,4-dihydroxy substituted analogs proved simple to prepare through our novel 4,5-epoxy ring opening methodology, but they rapidly oxidized in solution making pharmacological evaluation difficult. Preparation of the 3-hydroxy-4-methoxy analogs was envisioned by methylation of the 4-phenol of the 4-hydroxy-3-methoxy compounds, followed by selective O-demethylation with L-Selectride. However, attempted methylation under standard conditions proved troublesome, indicating that the 4-phenol in the indolomorphinans is quite different to the 4-phenol in morphinans without an edolology, but they rapidly oxidized in solution making pharmacological simple to prepare through our no v

683 SMOKING TOPOGRAPHY IN ADOLESCENT GIRLS SEEKING TREATMENT FOR TOBACCO ADDICTION

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The recent rise in smoking prevalence among teenage girls is of particular concern. Additionally, lower FTND scores among African Americans and other qualitative differences in nicotine dependence between African Americans (AA) and non-African Americans (non-AA) in both adults and teen smokers have been reported (Moolchan et al. 2000). These differences may be associated with differences in cigarette consumption, topography and/or cigarette brand. We examined smoking topography in 9 AA and 40 non-AA adolescent girls (mean age = 15.3 ± 1.3, mean FTND score = 7.3 ± 1.3) seeking treatment for tobacco addiction. 86% (n = 42) of girls smoked menthol cigarettes (100% of AA, 79% of non-AA). In a baseline session prior to treatment, participants completed one topography measure in which they smoked their usual brand of cigarette. We obtained topographical measures (number of puffs, puff interval, puff volume, puff velocity) and physiological measures (blood pressure, heart rate, carbon monoxide). AA girls took more puffs (P < 0.05), and had significantly shorter puff duration (P = 0.03) and shorter intervals between puffs (P = 0.01). There were no significant physiological differences observed between ethnic groups nor were there any differences in nicotine dependence as measured by FTND scores. While these data suggest potential differences in smoking topography in this small sample of AA and non-AA girls, replication is needed in larger studies that also include data with more variation in brand choice.

684 ADOLESCENTS WITH SUBSTANCE AND CONDUCT PROBLEMS: EXECUTIVE FUNCTIONS AND AGGRESSION

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Adolescents with substance use disorders (SUD) and conduct problems (CD) have high rates of aggression. History of substance use/abuse and higher rates of aggression have individually been associated with deficits in certain aspects of executive cognitive functioning (EF). This study examined aspects of EF and aggression in 22 adolescents in treatment for SUD and CD compared to 19 community controls. HYPOTHESES: We predicted that subjects in treatment would have higher aggression scores and lower EF scores than controls would. We also hypothesized that lower EF would be associated with higher aggression. METHOD: All subjects completed the Wechsler Abbreviated Intelligence Scale (WASI), Self-Ordered Pointing task, Bechara’s Gambling Task, Cognitive Bias Task, the Anger, Irritability, and Assault Questionnaire, and Youth Self Report (self-report version of the Child Behavior Checklist). Also, a Peak Aggression Rating based on self-report of the most aggressive behavior in the subject’s life was assigned. RESULTS: Subjects with SUD and CD obtained higher aggression scores than controls on all measures. With regard to EF, subjects in treatment made more errors on the Self-Ordered Pointing Task, a task of working memory, than controls did. No differences between the SUD group and the control group were found for the Bechara Gambling Task or for the total score on the Cognitive Bias Task. However, the SUD group’s response time on the Cognitive Bias Task was faster than the control group’s response time was. WASI IQ differences were also found between groups. When IQ was entered as a covariate, EF group differences were reduced and could only be considered trends. Pearson correlations between aggression measures and EF measures were generally not statistically significant. CONCLUSIONS: The hypothesis that subjects with SUD would be more aggressive was supported, and the hypothesis that subjects with SUD would have poorer EF was partly supported, but the hypothesis of significant associations between aggression and measures of EF was not supported.

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685 AFFECTIVE AND PHYSIOLOGICAL RESPONSES TO SMOKING CUES IN SMOKERS WITH SCHIZOPHRENIA

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Despite the high prevalence (60–80%) of cigarette smoking among people with schizophrenia, few treatments are available. Furthermore, little is known about environmental variables that alter cigarette smoking in this population. In non-schizophrenics, exposure to smoking cues under laboratory conditions increases smoking urges and negative affect, and alters heart rate and blood pressure. Furthermore, smoking cue reactvity prior to treatment prospectively predicts relapse to smoking, and reducing cue reactivity may enhance treatment outcomes. To our knowledge, this is the first study to assess smoking cue reactivity in smokers with schizophrenia. Smoking cue reactivity was assessed under two conditions: in a non-deprived state and after 2 h of smoking deprivation. Laboratory sessions consisted of a relaxation period, exposure to neutral cues (4 min), and two exposures to smoking cues (4 min each). At baseline and after exposure to neutral or smoking cues, participants reported levels of smoking urges, affect, and nicotine withdrawal symptoms, and were assessed for changes in heart rate and blood pressure. Psychiatric symptoms were assessed at baseline and after exposure to smoking cues. Results to date from 11 participants indicate that exposure to smoking cues increases smoking urges, negative affect, and nicotine withdrawal symptoms, and
decreases heart rate. The 2-h deprivation period increases smoking urges, nicotine withdrawal symptoms, negative affect and heart rate. Participants appear to be less sensitive to smoking cues after the deprivation period, perhaps because urges and nicotine withdrawal symptoms are substantially elevated at baseline. Psychiatric symptoms were not affected by cue exposure or the short deprivation period. These preliminary results suggest that smokers with schizophrenia respond to smoking-related cues with increases in smoking urges, withdrawal symptoms and negative affect. In turn, this reactivity may contribute to high rates of smoking in this population.

686 AN EXAMINATION OF ADOLESCENTS' REASONS FOR STARTING, QUITTING, AND CONTINUING TO USE DRUGS AND ALCOHOL FOLLOWING TREATMENT

Why do adolescents use drugs and alcohol? Research on the motives behind drug use have identified a variety of reasons for use – reasons that vary by drug, level of involvement with drugs, frequency of use, status as an abuser or user, severity of use-related problems, and demographics such as age, race, and gender. Reasons for quitting also vary along similar dimensions. This study examines the self-reported reasons behind the initiation, cessation, and/or continued use of substances among a sample of adolescents treated for their abuse or dependence on marijuana, alcohol, and other drugs. Adolescents’ reasons for starting, using, and quitting were collected at 30 months post-treatment (anticipated \( N = 595 \)) and categorized by dominant theme. Analysis of preliminary data reveals the most frequently mentioned reasons for initiation are ‘experimentation’ and ‘social conformity’; for quitting are ‘damage to body and mind’ and ‘getting in trouble’; and for continued use despite treatment are ‘relaxation’, ‘boredom’, and ‘enhancement’. Future analyses, including data collected at 3, 6, 12, and 30 months post-treatment, will examine the hypothesis that motives for initiation, use, and/or cessation are related to severity of use, use-related problems, and course of recovery. Findings are relevant to prevention and motivation-based treatments.

687 STUDIES ON THE OPIOID MECHANISM MODULATING IN MURINE MACROPHAGES
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We have shown that, whereas acute morphine inhibits phagocytosis in murine macrophages, chronic morphine results in a state of putative tolerance/dependence, where morphine withdrawal results in inhibition of phagocytosis. We now report that acute opioid studies, using receptor selective agonists and antagonists, show that both \( \mu \) and delta receptors are involved, but kappa receptors are not. The mechanism by which these agonists exert their effect is cooperative based on Hill coefficients of dose-response curves. In addition, observations using macrophages from \( \mu \) opioid receptor knockout mice indicate that, in the absence of \( \mu \) receptors, the effect of delta agonists is decreased in terms of potency and maximal effect. This suggests that \( \mu \) and delta receptors interact in macrophages, perhaps by allosteric or cross-talk mechanisms. In chronic exposure, we have found that tolerance develops before dependence, and that tolerant and dependent cells respond to morphine differently, suggesting different cellular mechanisms. RT-PCR reveals that chronic exposure to morphine also results in a decrease of \( \mu \) opioid receptor mRNA level, which may account in part for the decreased response of these cells to morphine. These results suggest that the opioid mechanism in macrophages resembles that in the nervous system in many respects.

688 PSYCHIATRIC COMORBIDITY IN DRUG USERS: CONCORDANCE BETWEEN DSM-IV DIAGNOSES OBTAINED BY PRISM, SCID AND LEAD PROCEDURE
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The identification of reliable and valid diagnosis of psychiatric comorbidity in substance abusers has long been problematic. In contrast to prior diagnostic systems, DSM-IV provides guidelines for distinguishing psychiatric symptoms in the ongoing substance use. Two interviews for psychiatric diagnosis based on DSM-IV criteria have been developed: PRISM and SCID-IV. The aim of present study was to assess the concordance between DSM-IV diagnosis of psychiatric comorbidity in drug abusers between PRISM (IV), SCID (IV) and a primary expert developing a LEAD procedure diagnosis (Longitudinal Evaluation performed by an Expert, employing All Data available). Subjects and method: 105 drug abusers, (69% males, mean age: 33.3 ± 7, years), were assessed, in a blind manner, by two independent interviewers, one with the Spanish version of SCID (IV), other with the Spanish version of PRISM (IV) and, by and expert psychiatrist developing a LEAD diagnoses. Kappa statistic was used to indicated the degree of agreement among three assessment methods. Results: in respect to current (last 12 months) psychiatric comorbidity, kappas found between LEAD and PRISM diagnosis were: 0.68 for Major Depression, 0.33 for Substance-Induced Depressive Disorder, 0.56 for Disthymia, 1 for Schizophrenia, 0.79 for Induced Psychosis, 0.79 for Panic Disorder, and 0.71 for Social Phobia. Between LEAD and SCID kappas found were: 0.28 for Major Depression, 0.29 for Substance-Induced Depression, 0.22 for Disthymia, 0.79 for Schizophrenia, 0.22 for Induced Psychosis, 0.71 for Panic Disorder, and 0.79 for Social Phobia. It was concluded that in current psychiatric comorbidity, the concordances among LEAD and PRISM were better than between LEAD and SCID for most of diagnosis.

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689 METHADONE MAINTENANCE TREATMENT AND DELEGATION OF PRACTICE TO GPs
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A follow-up retrospective study was carried out to investigate the predictive factors of non-compliance, range and severity of the complications expected, when outpatients were shared to GPs attendance. During the last 8 years, 1332 outpatients (3/4 males, 37 years old mean, 90% French) required more than once the serological 'scar' for B hepatitis or completed a full vaccination while another third actually showed positive HBS antibodies. The average dose of methadone was 73.17 mg. There was no dose difference when methadone was dispensed by GPs.
690  **NALTRINDOLE DERIVATIVES AS PET LIGANDS FOR THE DELTA OPIOID RECEPTOR**

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Delta opioid ligands are antinociceptive in hyperalgesic states, proconvulsant, effective in animal models of depression and the delta opioid system may be involved in dependence on cocaine, heroin and ethanol. The development of a delta selective ligand for Positron Emission Tomography (PET) scanning will provide a useful tool in understanding the role of delta opioid systems in normal and abnormal brain. Previously naltrindole derivatives have been employed as PET ligands but these exhibited relatively poor kinetics. This may be due to substitution on the indole nitrogen in these compounds. Consequently we have based our studies on substitution in other positions of the naltrindole nucleus. For example, the 7-methoxycarbonyl derivative of naltrindole had 100-fold selectivity for the delta receptor ($K_i = 0.29 + 0.03$ nM) with no significant agonist action in vitro or in vivo. In vivo regional brain distribution of its [11C] derivative in the mouse and the monkey (PET) showed greater retention of radioactivity in striatum and cortex relative to cerebellum.

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691  **AN AUTOMATED METHOD FOR MEASURING THE COCAINE PRIMING THRESHOLD**

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Administration of cocaine to rats trained to self-administer cocaine reinstates lever pressing behavior if cocaine level exceeds a certain minimal level, the cocaine priming threshold. We have developed a computerized method for measurement of the cocaine priming threshold. The hardware includes operant boxes equipped with two levers and signal light, syringe pump PHM-100. A PC equipped with an interface card can be connected by Smart Control Modules (Med-Associates, Inc., Albans, VT) with up to 12 operant boxes. Our program, developed over the last 3 years, written in Medstate Notation language (Med-Associates, Inc.) allows: (1) to determine when cue-induced lever pressing behavior has been reliably extinguished, (2) to give priming injections of cocaine with user-defined intervals, (3) to calculate the cocaine level in the body at every second of the session, (4) increase the dose of cocaine so that the peak level after each injection would be equal to preset values calculated according to a user-defined function (linear or exponential, for example), (5) to record every event (lever press, signal or injection) specifically coded, the cocaine levels and the time of all events, (6) to save the data in the ASCII file format, which is easily imported into any database, statistical or graphics program for further analyses. This flexible and comprehensive computerized system allows in real time the measurement of parameters fundamental to self-administration.

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692  **ETHNIC DIFFERENCES IN GLOBAL CEREBRAL BLOOD FLOW AND PATTERNS OF SUBSTANCE USE AMONG COCAINE ABUSERS**

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This study examines racial differences in cerebral blood flow (CBF) in 32 cocaine abusers and 20 normal control subjects. Global CBF was measured with 99m-Tc-HMPAO SPECT and analyzed with Statistical Parametric Mapping. Both African-American and white cocaine users demonstrate significantly more abnormalities in cerebral perfusion in comparison to control subjects (Mann–Whitney: hypoperfusion, $P = 0.002$; hyperperfusion, $P = 0.001$). However, the severity of hyperperfusion and hyperperfusion deficits is markedly different for African-Americans and whites. More hyperperfusion is exhibited by African-Americans ($P = 0.02$), while white participants demonstrate more areas of hypoperfusion. Among the control subjects, a similar pattern of racial differences in reductions in perfusion was noted, with white control subjects showing several times the amount of hypoperfusion than African–American controls. However, comparable amounts of hyperperfusion are observed in white and African–American controls. The finding of greater hyperperfusion deficits in African–American cocaine users may reflect racial differences in patterns of substance use. African–Americans reported smoking more cocaine and drinking more than twice the number of alcoholic beverages in the preceding month than whites. These results suggest that a combination of cocaine and significant alcohol abuse may be related to the severity of hyperperfusion. The relationship between alcohol/cocaine abuse and hyperperfusion appears to be more complex. The clinical significance of cerebral hyperperfusion/hypoperfusion and implications for cognitive functioning are discussed.

693  **A PARTNER’S DRUG-USING STATUS IMPACTS WOMEN’S DRUG TREATMENT OUTCOME**

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Introduction: The role sexual partners play in the treatment outcome of drug dependent pregnant women has received little scientific attention. The aims of the present study were (1) to examine the psychosocial characteristics of drug using and drug-free sexual partners of drug-dependent pregnant women and (2) to examine the impact of a partner’s drug using status in relation to the woman’s retention in a specialized drug treatment facility. Methods: A 25-item Relationship Survey was developed to assess various areas of psychosocial functioning. Women ($N = 189$) completed the questionnaire during an initial 7 day inpatient stay at the Center for Addiction and Pregnancy, and were categorized into two groups: those with drug-free ($n = 104$) or drug-using ($n = 85$) sexual partners. Results: Compared to drug-free partners, drug using partners were significantly older (33 years vs. 36 years; $P < 0.05$) with less education (11 vs. 12 years) ($P < 0.05$), and higher unemployment rates. On measures of legal involvement, drug-using partners were significantly more likely to currently be in jail, to have repeated arrests, and to be in need of legal assistance compared to drug-free partners. On relationship measures, drug-using partners had significantly more recent conflicts with their pregnant partners and were less likely to be supportive of her being enrolled in drug treatment relative to drug-free partners. Preliminary data from treatment retention suggest that women with drug-using partners are retained in treatment for a shorter time than women with drug-free partners. Final data will be presented in June. Conclusions: Drug-using partners have more severe psychosocial issues compared to drug-free partners. A partner’s drug-using status should be considered when treating pregnant drug dependent women.

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694  **DEEP VEIN THROMBOSIS AMONG INJECTING DRUG USERS: A COMMON COMPLICATION**

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Background: Very little is known about the severe medical complication of deep vein thrombosis (DVT) among injecting drug users. 

Objective: To focus on DVT that occurred in 19 patients out of 86 new patients, who had been referred to our MMT clinic between 1/12/00 and 31/12/01. Design: Prospective consecutive case series. Intervention and Measurements: Sonography to diagnose DVT, blood cultures to assay bacteremia, antibiotics and coumarin or low molecular weight heparin treatment, screening tests for thrombophilia and clinical assessment. Results: 18 IV current drug user patients (16 men and 2 women), mean age 23.5 (±5.2 S.D.), mean duration of injection 13.6 years (±6.1 S.D.) were studied. 89% were HCV positive (11% were HIV and HCV positive). They had 22 episodes of DVT, which were caused directly from injections of heroin or cocaine to the femoral or jugular veins. Bacteremia was evident in 73% of these DVT events. In contrast, the only one patient, (out of 44 new patients who were not current IV drug users, most probably), was found to have DVT due to major gynecological surgery. 12 patients were initially treated with coumarin, which was not effective due to poor compliance, and thus replaced with enoxaparin 1.5 mg/kg once or 1mg/kg twice daily, for at least 45 days, with appropriate antibiotics as needed. They did clinically well to this regimen with a good compliance, without side effects and without recurrent DVT events. Up to now, four patients were tested for thrombophilia and all were found to have hypercoaguable state (one patient had MTHFR C677T/DNA) heterozygote and elevated factor eight level, one patient homozygous for MTHFR and two patients with significantly elevated level of factor eight). Conclusion: Proximal DVT is a common complication among IV drug users, generally associated with bacteremia, and should be treated with low molecular weight heparin and appropriate antibiotics. Further studies in this new field including screening tests for thrombophilia are needed.

695 MOOD IMPAIRMENT IN MDMA USERS: A META-ANALYTIC REVIEW

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MDMA use is increasingly wide spread and clinical data suggest MDMA is neurotoxic to serotonergic (5-HT) neurons. Since 5-HT plays a central role in modulating mood it has been hypothesized that MDMA use may result in mood deficits. Although MDMA use has been associated with acute mood disturbance, little is known about persistent effects. Mixed findings suggest the need for a review of the extant literature. The present meta-analysis was undertaken to provide an objective quantitative review of the available literature and to provide preliminary data regarding the magnitude of the association between MDMA use and persistent mood effects. Nine studies were initially identified by an on-line literature search of PubMed and PsychInfo using the terms MDMA/Ecstasy, mood, and depression. Studies were included if: (1) they contained a statistical test of the association between MDMA and mood, (2) participants were abstinent for at least 1 week, (3) participants had used 50 MDMA pills. Meta-analytic results of the four included studies indicated persistent mood deficits in MDMA users that were of large effect size (Pearson’s r = 0.70, Cohen’s d = 3.38). These preliminary findings suggest MDMA users may be at risk for persistent mood disturbance, specifically in the area of depression. Future studies might examine other mood indices (i.e. anxiety) and the impact of potential moderating variables on effect sizes.

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696 THE SAFETY AND EFFICACY OF SUSTAINED COCAINE AGONIST EXPOSURES IN SUPPRESSING COCAINE CRAVING AND SELF-ADMINISTRATION IN HUMANS

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Previously we have shown that a 12 or 24-h cocaine infusion (0.25–0.5 mg/kg per h, total dose 6 mg/kg) suppresses cocaine craving and self-administration in humans. In this study we evaluated the safety and efficacy of a longer cocaine infusion. Eight cocaine-dependent volunteers were admitted to the GCRC for 17 days and underwent 2 double-blind, 3-day, 12-h cocaine (0.375 mg/kg per h) or placebo infusions. The days before and after infusions subjects could self-administer intravenous cocaine doses using a unique computer assisted paradigm (self-administered dose, 0.15 mg/kg; minimal interdose interval, 15 min; duration, 4 h for a total maximal cocaine dose of 2.4 mg/kg). Infusions were well tolerated and produced only small, clinically insignificant changes in heart rate and blood pressure. No subject required discontinuation for abnormal vital signs (HR > 100, SBP > 160, or DBP > 100 for more than 30 min) or subjective effects. The efficacy of sustained cocaine exposures in suppressing self-administration and craving or altering the pharmacologic response to cocaine will be determined after the study blind is broken (the last subject will complete all testing on January 26) and the data will be presented at the meeting.

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697 NEUROENDOCRINE RESPONSE TO DOPAMINERGIC AGENTS IN ADHD AND NICOTINE DEPENDENCE

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Objective: Growing body of literature indicates that the dopaminergic systems are involved in the pathophysiology of attention deficit hyperactivity disorder (ADHD) as well as nicotine dependence. However, there is a lack of research examining the dopaminergic systems in adolescents with ADHD, and nicotine dependence. We present preliminary results from a study examining the dopaminergic systems in adolescents with ADHD, and nicotine dependence. Methods: Thirteen participants (15–20 year) have completed the protocol to date. Neuroendocrine and behavioral response to the dopaminergic agents- methylphenidate (10 mg) and pramipexole (0.25 mg) were examined. Measures of these responses were spontaneous eye-blink rate, plasma prolactin (PRL), and growth hormone (GH). Additionally, participants completed a visual analog mood scale (VAMS). Results: No significant adverse events were reported after both methylphenidate and pramipexole administration. As expected with dopamine agonists, both methylphenidate and pramipexole administration resulted in increase in GH levels and decrease in PRL levels. Data on eye-blinks and VAMS will be presented. Conclusion: Adolescents tolerated the dopaminergic challenge well with no significant adverse events. Neurobiological studies of this kind can provide important information about the pathophysiology of ADHD and nicotine dependence in adolescents

698 DRUG USE RISK FACTORS AMONG WELFARE CLIENTS

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A representative sample of 511 applicants and recipients to California’s Temporary Assistance to Needy Families program were interviewed. Between November 2000 and June 2001, participants were
Circadian differences in cocaine-induced behavioral sensitization and arylalkylamine N-acetyltransferase

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Circadian rhythms might be involved in addictive behaviors. The pineal serotonin metabolite melatonin decreases cocaine sensitization in rats; mice naturally mutant for the critical melatonin-synthesizing enzyme, arylalkylamine N-acetyltransferase (AANAT), exhibit altered behaviors. We hypothesized that AANAT/melatonin system, which is up-regulated at night, affects cocaine sensitization in mice. Acute intraperitoneal cocaine treatment (10 and 20 mg/kg; n = 6) dose-dependently increased locomotor activity (P < 0.05, Duncan’s test) of both normal (C3H/HeJ) and AANAT mutant (C57BL/6J) mice. Locomotor stimulatory effect of single dose cocaine was similar during the day (low AANAT expression) and at night (high AANAT expression). On the other hand, repeated injections of cocaine during the day for 3 days resulted in behavioral sensitization in normal and AANAT mutant mice whereas treatment at night triggered sensitization in AANAT-deficient mice only (P < 0.05, Duncan’s test). For the first time, the present study demonstrates a circadian difference in the development of cocaine-induced behavioral sensitization during the day vs. at night in inbred mice, and provides new insight into possible mechanisms involved in addiction. Since AANAT-mutant mice showed cocaine-induced behavioral sensitization both during the day and at night, further studies are needed to elucidate the molecular mechanisms that link the AANAT system and the behavioral effects of drugs of abuse, such as cocaine.

Comparison of tobacco and marijuana withdrawal effects

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A review of tobacco and marijuana withdrawal studies indicates there is a considerable overlap of symptoms. We conducted cross-study comparisons to examine the presentation, magnitude and duration of effects for these two substances. Significant changes in irritability, anger/aggression, restlessess, sleep difficulty, appetite, mood, and cognitive ability have been documented following abrupt cessation of chronic use for both substances. Two outpatient studies of marijuana withdrawal in our laboratory have yielded effect sizes of r = 0.66, n = 12 and r = 0.72, n = 18 on a composite measure of withdrawal discomfort (WDS). An outpatient study of tobacco withdrawal that used a design similar to our marijuana studies yielded a comparable effect size (r = 0.74, n = 50) on a similar WDS measure (calculated from Hughes et al. 1986). Peak withdrawal effects for both substances occur within 5 days of abstinence and most symptoms dissipate by week 4. Such cross-study comparisons present several methodological limitations, therefore, we have initiated a within-subjects study designed to directly compare tobacco and marijuana withdrawal. Preliminary data from that study will be presented in addition to our cross-study analyses of common symptoms. A comparison of marijuana withdrawal to the more familiar tobacco withdrawal syndrome will provide important information for judging the clinical significance of marijuana withdrawal.

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Those with low PIL-R scores had poorer outcomes at 3-month and 6-month follow-up in terms of more cocaine use days, more drug use days and more alcohol use days, even after controlling for depressive symptomatology as measured by the BDI. Less purpose in life was associated with cocaine and alcohol relapse status at 6-month follow-up. The results suggest that purpose in life may be important to address in cocaine abuse treatment.

703 EFFECTS OF DELTA-9-THC ON SPATIAL WORKING MEMORY IN MICE ARE REVERSED BY THE GABA-A ANTAGONIST BICUCULLINE

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Delta-9-THC (the primary psychoactive ingredient of marijuana) and other cannabinoids have long been known to produce deficits in certain aspects of learning and memory, and it is widely believed that these effects are due in large part to activation of CB1 receptors located in the hippocampus, predominantly localized presynaptically on GABAergic nerve terminals. The present experiments were conducted to test the hypothesis that THC-induced memory impairments are mediated via their effects on GABAergic transmission. C57Bl/6 mice were trained to perform a working memory version of the Morris water maze, which required them to learn the location of a hidden platform that varied semi-randomly from session to session. As has been previously demonstrated, THC produces dose-related deficits in this task at relatively low doses, which are blocked by coadministration of the CB1 antagonist SR141716A. We now report that the deficits induced by a maximally-effective dose of THC (10 mg/kg) were reversed by coadministration of 1 mg/kg (but not lower doses) of the GABA-A antagonist bicuculline ([t27] = 2.5, P = 0.017). The GABA-B antagonist CGP 36 742 had no effect on the THC-induced deficits ([t19] = 1.2, P = 0.24). In subsequent experiments the GABA-A antagonist muscimol and the cholinergic antagonist scopolamine were both shown to produce working memory deficits that resembled those of THC, in that they occurred at relatively low doses and did not affect a cued version of the water maze task. Furthermore, maximally-effective doses of scopolamine (0.5 mg/kg) and muscimol (0.5 mg/kg) were also blocked by 1 mg/kg bicuculline. These results suggest that THC-induced working memory deficits may result from increases in GABAergic hippocampal networks and may be a critical downstream effect common to both.

704 2-FLUORO-3-[2-(S)-2-AMINOETHOXY]PYRIDINE ACQUIRES PHASE I APPROVAL AS A RADIO-IMAGING AGENT FOR IMAGING 4A2 NICOTINIC RECEPTORS IN HUMAN PET STUDIES


The selective, high affinity radioisologand [2-18F]-F-A-85380 (2-[18F]-fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine) is a new tracer with low toxicity developed to image 4A2 nicotinic receptors (nAChRs) in the brain using positron emission tomography (PET). In the bacterial reverse mutation assay, which measures mutagenic potential, 2-F-A-85380 was without effect in doses 7X10e8 eight times the proposed imaging dose of 10 nmol/kg, iv. Pharmacological effects produced by 2-F-A-85380 and nicotine in mice included Straub tail, labored breathing, hypothermia, motor incoordination, and convulsions. These actions are typical of a nicotinic agonist. ED50s for eliciting convulsions were 5.0 micromol/kg, iv for 2-F-A-85380 and 1.4 micromol/kg, iv for nicotine. No deaths occurred below ED50 values. Necropsy results from 2-day acute (0.4–4000 nmol/kg, iv) and 14-day expanded acute (40–4000 nmol/kg) toxicity studies of 2-F-A-85380 in mice demonstrated no gross pathological or histopathological changes. Cardiovascular effects of 2-F-A-85380 (10–300 nmol/kg, iv) in unanesthetized rats were rapid in onset and 300 nmol/kg significantly increased mean systolic and diastolic pressure (ca. 20 mm Hg) and heart rate (ca. 60 beats/min) within 5 min. Critical intervals of the electrocardiogram (PR, QRS, and QTc) were unaffected. Following raciotracer doses of 2-[18F]F-A-85380 administered to mice and non-human primates, 90% of the radioactivity was cleared through the urine making the bladder wall the critical organ for radiation exposure. In the brain, tracer uptake (1% injected dose) was highest in the thalamus, moderate in cortex, and lowest in the cerebellum. The absence of any in vivo tissue toxicity associated with 2-F-A-85380 and a sufficiently wide margin of safety have resulted in approval of a Phase I IND application for its use as an imaging agent for nAChRs in humans. Human studies, which were initiated in December 2001, may provide new insight into the dynamics of central nAChRs.

705 PTSD AND PSYCHOSOCIAL DISTRESS IN PREGNANT DRUG-DEPENDENT WOMEN

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Posttraumatic stress disorder (PTSD) is highly prevalent in patients with substance use disorders, especially women. Research has shown that drug dependent women with PTSD present for treatment with higher rates of psychopathology and other Axis I and Axis II disorders than drug dependent women without PTSD. Women with PTSD and drug dependence also present with more interpersonal and medical problems and tend to have more severe drug use disorders. The present study compared levels of psychological and psychosocial distress in a sample of 66 treatment seeking pregnant drug dependent women with and without a current diagnosis of PTSD. All participants had a history of traumatic event exposure. Psychological distress was measured by the Symptom Checklist 90 Revised (SCL-90R), and PTSD and psychosocial distress were assessed using the Post-traumatic Stress Diagnostic Scale (PDS). Participants were predominantly African American (47.5%), mean (S.D.) years of age 29.6 (4.7) with a mean (S.D.) of children 3.1 (2.2). Preliminary analyses found that nearly half (45%) of women met criteria for current PTSD. Although the majority of women presented for treatment with significant amounts of psychological distress, those women with PTSD had higher scores than non-PTSD women on all SCL-90R sub-scales as well as the Global Severity Index (1.72 vs. 0.85; P < 0.0001), and the Positive Symptom Distress Index (2.35 vs. 1.74; P < 0.0001). Patients with PTSD were more likely to report that their symptoms were currently interfering with enjoying leisure activities, family relationships, life satisfaction, and overall functioning (P’s < 0.05). These results suggest that comorbid PTSD in a sample of chronic drug dependent women is associated with greater psychological distress, which adversely affects their life functioning. Drug dependent women with PTSD may need intensive intervention at time of admission to minimize premature discontinuation of treatment participation.

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706 BUPROPION VERSUS PLACEBO FOR SMOKING CESSATION IN SCHIZOPHRENIA

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Schizophrenic patients have high rates of smoking compared to the general population. In this preliminary study, we compared sustained-release (SR) bupropion (BUP, 150 mg po bid) versus matching placebo (PLA) for smoking cessation in patients with schizophrenic disorders. Furthermore, we examined how antipsychotic class predicts smoking cessation outcomes with bupropion. About 32 subjects who met DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were studied. All participants received specialized weekly group therapy. Outcome measures included treatment retention, smoking abstinence rates, expired breath carbon monoxide (CO) levels, psychotic symptoms and medication side effects. BUP significantly increased trial endpoint 7-day point prevalence smoking cessation rates compared to placebo [BUP, 8/16 (50.0%), PLA, 2/16 (12.5%); Z = 5.24, df = 1, P < 0.05], and produced significant reductions in CO levels, as evidenced by a significant Medication X Time interaction with hierarchical linear modeling (Z = 3.09, P < 0.01). Treatment retention was not significantly different between study groups. Positive symptoms of schizophrenia were not significantly altered by BUP, but there was a significant reduction in negative symptoms. Prescription of atypical versus typical antipsychotic drugs appeared to enhance smoking cessation responses to BUP. BUP was well tolerated, and the major side effects were dry mouth, gastrointestinal symptoms, headache and insomnia. The results of this preliminary study suggest that: (1) BUP enhances smoking cessation rates compared to PLA in nicotine-dependent schizophrenic smokers; (2) BUP is well-tolerated and safe for use in these patients; (3) atypical antipsychotic agents may enhance anti-smoking responses to BUP.

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707 Activation of Group II Metabotropic Glutamate Receptors Inhibits the Self-administration of Amphetamine
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Recently we reported that the production of locomotor sensitization and the enhancement of cocaine self-administration induced by pre-exposing rats to amphetamine in the ventral tegmental area requires the activation of metabotropic glutamate receptors (mGluRs) in this site. The present study examined the contribution of a subgroup of these receptors, the group II mGluRs, to the intravenous self-administration of amphetamine. Given that group II mGluR blockade produces hyper-locomotion in amphetamine pre-exposed rats, it was hypothesized that activation of these receptors would diminish amphetamine self-administration. Rats were trained to self-administer amphetamine (100 mg/kg per infusion) first on an FR1 and then on an FR2 schedule of reinforcement. Once satisfactory amphetamine self-administration was attained, animals in different groups were tested under a PR schedule on six subsequent days for their self-administration of saline, amphetamine, amphetamine + the group II mGluR agonist LY379268 (100 mg/kg per infusion) or LY379268 alone. Not surprisingly, rats with access to amphetamine continued to engage in self-administration behaviors while those with access to saline showed progressively decreasing levels of these behaviors. Rats with access to LY379268 resembled those with access to saline. Interestingly, rats with access to amphetamine + LY379268 showed much reduced self-administration when compared to rats self-administering amphetamine alone. These results, together with others, further support an important role for group II mGluRs in the generation of appetitive behaviors by psychomotor stimulant drugs.

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708 Native-American Treatment Engagement, Satisfaction, and Outcome in Project MATCH: A Retrospective Study
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Despite academic, tribal, and state programmatic calls for culturally sensitive and culturally appropriate treatments, to date little, if any, empirical evidence exists from randomized clinical trials that suggests Native American drug abusers respond better to culturally sensitive treatment. This study retrospectively investigated the extent that Native American clients (N = 25) reported positive therapeutic engagement, treatment compliance, treatment satisfaction, and positive treatment outcome relative to non-Hispanic White clients within an alcohol treatment program. No mean differences were found between Native American and Anglo clients in the extent of reported alliance with therapeutic tasks (P > 0.66), goals (P > 0.34), or bonding with therapists (P > 0.65). Likewise, there was no difference in the percentage of therapy sessions attended by ethnic group: Native American, 66%, Anglo, 71%, P > 0.46. While Native American clients reported less global satisfaction with treatment relative to Anglos, this difference was not significant, P > 0.14. Logistic Regression used at 3, 6, 12, and 15 month follow-up intervals showed that Native Americans reported no differentially drug use post-treatment. Reported drug use was primary marijuana and cocaine. While analyses at 9 months indicated a significant difference, that finding can be attributed to a Type I error. This overall pattern of null differences between ethnic groups post-treatment highlights a potentially erroneous assumption embedded within the phrase ‘culturally sensitive and culturally appropriate treatments.’ That Native American drug abusers fare more poorly while in mainstream treatments with dominant culture treatment providers. However, more importantly, before terms like ‘culturally sensitive treatment’ and ‘culturally appropriate treatment’ can be used, reported, investigated and their efficacy determined, they must first be defined and operationalized. Prospective RCT studies are necessary to determine which treatment approaches are more efficacious for Native American drug abusers.

709 Longitudinal Examination of Current Drug Use and Mothers’ Conflict Resolution Strategies with their Children
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This study estimated the impact of current maternal drug use on parent-child conflict resolution strategies (reasoning, verbal aggression, minor physical aggression, and severe physical aggression) as reported by mothers on the Conflict Tactics Scale (CTS) when their children were 3, 5, and 7 years of age. Methods: The sample, drawn from the Miami Prenatal Cocaine Study, consists of 326 African-American biological mothers with data from CTS and self-report use of alcohol, tobacco, marijuana, and cocaine in the year prior to assessment. Prenatal drug use was measured via mother’s self-report and assays of maternal urine and infant urine and meconium. Latent class analysis was used to categorize current drug use into two classes, and longitudinal generalized linear models with generalized estimating equations (GLM/GEE) were used to estimate associations between drug use and conflict strategies. Results: Mother’s minor and severe physical aggression toward her child was associated with current drug use of cocaine and/or marijuana even with adjustment for child sex, maternal age, and maternal education (P < 0.05). These associations were not explained by prenatal cocaine use. Mother’s verbal aggression toward her child was associated with both prenatal cocaine use and...
current drug use of cocaine and/or marijuana (P < 0.05). Reasoning strategies were not related to current or prenatal drug use. With or without drug use, mothers used reasoning and severe aggression more frequently as the children grew older. Discussion: Subject to study limitations, we observe that specific facets of mother’s conflict resolution strategies may depend upon her drug use. These relationships merit more detailed study.

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710 ACCOUNTING FOR BASELINE IN ANALYSES OF COCAINE TREATMENT EFFICACY

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Baseline measurements have been described as important prognostic indicators of treatment response, but few studies have systematically explored the effects of baseline values on the statistical modeling of treatment efficacy data. This study is an analysis of data from a clinical trial that was designed to test whether desipramine was more effective than placebo in reducing cocaine use in cocaine-dependent, depressed individuals. The current set of analyses were carried out to examine the effects of baseline values on the outcome variables of days per week using cocaine, days per week craving cocaine, and dollars per day spent on cocaine. Mixed models were used due to their usefulness in handling data sets with repeated measures and missing data points. The factors of time, treatment, and mood response were entered into all models; baseline scores were both included and excluded. Backwards elimination was used to arrive at the final solution. Results were similar for each outcome variable. Exclusion of the baseline factor yielded a model with main effects of time and no statistically significant interactions with treatment. Inclusion of the baseline factor led to models with main effects of baseline and significant interactions of treatment with time, mood response and/or baseline. The meaning of these differences is discussed, various measurements of baseline use are considered, and inclusion of baseline measurements as covariates for analysis of treatment studies is suggested.

711 STRUCTURE OF SYMPTOMS IN VOLATILE SOLVENT-INDUCED PSYCHOSIS


Solvent-induced psychosis (‘Solvent psychosis’) has been clinically identified among patients suffering from dependence on volatile solvents and those in psychotic state due to solvent use. To identify symptomatological characteristics of solvent psychosis, 41 patients (36 male and 5 female, mean age, 25.1 years) with ‘Mental and behavioral disorders (ICD-10) due to volatile solvent use’ and 47 patients with schizophrenia (24 male and 23 female, mean age, 25.9 years) were studied. Symptoms were estimated due to the checklist developed by the authors, including 71 symptom items. The principal component analysis with Varimax rotation was applied to the point and duration estimates of symptoms observed among the subjects. The study findings are as follows; 1) It is difficult to distinguish two groups based on the prevalence rates of symptoms alone. 2) However, the principal component analysis of the prevalence and duration observing among those with solvent psychosis revealed seven factors consisting of ‘amotivation’, ‘intoxication’, ‘emotional instability’, ‘delusion’, ‘hallucination’, ‘deinhibition’ and ‘memory loss’. The seven factors explained 75.4% of the variance of the symptoms in this group. 3) The same analysis applied to the data from the patients with schizophrenia showed six factors consisting of ‘ego disorders’, ‘emotional instability’, ‘amotivation (or negative symptoms)’, ‘delusion’, ‘hallucination’ and ‘anxiety’. These factors explained 62.9% of the variance in the data in the latter group. These results support clinical observations that ‘amotivational syndrome’ may be a characteristic feature of patients suffering from solvent psychosis. The results also suggest solvent psychosis is a discernible syndrome, and is distinctive from psychotic symptoms typical of schizophrenia.

712 OPPORTUNITIES TO USE MARIHUANA AND COCAINE AMONG MEXICAN MIDDLE SCHOOL STUDENTS AND YOUNG ADULTS

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INTRODUCTION. In prior CPDD meetings, our research group has presented evidence on exposure opportunity as an important element in the epidemiology of drug use. In this report, we use quantitative and qualitative methods to produce and analyze new data on Mexican youth and young adults. METHODS. Focal groups were conducted by trained facilitators in two middle schools located downtown in Mexico City. Vignettes were used to facilitate assessment of item comprehension and report accuracy among 13–16 year-old participants, gathered in same-sex groups. A panel survey before and after each group meeting asked questions on opportunities to use marihuana and cocaine, as well as actual use of these drugs. In addition, based upon the central location sampling method, approximately 100 young adults were interviewed in public plazas. RESULTS. Qualitative analyses suggest that exposure to opportunities to use drugs can be assessed reliably among young students. Drug use was found to be strongly stigmatized, highlighting the importance of instruments to assess early drug involvement. A total of 96 respondents 18–35 years were interviewed, of whom 57% were males. An estimated 80% had an opportunity to use marihuana and 40% actually used it. With respect to cocaine, 46% had an opportunity and 19% actually used it. While figures for drug use in this survey are higher than in other surveys, getting closer to estimates in the U.S., the base population differs substantially in terms of age and education compared to available surveys. DISCUSSION. This study extends the evidence on exposure opportunity as an important element on exposure opportunity concepts and measurements, and offers new insights on the epidemiology of drug use in Mexico. Future research plans on this topic include comparisons of mechanisms leading to opportunities to use drugs in Mexico and other countries.


713 REINFORCERS DECREASE VARIATION OF BEHAVIOR IN AN OPERANT RUNWAY

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The reinforcing strength of a drug of abuse or of a physiological stimulus such as food can be quantified using an operant runway. We used a modified Ettenberg runway (160 × 10 × 10 cm; alley length, 100 cm) to examine the characteristics of reinforced behavior in male albino Sprague-Dawley rats (300–350 g) running for a food reinforcer, sweetened condensed milk (Nestle), and a drug reinforcer, the ultra-short-acting mu opioid receptor agonist remifentanil (Ultiva®). Sweetened condensed milk (diluted in water 1:3, 1:10, 1:30, and 1:100) was offered to the rats (N = 16) during two consecutive testing
days/milk dilution. Milk reinforcement showed distinct concentration dependence. Interestingly, the behavior of the rats was not only changed quantitatively, i.e. a high milk dose resulted in short runtimes, but also qualitatively: High milk concentrations resulted in a more uniform and therefore more predictable behavior than low milk concentrations. The same held true for a drug reinforcer, i.e. remifentanil (0.0032–0.1 mg/kg i.v.; N = 12). To summarize, the operant runway experimental paradigm is able to demonstrate that drugs of abuse decrease variation of behavior, thus modeling a central DSM IV criterion for human drug dependence.

714 THE INFLUENCE OF SIGNIFICANT OTHERS IN THE TREATMENT OF COCAINE AND METHAMPHETAMINE DEPENDENCE: A PROSPECTIVE STUDY

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The Community Reinforcement Approach (CRA) in combination with vouchers has demonstrated success in reducing the cocaine use of patients seeking treatment for cocaine dependence. However, practical considerations such as the cost and intensity of such treatment may limit the implementation of the CRA plus vouchers in natural settings. One avenue of research that has received less attention is the use of significant others (SOs) of the drug dependent individual as a natural reinforcer in the treatment of cocaine and methamphetamine (MA) dependence. Recent advances have been reported in relation to training SOs of drug dependent individuals in operant behavioral principles in order to encourage treatment engagement of the individual abusing drugs. The present study’s aim was to investigate the possible benefits of involving a SO in the treatment of cocaine and MA dependence. Twenty-five cocaine or MA dependent individuals (IPs, identified patients) were randomized to receive one of two treatment protocols. Group 1 consisted of the CRA alone without the involvement of a SO (n = 13). Group 2 consisted of the CRA plus SO involvement. Each SO was encouraged to participate in the treatment sessions of the IP, and was offered 6 individual treatment sessions designed to train the SO to support the non-drug use of the IP (n = 12). Participants’ drug use was assessed at baseline and 3- and 6-month follow-ups. Repeated measures ANOVA indicated both groups significantly decreased their use of cocaine and MA over time (P < 0.001), however, no between group differences were found for percent days abstinent for drug of choice. Effect sizes between groups indicated that the Family Involved Group attended more treatment sessions (0.63) and had higher percent weeks of continuous abstinence (0.36) than the non-family involved group. Although the small sample size limits conclusions, the data suggest that a full clinical trial is warranted.

715 VARIABLE DOSE-RESPONSE CURVES FOR THE VOLATILE ANESTHETIC, SEVOFLURANE

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The present study was designed to characterize the subjective and psychomotor effects of sevoflurane, a volatile inhaled general anesthetic, in healthy non-drug-abusers. Twelve volunteers (21–34 years old) participated in six sessions, during which six end-tidal concentrations of sevoflurane (0, 0.2, 0.3, 0.4, 0.5, 0.6%, mixed with 100% oxygen) were administered for 30 min, followed by a 60-min recovery period. Before, during, and after drug administration, subjects rated subjective effects by filling out paper-and-pencil questionnaires and by speaking their ratings to the research technician. They also performed two psychomotor tests. The blinded technician rated their level of sedation. Observed sedation and psychomotor impairment increased as a function of dose. Although mean subjective effects were dose-related, there was extensive variability of effects across subjects. Ratings for some subjects increased abruptly from 0 to 0.2 or 0.3% sevoflurane then reached asymptote, whereas some subjects showed more gradual increases in effect across doses. Other subjects showed unexpected decreases in effect at the highest concentration, and occasionally, effects were not dose-related (e.g. ‘sawtooth’-shaped dose-response curves). These results held whether the ratings were written or spoken. Four (25%) subjects could not complete some of the forms legibly at one or more doses (0.4–0.6%). The present study demonstrates individual differences in sevoflurane effects, including differential sensitivity to dose. The data also show that group means are not necessarily representative of data from individual subjects. Finally, the impairment of self-reporting via written questionnaires in a minority of subjects is a methodological issue that warrants further discussion.

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716 EFFECTS OF PRENATAL EXPOSURE TO CANNABIS ON THE mRNA EXPRESSION OF CB1 AND DOPAMINE RECEPTORS IN HUMAN FETAL BRAIN

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Cannabis is the most widely used illicit drug in many western countries and has extensive effects on motor and cognitive functions. The cannabinoid receptor, CB1, is responsible for the psychoactive components of cannabis. A disturbing trend among cannabis users is the growing number of women who are pregnant or lactating. Prenatal exposure to cannabis has been demonstrated to cause long-term behavioral and cognitive disturbances in animal and clinical studies. There is, however, to date virtually no information about the molecular consequence of prenatal cannabis exposure in humans. To understand the molecular effects of cannabis on the developing human brain, we studied the expression of the CB1 mRNA using in situ hybridization histochemistry in normal human fetal brain specimens at 20 weeks of development after elective abortion. The brain dopamine system is important for motor control, cognition, and emotional regulation and linked to CB1 neuronal populations. As such, the major dopamine receptor subtypes, D1 and D2, were also examined in the human fetal brains. Our results revealed that the CB1 mRNA is expressed specifically in the cerebral cortex, caudate nucleus, putamen, amygdala and hippocampus. There was a clear hereogeneity of the signal in these areas. The D1 expression was mainly detected in the caudate nucleus and putamen, and the D2 mRNA was primarily abundant in the striatum and basal nucleus of amygdala, hippocampus and medial group of thalamus. In a second series of experiments, the CB1, D1 and D2 mRNA expression levels were studied in the fetal subjects exposed to cannabis during gestation determined by maternal self-report, mother’s urine and fetal meconium toxicology test. The control group contained 23 subjects and the cannabis group 18. The initial analysis of the CB1, D1, D2 mRNA expression was focused on the amygdala, hippocampus and caudal striatum. Preliminary results indicate a trend of decreased expression levels of the CB1 and D1 mRNA by prenatal exposure to cannabis. Supported by NIH DA12030.

717 BETA-FUNALTREXAMINE MICROINJECTED INTO THE VENTRAL TEGMENTAL AREA DECREASES COCAINE SELF-ADMINISTRATION UNDER A PROGRESSIVE-RATIO SCHEDULE OF REINFORCEMENT

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Dopaminergic innervations originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAcc) play a significant role in cocaine reinforcement. While μ-opioid receptors are located in both the VTA and the NAcc and are known to modulate the dopaminergic system, little is known about the role of these receptors in the neurobiology of cocaine addiction. Irreversible antagonists provide a powerful tool for linking the behavioral actions of drugs with specific receptor subtypes. For example, irreversible blockade of mu-opioid receptors by the alkylating agent beta-funaltrexamine (beta-FNA) shifts the dose-response curve for heroin self-administration to the right on a fixed-ratio schedule. In the present study, beta-FNA was used to investigate the effects of mu-opioid receptor blockade on the reinforcing effects of cocaine. Fischer rats trained to self-administer cocaine on a progressive ratio schedule of reinforcement were microinjected with either beta-FNA or saline into the VTA. Beta-FNA, but not saline, caused a time-dependent decrease in breakpoint in responding for cocaine. This decrease in responding in beta-FNA treated rats lasted for 7–9 days, and follows the time course of re-synthesis of mu-opioid receptors following beta-FNA administration. This study identifies the VTA as a site in which mu-opioid receptors may play a role in the modulation of the reinforcing effects of psychomotor stimulants.

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718 Life satisfaction, depression, and abstinence from opiates and cocaine in opioid-replacement patients

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Clinical psychological variables are frequently studied as predictors of drug abuse treatment outcomes. Indices of psychopathology, usually depression, are employed more often than measures of psychological well-being, despite a lack of evidence that psychopathology is more important in treatment response. We compared a measure of well-being, the five-item Satisfaction with Life Scale (SWLS), with the 21-item Beck Depression Inventory (BDI-II) for their ability to predict opiate and cocaine abstinence in 129 male and female opioid replacement patients (median time in treatment = 9 months). With baseline drug use and other statistically important covariates adjusted, logistic regressions showed that higher baseline SWLS scores, but not lower BDI scores, were positively related to cocaine abstinence at a 3-month study follow-up assessment ($P < 0.01$). SWLS scores still predicted abstinence when scores on the BDI-II and other positive and negative psychological measures were added to the model. Neither measure predicted opiate abstinence. The results suggest that psychological well-being cannot be understood merely as the absence of pathology and is worthy of investigation in its own right for its potential role in drug abuse treatment outcomes.

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719 Investigation of Hypericum as a Pharmacologic Treatment for Cocaine Dependence

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The herbal preparation of Hypericum perforatum is one of a family of herbs that has been used as treatment for mild to moderate depression in Europe and in the United States. Though the mechanisms of action for hypericum are not fully understood, hypericum extract (LI 160) has been shown to inhibit both serotonin and norepinephrine uptake in dose dependent manner. This 55-subject, two-arm CREST II study compared the safety and efficacy of hypericinum extract (LI-160) against placebo. The data pattern of the data in this study would indicate that the dosage of hypericum administered has little effect on drug use and its associated problems; the lack of differential reports of rates or severity of adverse events provides evidence that the medication tested is safe and tolerated sufficiently by the affected population. In conclusion, our analyses do not provide empirical reason for further investigation of (LI-160) as a cocaine pharmacotherapy.

720 Cocaine’s Effects on Circadian Rhythms of Body Temperature and Gross Motor Activity in Pig-Tailed Macaques

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Cocaine has been reported to increase body temperature and locomotor activity in rodents and primates in numerous studies. However, most of these studies investigated the acute effects of cocaine, recording measures over only a few hours. Furthermore, studies of body temperature frequently involve the use of restraint during data collection, and restraint may influence body temperature in its own right. The effects of daily cocaine injections on circadian temperature and activity rhythms in freely moving animals have been studied far less often. Six male pig-tailed macaques (4–7 kg) were administered doses of cocaine ranging from 0.1 to 3.0 mg/kg. Each dose was administered i.m. once daily (9 am) for seven consecutive days in a mixed order and interspersed with several weeks where saline was administered. All monkeys were implanted i.p. with radio-telemetry devices for monitoring core body temperature and gross motor activity. The implanted radio-telemetry devices allow for complete freedom of movement within the animal’s home cage. Temperature and activity were recorded every 10 min throughout the study. Compared to data following saline administration, cocaine produced statistically-significant, dose-dependent increases in core body temperature and gross motor activity 1–2 h following administration. Interestingly, additional dose-related increases in motor activity began in the evening, approximately 10–12 h post-injection. Body temperature was not systematically affected in the evening. These data replicate previous findings, extending previous work to freely moving macaques. These results also demonstrate that single daily injections of cocaine may have multiple effects on circadian rhythms in macaques.

721 Cocaine-seeking and self-administration in Baboons: Differential Effects of Baclofen

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The primary mechanism involved in the reinforcing effects of cocaine is activation of the mesolimbic dopamine (DA) system. Recent studies have indicated a modulatory role of gamma-aminobutyric acid (GABA) on mesolimbic DA activity. Drugs that facilitate GABAergic neurotransmission may reduce the reinforcing effects of cocaine. The current study evaluated the effects of the GABA-B receptor antagonist baclofen (0.1–3.2 mg/kg) on cocaine self-administration and the reinstatement of extinguished lever responding previously maintained by cocaine (i.e. cocaine-seeking) in baboons (n = 4). To evaluate the specificity of any effect on cocaine-maintained behavior, the effects of baclofen on lever responding maintained by food were also evaluated. Up to 30 injections of 0.032 mg/kg cocaine or 30 deliveries of 1-g food pellets were available under a Fixed Ratio (FR10) schedule of reinforcement during daily 2-h sessions. Cocaine and pellets maintained similar numbers of reinforcers (i.e. 25–30) per session. For reinstatement tests, lever responding behavior was extinguished by substituting saline for cocaine; extinction was defined as < 10
injections/session for two consecutive sessions. During extinction, priming doses of cocaine (0.1–3.2 mg/kg, i.v.) administered prior to the saline session dose-dependently increased cocaine-seeking. A low dose of baclofen (0.32 mg/kg) blocked the reinstatement of cocaine-seeking produced by priming doses of cocaine. Doses of 0.1–0.56 mg/kg baclofen did not alter food-maintained behavior and did not restate cocaine-seeking when administered alone. When administered prior to cocaine self-administration sessions, baclofen reduced the number of cocaine injections, but only at doses that also reduced food-maintained behavior (1.0–3.2 mg/kg). These data suggest that activation of GABA-B receptors may modulate the reinstatement of cocaine-seeking behaviors, but do not appear to influence the maintenance of cocaine-taking behaviors. These data highlight the importance of examining potential medications for treatment of cocaine abuse under both self-administration and reinstatement procedures.

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722 A COMPARISON OF TWO FORMS OF GROUP THERAPY FOR BIPOLAR DISORDER AND SUBSTANCE DEPENDENCE

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Bipolar disorder (BPD) and substance use disorder (SUD) frequently coexist. However, we know of no published trials of psychotherapy for patients with BPD and SUD. We designed Integrated Group Therapy (IGT) to combine treatment for BPD and SUD. IGT examines similarities in recovery from BPD and SUD, using cognitive-behavioral methods. After an encouraging pilot study, we are currently conducting a randomized controlled study comparing IGT with standard Group Drug Counseling (GDC). Among the first 24 subjects (12 each in GDC and IGT), mean days of drug use declined during treatment, from 10.3 to 7.2 days per month; there were no significant group differences. Days using alcohol to intoxication declined significantly more for IGT patients during treatment (P < 0.01) and at 3-month follow-up (P < 0.03). During treatment, mood episodes, assessed with the LIFE, occurred in 23% of weekly determinations, compared to 61% at baseline. There was no significant difference between IGT and GDC. However, in the 12 weeks following treatment completion, there was a large difference favoring IGT in frequency of mood episodes (47% for GDC vs. 21% for IGT, P < 0.001). Preliminary results of this ongoing study suggest promise for IGT in treating BPD and SUD.

723 EFFECTS OF MORPHINE IN C57BL/6J, DBA/2J AND 129P3/J MICE RESPONDING UNDER A MULT FR30 FI600 SCHEDULE OF MILK PRESENTATION.

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Previous reports in the literature have shown both quantitative and qualitative differences in the effects of morphine on motor activity in C57BL/6j and DBA/2j mice. Thus, it was of interest to determine the response to morphine in C57BL/6j and DBA/2j mice responding under a multiple fixed-ratio 30 fixed-interval 600 s (mult FR30 FI600) schedule of milk presentation, and to compare these results to those obtained in 129P3J mouse. Young adult, male C57BL/6j, DBA/2j, and 129P3J mice were trained to respond under a mult FR30 FI600 schedule of milk presentation. Dose-response curves were determined for morphine (1–30 mg/kg) in the absence and presence of 1 mg/kg naloxone. Control performance in all three strains was characteristic of responding under a mult FR30 FI600 s schedule with the exception of a lower FI-life (37.2%) in the 129P3/J mice. No effect of morphine was observed at 1 mg/kg in any strain. FR30 responding was markedly decreased in the DBA/2J and 129P3/J strains following 3 mg/kg while similar decreases were not observed until 10 mg/kg in the C57BL/6J mice. FI responding for all 3 strains was decreased following 10 and 30 mg/kg. The morphine dose-effect curve in all three strains was shifted to the right in the presence of 1 mg/kg naloxone. These data indicate little strain difference in morphine’s effect on responding maintained by milk presentation under a mult FR30 FI600 schedule.

724 CARBOXAMIDO ANALOGUES OF NALTRINDOLE AND BUPRENORPHINE


We recently reported the synthesis and unexpectedly high opioid receptor binding affinity of opioids where the prototypic phenolic-OH was replaced by a carboxamido group (Bioorgan. Med. Chem. Lett. 2001, 11, 623 and Bioorgan. Med. Chem. Lett. 2001, 11, 1717). As a continuation of these studies, we recently prepared and evaluated the corresponding carboxamido analogues of buprenorphine and naltrindole. Exposure of the 1-triflate ester of naltrindole to CO/NH3 and Pdcatalysis gave carboxamido-naltrindole. Carboxamido-buprenorphine was made by first treating the 3-triflate ester of buprenorphine with CO/HN(SiMe3)2 and Pd-catalysis followed by mild acid treatment. High affinity for delta opioid receptors (Ki = 0.33 nM) was observed for carboxamido-naltrindole (Ki = 0.13 nM for naltrindole). Like naltrindole, carboxamido-naltrindole was a delta antagonist in the [35S]GTPgS assay. For mu, delta and kappa opioid receptors, carboxamido-buprenorphine had Ki values of 2.3, 7.3 and 4.3 nM, respectively (0.98, 0.72, 0.90 nM, respectively for buprenorphine).

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725 DRUG ABUSE, VIOLENCE, AND HIV/AIDS AMONG IMPOVERISHED WOMEN


RAND Drug Policy Research Center, Santa Monica, CA, Drug use and abuse, violence against women, and HIV/AIDS are public health priorities of epidemic proportion and are significant, overlapping threats to the health of women. Although these public health problems are receiving greater attention as they affect women, comprehensive understanding of these threats among traditionally underserved women is still lacking, as is an understanding of the linkages among these problems. Understanding interrelationships among violence, substance use and abuse, and HIV/AIDS risk behaviors is necessary to the development of strategic community interventions for preventing and alleviating these problems and their impacts among impoverished housed and homeless women. Longitudinal interview data collected from probability samples of approximately 400 women living in shelters and 400 women living in low-income housing in Los Angeles County will shed light on these epidemics and their interrelationships. Bivariate analyses based on 414 total baseline interviews conducted thus far reveal higher rates of drug use and dependence, physical, sexual, and psychological victimization, and HIV risk (e.g. prostitution, less condom use) among sheltered women than housed women. Multivariate analyses on these 414 cases suggest, for example, that having multiple partners and having partners who use alcohol to intoxicate are dramatically associated with women’s victimization by
their partners after adjusting for women's own drug problems and other key life context variables. Results from analyses of baseline data will be presented and implications for prevention will be discussed.

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**726 Inhibition of [3H]MK-801 binding by noncompetitive NMDA receptor antagonists in dark Agouti rat brain membranes**

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The dark Agouti rat strain lacks the ability to metabolize many CNS active drugs normally metabolized by the CYP2D family of cytochrome P450 isozymes. Thus, this rat strain is a useful model to isolate the effects of dextromethorphan (DXM), an OTC antitussive that is also subject to abuse, from those of its primary metabolite, dextromethorphan (DOR). Abused DXM produces effects similar to phencyclidine (PCP) and both DXM and DOR share discriminative stimulus properties with PCP. The ability of noncompetitive NMDA receptor antagonists to inhibit [3H]MK-801 binding in dark Agouti rat brain membranes was evaluated using competition binding assays. One- and two-site binding models were fit to the resulting competition binding curves using nonlinear regression curve-fitting procedures. All the noncompetitive NMDA receptor antagonists were best fit to a one-site competition model; Hill Slopes did not differ from −1. The rank order of affinity for inhibition of [3H]MK-801 binding (Ki, nM) was: MK-801 (5.5) > dexoxadrol (21.5) > TCP (24.2) > PCP (100.8) > (+SKF10,047 (357.7) > DOR (405.2) > ketamine (922.2) > DXM (2913). The inhibition binding constants (Ki) determined in dark Agouti rat brain were significantly correlated (P = 0.0002; r2 = 0.95) with those reported for Sprague-Dawley rats (Wong et al., J. Neurochem. 50:274–281, 1988). The PCP binding site associated with the NMDA receptor-complex ion channel appears to have the same characteristics in both dark Agouti and Sprague-Dawley rats.

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**727 Fentanyl, but not buprenorphine, produces the discriminative stimuli associated with withdrawal from acute opioid dependence in squirrel monkeys**

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In the squirrel monkey (Saimiri sciureus), the discriminative stimulus effects of a combination of acute morphine followed by naltrexone (MOR → NTX) are dose and time dependent and stereoselective. The purpose of this study was to determine the effects of substituting the mu-selective agonists fentanyl (FEN; high efficacy) and buprenorphine (BUP; low efficacy) for morphine on MOR → NTX-appropriate responding. Seven monkeys were trained in a discrete-trial avoidance/escape procedure to discriminate MOR (1.7 mg/kg, i.m., 4 h) → NTX (0.1 mg/kg, i.m., 0.25 h) versus saline (1 ml/kg, i.m., 4 h) → NTX (0.1 mg/kg, i.m., 0.25 h). Monkeys (n = 4–5) were tested with FEN (0.03 mg/kg) or BUP (0.01 and 0.03 mg/kg) and NTX (0.01–1.0 mg/kg). FEN fully substituted for MOR. However, BUP did not produce MOR → NTX-appropriate responding at either dose tested. These findings extend the range of agonists that produce MOR → NTX-appropriate responding to fentanyl and suggest that the behavioral manifestation of interoceptive stimuli associated with withdrawal from acute opioid dependence is a function of agonist efficacy.

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**728 Pharmacokinetic basis for variability in duration of withdrawal suppression in methadone maintenance patients**

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Up to one third of methadone patients maintained on apparently adequate doses experience withdrawal in the latter part of each interdosing interval. This non-holding status has been attributed to inadequate plasma methadone concentrations and various minimum concentrations of racemic methadone (usually 150–200 ng/ml) have been recommended. Analysis of trough plasma samples collected from patients complaining of withdrawal have been used in determining dose increments. These are several problems with this approach (1) trough plasma methadone concentrations of non-holders are not different than those of holders; (2) while dose increments may eliminate withdrawal, adverse effects of high methadone doses can occur. The present study was designed to investigate whether there is a pharmacokinetic basis for non-holding status and, if so, whether this could be used to improve assessment and response to this problem. Multiple blood samples collected over a single interdosing interval from six holders and six non-holders were analysed by HPLC to determine concentrations of the active R-enantiomer. Non-holders did not differ from holders in peak or trough plasma R-methadone concentration, clearance, volume of distribution or terminal half-life. However, non-holders had greater fluctuations in plasma concentration over the dosing interval (83.4+24.4 vs. 47.1+13%), mean ISD, P = 0.008; number of hours during which R-methadone concentration was greater than 75% of the peak concentration also differed (4.3+2.0 h in non-holders vs. 11.5+6.1 in holders, P = 0.02). These results indicate that stability of plasma methadone concentration over the dosing interval rather than absolute concentration may be the determinant of withdrawal in methadone patients. Mesurement of changes in plasma concentration from the peak could therefore be used to confirm holding/non-holding status. A sustained release formulation of methadone to flatten the concentration-time profile may be useful in reducing the problems of non-holding and minimising unnecessary dose increments.

**729 Amphetamine affects behavior on a computerized impulsivity/risk task: individual differences in drug effects**

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Clinical evidence suggests that impulsivity increases after drug consumption in addicted individuals, and addicted individuals score high on trait measures of impulsivity. This increase in impulsive behavior could contribute to continued drug use, and facilitate the transition to drug abuse through increased drug exposure. To date, however, the direct effects of drugs on impulsive behavior have not been well studied in normal, nonaddicted subjects. The present study was designed to determine the acute effects of amphetamine on impulsive behavior, as measured using a computerized measure of risk-taking behavior in normal, healthy volunteers. Three doses of d-amphetamine (0, 10 mg, and 20 mg oral) were tested on a validated impulsivity/risk task (BART) in a placebo controlled, within-subjects design. Participants also completed a standardized personality questionnaire (MPQ short form). Preliminary data from 33 participants indicate that d-amphetamine (10 and 20 mg) increased impulsive responding on the task when there were low adverse consequences of
impulsive choices. The magnitude of impulsivity induced by AMPH was positively associated with the personality trait of Agentive Positive Emotionality (trait reward sensitivity), and negatively associated with the personality trait of Harm Avoidance (trait fear). These data suggest that relatively fearless and reward-sensitive individuals may be most vulnerable to the behavioral impulsivity induced by psychostimulant drugs.

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**730 Preference for HIV home-collection test kit among drug users in methadone maintenance, detoxification and syringe exchange programs**

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In some states publicly funded voluntary HIV testing and counseling (VCT) data show high failure to returns (FTR); as high as 50% (CDC 2000). Locally, in Philadelphia the public VCT programs suffer from high FTR rates. For the year 2000, 23383 tests were conducted in Philadelphia and only 10494 (45%) of those tests had returns In this study we compare test completion rates by mode of HIV testing among 489 high-risk drug users in Philadelphia. Those eligible and consented were randomly assigned to two testing modalities: (1) home-collection test kit (HCTK) and, (2) clinic-based traditional counseling and testing (TCT). Participants were drawn from methadone treatment (N = 159); detoxification (N = 196) and syringe exchange (N = 134) programs. At the two-month follow-up visit more people in the HCTK group reported that they had obtained their test result (n = 137) compared to (n = 111) the TCT group (57.1% vs. 44.6%). \( \chi^2 = 7.65, P < 0.01 \). We were able to confirm participant receipt of results on 121 of the HCTK and 87 of the TCT participants. These data suggest that home-collection test kits are able to attract more test completions than clinic-based testing among high-risk drug users. Furthermore, 64% of those who used HCTK stated that they preferred this method for future testing whereas 41% of those who used TCT preferred the clinic-based method for future testing. Importantly, 44% of the TCT group stated that they would prefer to use HCTK in future testing. The distinct preference coupled with higher return rates for HCTK among this high risk drug users who used this method suggests that this technology can play a role in increasing HIV test acceptability and completion rates among high-risk drug users.

**731 Suicide ideation and attempts: the role of early drug use**

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Aim: We seek to estimate the degree to which the early use of tobacco, alcohol, marijuana, and inhalants might account for later suicide ideation and attempts. Methods: As part of this epidemiological-based longitudinal study, yearly standardized assessments on drug use in 1989–1994 were completed with 1516 youths age 8–15; to date, a total of 1253 have completed depression assessments in young adulthood (mean age = 22), with 127 found to have had suicide ideation and 45 to have attempted suicide. Eight youths reported suicide ideation or attempts prior to drug use and were dropped from the analysis. Results: With survival analysis methods used to estimate relative risk (RR) and to account for possible confounding by age, sex, and minority status, risk of suicide ideation was associated with preadolescent tobacco use (RR = 1.9; P < 0.05), having been drunk before age 16 (RR = 2.1; P < 0.05), and marijuana use before age 16 (RR = 1.7; P < 0.05). Risk of suicide attempt was associated with having been drunk before age 16 (RR = 3.8; P < 0.01) and marijuana use before age 16 (RR = 2.4; P < 0.05). Discussion: These preliminary results add to the body of epidemiological evidence linking early drug use with later risk of suicide-related thoughts and behaviors. In our next steps we will examine patterns of association involving possible mediators and effect-modifiers such as levels of teacher-rated aggression, and will account for frequency of illegal drug use.

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**732 Does the pharmacotherapy of ADHD beget later substance abuse? a meta-analysis of the literature**

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Objective. Using meta-analytic techniques, we evaluated the literature to determine if stimulant treatment of Attention Deficit Hyperactivity Disorder (ADHD) is related to a heightened risk, no appreciable effect, or a protective effect on later substance use disorders (SUD). Methods. A systematic search of the literature was conducted. Meta-analytic techniques were applied to the data to evaluate overall risk of SUD in treated vs. untreated ADHD youth, class of substances affected by ADHD treatment, and influencing factors in outcome. Odds ratios depict the protective effect of treatment. Results. This search revealed five studies of ADHD youth followed at least four years (N = 576 treated and 339 untreated subjects). ADHD pharmacotherapy was associated with a reduction in risk for SUD (OR = 2.3; CI 1.1–4.6, \( P = 0.02 \)). Similar reductions were found in risk for later drug or alcohol use disorders. In accounting for findings, only severity at baseline was associated with outcome (\( P < 0.001 \)). The effect was stronger in older adults compared to young adults. Discussion. Despite the limitations of a largely naturalistic sample, the literature suggests that stimulant treatment of ADHD does not increase but actually decreases the risk for SUD. Further evaluation attendant to the baseline severity of illness, adequacy of treatment, and mechanism of risk reduction is warranted.

**733 Abused inhalants differentially affect nicotine-induced hypothermia**

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Previous research has shown that the abused inhalant toluene inhibits recombinant α4-β2 and α3-β2 nicotinic receptors expressed in oocytes. In order to investigate possible in vivo correlates of these findings, we examined the effects of toluene and other inhalants on hypothermia induced by nicotine in mice (n = 6 mice/group). Nicotine decreased body temperature, as did ethanol, flurothyl, and the abused inhalants, toluene and 1,1,1-trichloroethane (TCE). In contrast, the anesthetic methoxyflurane did not affect body temperature. At concentrations that did not significantly affect body temperature when administered alone, TCE and methoxyflurane attenuated the hypothermic effects of 1 mg/kg nicotine whereas toluene, ethanol, and flurothyl did not. Differences among inhalants in their interactions with nicotine mirror differences found among their other behavioral effects and suggest that different inhalants may have different mechanisms of action. Further, these results suggest that TCE, toluene, and methoxyflurane may interact with nACh receptors in functionally important ways.

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Remifentanil is a relatively new opioid agonist with short duration of action compared to other opioid agonists. Panlilio and Schindler (2000) recently showed that rats will intravenously self-administer remifentanil. The purpose of this study was to replicate the self-administration curves in rats and to determine the effects of increasing post-reinforcement time-out (TO) duration on low response rates maintained by high remifentanil doses and on high response rates maintained by low remifentanil doses. Dose-effect curves were conducted using 24 male Sprague–Dawley rats responding on a lever for intravenous injections of 0.1–6.4 mcg/kg per injection for 1 h/day on a fixed ratio 1 (FR1) with no post-reinforcement TO and only one dose available per session. Next, two groups of rats were allowed access to either 0.2 mcg/kg per injection (low-dose group, n = 12) or 3.2 mcg/kg per injection (high-dose group, n = 12). The post-reinforcement TO was then increased to 5, 10, 20, and 40 s. For the dose effect curves, rate (in/min) and intake (mg/kg) were analyzed using 1-way ANOVAs. For the TO changes, the same dependent variables were analyzed with both groups (2-way ANOVA; dose group × time-out) and with each group individually (1-way ANOVAs) because the high-dose group continued to respond at higher TOs. The dose-effect curve for rate had the typical inverted-U shaped form with a peak of over 10 in/min at 0.2–0.4 microgram/kg per injection. The intake curve was a positively accelerating function with the highest dose maintaining more than 1.2 mg/kg. The rate of injections for the low-dose group decreased as to increased, reaching approximately zero during the 10 s TO. Intake was less than 0.1 mg/kg. The rate of injections for the high-dose group increased during the 5 and 10 s TO and then decreased. Intake remained constant after the first TO increase and then decreased. The data replicate the previous study showing that remifentanil is self-administered in rats. Method of infusion and TO duration may account for the peak rate of infusion occurring at a smaller dose in our study. And, low vs. high remifentanil doses were differentially responsive to increases of post-reinforcement TO duration.

### 735 Oral nicotine self-administration in rats during adolescence

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Smoking rates are high among adolescents in our society, yet little research has been conducted on nicotine’s effects during this developmental period. Recent evidence suggests that adolescents exhibit a different behavioral response profile to nicotine as compared to adults. These differences may influence the amount of nicotine adolescents must consume to produce desired psychoactive properties. In the present study, we examined voluntary oral nicotine consumption of adolescent and adult rats using a two-bottle free choice paradigm. Sprague–Dawley rats were given access in their home cage to two bottles, one containing nicotine solution (at concentrations ranging from 0.003 to 0.012%) and the other water. Adolescents voluntarily consumed considerably more nicotine than adults. A gender difference was apparent in adolescents, with females consuming significantly more nicotine than males. Six days of forced nicotine intake did not enhance subsequent free choice nicotine intake in adolescents. Adolescent rats seem to titrate consumption of nicotine solution across different doses to obtain average daily intakes of approximately 2.5 mg/kg per day. Together these results suggest that adolescents consume oral nicotine seemingly for its pharmacological effects and voluntarily consume substantially more nicotine than adults, an increase that we suspect may be related to an adolescent-associated decrease in psychopharmacological sensitivity to the drug. Given that adolescent nicotine exposure has been shown to result in permanent neural damage and behavioral changes, elevated consumption during this developmental period may be particularly detrimental.

### 736 Thirty-year follow-up of the influence of early parenting on persistent drug use

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Earlier reports indicated that maternal unresponsive behavior in infancy signaled increased risk of problem drug use in the offspring. This study extends previous work by: (1) examining the role of maternal behavior on the progression from non drug use to transient use and persistent use and (2) investigating the potential mediating role of known adolescent risk factors, i.e. deviant peer affiliation, parent monitoring, and delinquent behavior. Data are from a long-term follow-up of a cohort of mother-infant pairs who represent a population-based sample of low to middle income families (n = 1758). The offspring were followed up when they were approximately 30 years old. Maternal behavior was rated when the child was 8 months old and is categorized as either ‘unresponsive’ or ‘nurturing.’ Unresponsive refers to behavior that is critical, unresponsive and inconsistent. Nurturing reflects consistent, affectionate and responsive behavior. Study outcomes included lifetime (transient) and past year (persistent) marijuana, cocaine and heroin. Each drug was studied separately; transient and persistent drug use categories were mutually exclusive and were compared to the reference group of non-drug users for the respective drug. Unresponsive maternal behavior was unrelated to either transient or persistent marijuana use (AOR = 0.94, 95% CI = 0.70–1.27; AOR = 1.00, 95% CI = 0.66–1.52, respectively); unresponsive behavior was related to persistent cocaine use for women only (AOR = 1.91, 95% CI = 1.01–3.61; AOR for transient versus no use = 1.04, 95% CI = 0.63–1.72) and persistent heroin use for both women and men (AOR = 2.00; 95% CI = 1.24–3.24; AOR for transient use = 1.09; 0.67–1.77). While the adolescent risk factors had independent associations with maternal behavior, as well as the drug outcomes, there was no evidence that they mediated the associations observed between unresponsiveness and drug use. These findings indicate that very early parenting behavior may have long term effects on the developing child’s subsequent drug use, specifically drug use that persists into adulthood. The effects appear to be independent of risk factors present in adolescence. NIDA Individual Training Grant # DA14163

### 737 Suicide attempts in patients with substance-related disorders

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Previous suicide attempt and substance abuse are both significant risk factors for completed suicide. The use of alcohol or other drugs is associated with a significant percentage of completed suicides. Extensive research has clearly documented the statistical association between substance use and suicidality, yet understanding the clinical aspects of this relationship is incomplete. Medical records were reviewed for 940 inpatients consecutively admitted to a locked, dual-diagnosis unit. Preliminary Results: (a) Two hundred sixty-three patients (28%) were identified as lifetime suicide attempters (SA); fifty-three patients (6%) were admitted following a suicide attempt; (b) Demographics for lifetime suicide attempters (SA) vs Non- attempters (NA) respectively: Male 58 vs 70%, Age (mean ± S.D.): 38 ± 10 vs 41 ± 12, Causation: 93 vs 91%, Unmarried 76 vs 67%; Unemployed 83 vs
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738 EFFECTS OF HALOPERIDOL ON COCAINE SELF-ADMINISTRATION AND THE ACQUISITION AND PERFORMANCE OF RESPONSE SEQUENCES IN MONKEYS

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A three-component multiple schedule was used with 4 rhesus monkeys to examine the effects of intramuscularly-administered haloperidol (0.0032–0.01 mg/kg) on cocaine self-administration and two food-maintained tasks, a learning task (repeated acquisition) and a performance task. Prior to testing haloperidol, cocaine self-administration was determined in one component for 4–5 unit doses (0.0032–0.32 mg/kg) under a fixed-ratio 30 schedule. When compared to substitution with saline, which was not self administered and had little or no effect on responding in the acquisition and performance components, increasing unit doses of self-administered cocaine produced an inverted U-shaped curve for infusions and decreased overall response rates in both the acquisition and performance components. In addition, in two of the four subjects, cocaine produced dose-dependent increases in the percentage of errors in the acquisition component, but only at doses that also produced large rate-decreasing effects. Pretreatment with 0.0032 mg/kg of haloperidol shifted the inverted U-shaped curve for infusions of cocaine to the right, whereas 0.01 mg/kg of haloperidol tended to shift the dose-effect curve for cocaine upward, thereby increasing the area under the curve. More important, only a few of the haloperidol-cocaine combinations were less disruptive to overall response rate and accuracy of responding in acquisition and performance components than cocaine alone. In fact, in many instances, the higher dose of haloperidol alone was disruptive to responding in the acquisition and performance components, and some of the haloperidol-cocaine interactions were as disruptive as cocaine alone. Together, these data suggest that haloperidol has a limited potential as an effective clinical antagonist for cocaine self administration or as a pharmacotherapy for cocaine dependence.

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739 YOUTH DRUG ABUSE AND GAMBLING

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The prevalence data on adolescent gambling behaviors are provocative. General gambling involvement is common among young people, with some gambling occurring among most American teenagers (Jacobs, 1989; Stinchfield and Winters, 1998). Estimates of problem gambling rates among youth, while not extravagant, range from 1 to 9% past year (median = 6%), and these rates tend to be higher than for adult populations (National Research Council, 1999; Shaffer, Hall, and Bilt, 1997). The literature on youth gambling often notes the relationship of gambling involvement to drug use. For example, most studies have found that drug abuse is one the most common ‘comorbid’ disruptive behaviors associated with youth problem gambling (Stinchfield, 2000). The extent of this association and its importance toward advancing knowledge about the origins and course of adolescent drug abuse and gambling will be discussed. Data from a series of cross-sectional and prospective studies conducted by the authors will provide the empirical basis for the presentation. The cross-sectional data represent three waves of health survey data (1992, 1995, 1998) collected from nearly all 9th and 12th grade students attending public schools in Minnesota. The prospective study represents a sample of 335 youth who are assessed at mid-adolescence, late adolescence and young adulthood. The data from both sets of studies support the views (a) adolescent gambling, like drug use, is a normal part of adolescence, (b) the prevalence rate of problem gambling is comparable to the rate of substance use disorders, (c) in contrast to drug abuse, negative consequences associated with gambling are difficult to pinpoint, and (d) similar risk factors may be important determinants for both behavior domains.

740 INTIMATE PARTNER VIOLENCE AMONG DRUG-DEPENDENT FATHERS


Objectives: This paper examines the association between fatherhood and intimate partner violence (IPV) among a sample of 355 predominantly African American and Latino men attending methadone maintenance treatment programs (MMTPs). Studies on the status of drug-dependent men show that drug use and intimate partner violence (IPV) can both compromise positive fathering attitudes and behaviors, and constitute barriers to father-child relationships. These studies also indicate that the substance abuse treatment system may be an effective mechanism for providing support to men in their role and status as fathers through gender-specific parenting interventions. Methods: This paper used data from the Men’s Health Project (MHP), a NIDA-funded study examining over time the co-occurrence of substance abuse, HIV risk behavior, and perpetration of IPV among a random sample of men in MMTPs. Findings: More than half (n = 206, 60%) of the men were fathers of minor children; and just under half of fathers (n = 95, 46%) were living with at least one of their children. Two thirds of fathers (n = 129, 63%) had children with their current intimate partner, and more than half of these men (n = 78, 38% of total sample) reported spending time caring for their children 6 or more times a week. More than half of fathers (n = 116, 58%) reported having been raised by parents who abused alcohol or other substances, while 41% (n = 85) reported witnessing interpersonal violence in childhood. Perpetration of severe IPV in the past 6 months was found to be significantly higher among fathers compared to non-fathers. More violence was found among fathers than non-fathers in the following severely abusive acts: choking the partner (2 vs. 8.7%, P < 0.01); slamming the partner against a wall (3.4 vs. 10.1%, P < 0.02); and using a knife or gun on the partner (0 vs. 1.9%, P = 0.09). Preliminary findings highlight the need for more research on the prevalence of IPV among drug-dependent fathers and how drug use and IPV may constitute barriers to parenting. Findings suggest that fathering skills interventions may need to incorporate trauma-focused knowledge and prevention skills-building components.

741 PREDICTING SUICIDAL BEHAVIOR IN ADOLESCENTS WITH CONDUCT AND SUBSTANCE USE PROBLEMS

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Suicide is the leading cause of death among adolescents. Severity of substance problems, conduct disorder, and history of abuse/neglect have been associated with suicide attempts in adolescent patients. Hypotheses: More severe substance dependence, abuse/neglect, and conduct disorder, together with age and gender, will be associated with more frequent suicide attempts among adolescent patients with conduct and substance problems. Methods: We examined the suicidal behavior of 98 patients (60 males and 38 females) in a substance treatment program. For certain analyses, we compared patients with 101 controls (62 males and 39 females). We analyzed responses to questions targeting depression, suicidal ideation, past suicidal behavior, history of abuse/neglect and severity of conduct disorder and substance dependence. Results: A significantly higher percentage of patients versus controls reported ever having tried suicide (23% vs. 3%). Interestingly, within the sample of patients who are being treated for substance and conduct problems, severity of substance use and conduct disorder, as well as age and gender, were not predictors of attempting suicide. In separate logistic regression analyses within the patients, the number of suicide attempts was associated with reported lifetime symptoms of depression (P < 0.007). Conclusions: Adolescents in treatment for conduct and substance problems are at an increased risk for suicide if they have experienced abuse/neglect or if they have endorsed lifetime depressive symptoms. Although the greater conduct and substance problems of patients (compared with controls) do indicate a greater risk of suicide attempts, within patients they are not predictive. Identifying other risk factors, danger signs, and other characteristics of suicidal behavior among patients who are at an increased risk for suicide will be useful in the prevention of suicide within drug treatment programs.


742 EXTENT AND CORRELATES OF COMPUTER/INTERNET USE AMONG SUBSTANCE ABUSERS

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Problematic computer and internet (C/I) use is a recent phenomenon which appears to have some of the features of substance addictions. To explore this issue, we are interviewing persons recently admitted to substance treatment to determine whether C/I use and/or problematic use is associated with gender, age, race, and specific substance (marijuana, alcohol, cocaine, amphetamine, and opiate) or psychiatric (anxiety, depression, and AD/HD) disorders. Among the first 128 subjects assessed with the Diagnostic Interview Schedule and the Internet/Computer Assessment Module (35% female, 65% white race, mean age 30.0 years), 77% reported ever using a computer and such use was associated with younger age (P < 0.01), cocaine disorders (P = 0.07), and lack of AD/HD (P = 0.04). Non-work or school internet use was reported by 52% (associated with younger age [P = 0.04], white race [P = 0.02] and male gender [P = 0.09]). Typical uses of the internet were for: information (50%), playing games (43%), e-mail (35%), downloading music (33%), chat rooms (31%), shopping (16%), sex sites (15%) and gambling (8%). Nearly half (45%) reported deriving pleasure or satisfaction from computer use (associated with amphetamine [P = 0.01] and cocaine [P = 0.07] disorders); while 27% used the computer as a way of improving their mood (associated with cocaine disorders [P = 0.04] and depression [P = 0.06]). Considering evidence for an addiction-like syndrome within the past 12 months, 16% reported that they used a computer for longer than intended (associated with AD/HD [P = 0.04], alcohol [P = 0.03] and amphetamine [P = 0.09] disorders, and depression [P = 0.02]); 7% reported that others complained about their computer use, and 5% reported reducing activities because of computer use. These preliminary results demonstrate that a large number of substance abusers use computers and the internet on a regular basis and exhibit some warning signs of C/I addiction. Further work will include completing collection of baseline data and developing and exploring statistical models.

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743 CONTINGENCY MANAGEMENT INTERVENTION TO IMPROVE ATTENDANCE IN A THERAPEUTIC WORKPLACE BUSINESS IN DRUG ABUSE PATIENTS WITH CHRONIC HISTORIES OF UNEMPLOYMENT

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Chronic unemployment is common among drug abuse patients. The Therapeutic Workplace intervention is an employment-based drug abuse treatment for patients with histories of substance abuse and unemployment. In a Therapeutic Workplace business, drug abuse patients are hired as data entry operators and paid to perform data entry work contingent upon documented drug abstinence. Punctual and reliable attendance has been difficult to maintain despite the opportunity for operators to earn as much as $10 in hourly and productivity pay, 6 h per day, 5 days per week. In a previous study, a contingency management intervention increased punctuality and the frequency of completed workshifts. During the intervention, operators were not allowed to work if they did not arrive to the workplace on time. In addition, operators’ pay was temporarily decreased if they did not arrive to work on time or if they failed to work a complete 6-h workshift. The present study used a within-subject reversal design to evaluate a contingency management intervention that allowed for greater flexibility regarding when operators could arrive to work, yet maintained a contingency for reliable workplace attendance for six operators. Specifically, if an operator did not complete a workshift, the operator’s pay was temporarily decreased to $6.00 per day. The within-subject reversal design clearly demonstrated the contingency management intervention to be effective in increasing the frequency of completed workshifts in four of six operators. Repeated measures ANOVA and Tukey’s post hoc tests of grouped data showed that the contingency management intervention significantly (P < 0.05) increased the mean percent of days that operators completed workshifts (17% baseline; 58% contingency management; 15% baseline) and increased the mean number of minutes worked per day (204 min baseline; 252 min contingency management; 175 min baseline). This study demonstrates an effective procedure for maintaining attendance in Therapeutic Workplace participants, a fundamental practice for sustaining long-term employment.

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744 NEED FOR ALCOHOL AND OTHER DRUG TREATMENT AMONG IN-SCHOOL ADOLESCENTS IN CALIFORNIA

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The need for alcohol and other drug (AOD) treatment often exceeds the availability of treatment. Much of what is known about the ‘true’ need for AOD treatment is based upon adults. Even so, estimates from these populations may be under- or over-estimates, depending on the criteria used in the definition of ‘need.’ Even rarer are attempts to identify this need among adolescent populations. The generalizability of an adult needs assessment framework to adolescent populations may be limited because of developmental issues and adolescents’ lower likelihood of prior treatment experience. Adolescents, like adults, are
diverse in their AOD behaviors, ranging from no use to problematic use. Addressing AOD treatment needs of this younger population may help in reducing AOD consequences and the need for treatment over the lifetime. California recently completed an assessment of AOD treatment need for in-school adolescents ages 14–17. Using the DSM-III-R as a guide, treatment need was based upon satisfying criteria that address risky use, AOD consequences, and self-awareness of AOD problems. Among those ages 16–17 in regular schools, about 14% had treatment need, vs. 38% of agemates in continuation schools. Roughly 14% of males and females ages 16–17 in regular schools had treatment need, vs. 36% of male and 43% of female counterparts in continuation schools. Among those in regular schools ages 14–17, about 7% of Asian/Pacific Islanders and African Americans, 11% of Hispanics, 12% of Whites, and 17% of those of mixed race had treatment need. These findings suggest that the need for AOD treatment exists among in-school adolescents and that these needs vary by school setting, gender, and ethnic group. The types of treatment and ancillary services needed will likely vary by these factors, among many others, as well.

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745 CONTINUING DRUG USE BY METHADONE PATIENTS: HIGH VS LOWER DOSE AND MET VS DC

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Though the benefits of methadone maintenance have been shown in many studies, relatively little research has been done on patients who continue to use opioids while on apparently adequate doses. In an attempt to improve outcome, we randomly assigned 59 consenting patients who had been on 60–80 mg methadone for at least 4 months but whose urine tests were 75% or more opioid positive to a new counselor, and to either 80 mg methadone+Motivational Enhancement Therapy (MET) or Drug Counseling (DC); or to 120 mg + MET or DC. Patients were returned to their original counselor at study endpoint (6 months) and follow-ups were done at that time and 6 months later. The ASI drug composite score, amount of money spent for drugs and days using cocaine showed significant decreases at study endpoint in the high dose groups as compared to the lower dose groups. Opioid positive urine tests were 84% positive at study entry across all groups and 82% at study endpoint. At follow-up they decreased to 80% positive in the lower dose group and 72% positive in the high dose group, neither of which was significant. No clear advantage was seen for MET as compared to DC though there was a trend for a reduction in opioid positive urines across all groups at follow-up (P < 0.08). A comparison of ASI ratings of all study patients at the time they entered maintenance treatment to ASI ratings done at the time they entered the study showed significant reductions in days heroin used (P < 0.001), money spent for drugs (P < 0.0001), money from illegal activity (P < 0.01) and injections/week (P < 0.001). We conclude that modest improvements can result from increasing doses to the 120 mg range in these ‘hard to treat’ patients. In spite of continuing drug use, most are doing better than when they began methadone treatment.

746 SYNTHETIC APPROACHES TO GHB ANALOGS

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Gamma-Hydroxybutyric Acid (GHB) is currently under investigation for the clinical treatment of alcoholism and narcolepsy, but is also becoming increasingly abused. The exact mechanism of action of GHB is currently not known, but specific GHB binding sites have been described. In addition to GHB binding sites, GHB also interacts with GABA-B receptors, and it is known that GHB is subject to metabolism to GABA. This interaction with two sites may account for the often contradictory reports of the activity of GHB in the literature. Thus, it is essential that selective ligands are developed for GHB binding site, which are also not prone to metabolism to GABA-active compounds, in order to separate the GHB from GABA effects. General methods of two series of GHB derivatives which will not be prone to oxidation were developed. In one series, butanediol was monoetherated by phenyl alkyl halide, Ph(CH2)nX (n = 1,2,3, X = Br, CI), to give mono ether derivatives. These intermediates were then oxidized to gamma-phenylalkoxy butyric acids. Tertiary alcohol analogs were also prepared from the reaction of succinic anhydride and glutaric anhydride with Grignard reagents). The tertiary alcohols were found to be somewhat unstable under acidic conditions, and required storage as lactones or sodium salts.

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747 EFFECTIVE MEDICATION REGIMENS IN CHRONIC PAIN PATIENTS WITH OPIOID DEPENDENCE

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PROJECT PAIN was designed to improve medication adherence among patients with opioid dependence and chronic pain. To date, 8 patients have been medicated. Most were male (67%), white (78%) with mean age of 42.4 years (S.D. = 11.25). All patients had a component of neuropathic pain. At the start of the trial, 6/8 patients were taking opioids; 3 of these were also receiving tramadol. For patients on opioids, current medication dosages were converted to equianalgesic amounts of methadone. Patients who were not taking opioids were started on 25 mg q6h with 5 mg rescue doses. Initially, methadone was given q6h (M = 18 mg; S.D. 8.8; range 10–30 mg) and breakthrough was prescribed q 4–6h prn, for a maximum of three breakthrough dosages a day. The mean initial breakthrough dose was 7.5 mg (S.D. 4.18; range 5–15 mg). At subsequent visits, breakthrough doses used routinely were added into the regular dose. ‘Regular’ (maintenance) and breakthrough medications were given in separate prescription bottles and patients kept medication diaries documenting their use. It took an average of 10 weeks (of 16) to establish a stable, effective dose regimen (range 7–12 weeks). After titration, the regular dosage was 38 mg q6h (S.D. 21.57; range 10–75 mg) and the breakthrough dosage was 15 mg (S.D. 10; range 5–30 mg). All patients had at least one urine drug screen positive for unauthorized substances with 50% positive for THC, 45% for oxycodone, and 11% for cocaine. After 1 week of treatment 44% each reported insomnia and dry mouth and 33% sweating, lightheadedness, and nausea. By week four, 56% of patients reported no side effects, with the remainder reporting constipation, dry eyes, and insomnia. One patient was removed from the study when cognitive difficulties developed; another left following an episode of gastroesophageal reflux. Due to the pharmacology of methadone, our patients required divided dosing and breakthrough medication in order to achieve adequate pain relief. The amount of medication needed and the time to stabilization varied. These pilot data reveal some useful information for physicians regarding effective treatment of pain in this population.

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748 Does methylphenidate cross-sensitize with amphetamine?

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The psychostimulants methylphenidate (MPD) and amphetamine (Amph) are among the most common medications used for the treatment of attention deficit hyperactivity disorder (ADHD). However, the long-term use of psychostimulants as treatment for ADHD is unknown, particularly whether treatment with psychostimulants increases an individual’s potential for cross-sensitization to other stimulants. Cross-sensitization occurs when pretreatment with one psychostimulant leads to greater sensitivity to treatment with another stimulant. Cross-sensitization has been demonstrated between Amph and fencamfamine, a cocaine substitute, and between cocaine and MPD. The objective of this study was to investigate whether treatment with MPD in both juvenile and adult rats elicits behavioral cross-sensitization to Amph. A total of 68 Sprague-Dawley (S.D.), 75 Wistar–Kyo (WKY), and 73 spontaneously hypertensive rats (SHR) were used. Male juvenile SHR, WKY, and S.D. rats were divided into the following groups: (1) 0.6, 2.5, or 10 mg/kg, i.p., MPD for 6 days as juveniles and again similarly treated as adults and (2) saline as juveniles and 0.6, 2.5, or 10 mg/kg, i.p., MPD as adults. To induce cross-sensitization, all of them received an Amph challenge at the end of their treatment regimen. Changes in locomotor activity and stereotypic behavior were recorded using a computerized activity monitoring system and compared to control SHR, WKY, and S.D. rats that received either saline as juveniles and adults or 0.6 mg/kg, i.p., Amph as juveniles and adults. Results showed that adult rats treated with MPD as juveniles displayed a greater cross-sensitization to Amph than those adult rats treated with saline as juveniles. Furthermore, this cross-sensitization was both dose- and strain-dependent.

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749 Dopamine and psychostimulants induce c-fos in cells expressing the dopamine transporter: potential mechanisms and relevance to pre synaptic neuroadaptation

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The dopamine transporter on presynaptic dopamine neurons is the direct target of the psychostimulants cocaine and amphetamine. In cells post-synaptic to dopamine neurons, cocaine and amphetamine increase expression of the immediate early gene (IEG) c-fos indirectly via D1 dopamine receptor activation. To determine whether dopamine transporter substrates and inhibitors affect c-Fos protein expression directly, we investigated their effects on c-Fos protein and c-fos mRNA in HEK-293 (HEK) cells transfected with the human dopamine transporter (hDAT). In hDAT cells, DAT substrates (dopamine, amphetamine) increased c-Fos immunoreactivity 6- and 3-fold (respectively). Even though the DAT inhibitors cocaine, methylphenidate and bupropion alone increased c-Fos approximately 3-fold in hDAT cells, they attenuated dopamine-induced c-Fos. c-Fos protein immunoreactivity paralleled the magnitude of c-fos mRNA induction. As dopamine is converted to reactive oxygen species known to induce c-Fos expression, we investigated whether an antioxidant would attenuate this process. The antioxidant trolox (100 mM) blocked 27% of the dopamine-induced c-Fos, suggesting that other mechanisms may also contribute to IEG induction. Protein Kinase C (PKC) activation by the PKC activator PMA (500 nM) induced c-Fos in this cell line and promoted hDAT internalization, indicating a possible link between hDAT regulation by PKC and c-Fos induction.

In summary, substrates or inhibitors of the hDAT can trigger induction of immediate early gene expression directly in hDAT expressing cells, and in the absence of D1 dopamine receptors. DAT substrate and inhibitor effects on IEGs warrant investigation in presynaptic neurons, as this process may contribute to the long-term neuroadaptive mechanisms triggered by psychostimulants.

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750 Assessment of TES as an indicator of overall cocaine use in treatment-seeking cocaine-dependent patients

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There are numerous problems that result from attempting to quantify the cocaine metabolite benzoylecgonine in urine. These problems involve additional costs in human and fiscal resources leading many researchers to use less expensive semi-quantitative methods. However, semi-quantitative urine toxicology screens yield data that are skewed and subject to both ceiling and floor effects. TES is a simple and effective way to assess therapeutic benefits by assigning 1 point to every patient that attends their scheduled visit and has a clean urine toxicology screen. This method is advantageous because it requires a less expensive and more convenient qualitative urine toxicology screen. The purpose of this study is to determine if the qualitative TES method is comparable to median semi-quantitative benzoylecgonine level in assessing overall cocaine use among treatment seeking cocaine-dependent patients. The present study examined the relationship between median semi-quantitative benzoylecgonine levels and TES in 78 cocaine dependent male and female outpatients with 29 bi-weekly data points (14 continuous weeks and 3 month follow-up). Accordingly, we created a TES variable based on benzoylecgonine level data and attendance. In order to standardize across differing study durations and number of observations per week, the binary TES data were converted into a proportion. Then, given the skewness of the benzoylecgonine data, we produced median benzoylecgonine levels for each subject. Based on these adjustments, we correlated TES rate with median benzoylecgonine levels and determined the correlation coefficient to be ~ 0.64. Analysis were repeated within two treatment groups. The correlation between these two variables was found to be similar across groups. This result suggests a strong relationship between TES and median semi-quantitative benzoylecgonine levels.

751 Age of onset is associated with decreased hippocampal volume in heavy cannabis users

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Objective: To explore the relationship between age of onset of cannabis use and hippocampal volume. Methods: We acquired neuropsychological data and high-resolution MR images from 26 healthy controls and twenty-two current, long-term marijuana users before and after a supervised 28-day abstinence period. We divided marijuana users into groups by onset of use; either 15 years or older or below 14 years of age. Differences between groups were assessed using analysis of variance. Results: We found that smokers overall displayed a significant reduction in hippocampal volume (P < 0.001) although no significant difference in gray matter, white matter or hippocampal volume was found between the early and late onset groups. In addition, no differences in total number of smokes or THC concentration at Day 0 or Day 28 were seen for the two groups. Conclusion: These findings suggest that long-term cannabis use is associated
with decreases in hippocampal volume independent of the age of onset of use. The association of long-term cannabis use with reduced hippocampal volume, even in individuals who began smoking after the age of 15, is a cause for concern. Further studies will be required to assess the degree to which this finding is attributable to cannabis itself and the degree to which it may be due to other factors.

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752 GENETIC AND ENVIRONMENTAL LINKS BETWEEN TOBACCO, ALCOHOL, AND MARIJUANA PROBLEM USE IN ADOLESCENCE

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Genetic and environmental risks for adolescent substance use may be substance-specific or general across substances. We hypothesized that problem use in adolescence would be heritable and that genetic and environmental risks underlying tobacco, alcohol, and marijuana problem use would be significantly correlated. Participants were 345 MZ twin pairs, 337 DZ twin pairs, 306 biological sibling pairs, and 74 adoptive sibling pairs ascertained from community-based samples, and ranging in age from 12 to 18 years. Problem substance use was assessed using structured psychiatric interviews. Results of biometrical model fitting showed significant heritable factors for tobacco (h2 = 0.88), alcohol (h2 = 0.43), and marijuana (h2 = 0.39) problem use, and significant shared environmental factors for alcohol (c2 = 0.25) and marijuana (c2 = 0.32) problem use. Multivariate analyses yielded significant genetic correlations between each of the substances (rG = 0.54–0.93), and significant shared (within sibling pairs) environmental correlations between alcohol and marijuana (rE = 1.0) only. Findings suggest that tobacco, alcohol, and marijuana problem use are mediated by common genetic influences, but shared environmental influences may be more substance-specific for tobacco problem use.


753 AN IN-PATIENT PHASE III STUDY OF LOFEXIDINE (ALPHA2-ADRENERGIC AGONIST) FOR OPIATE DETOXIFICATION


Lofexidine HCl appears to be effective for the clinical management of opiate detoxification. Lofexidine also appears to produce less hypotension than clonidine. This study was conducted to assess the safety of lofexidine and to obtain information related to its potential efficacy. Opiate-dependent individuals were admitted to the hospital and stabilized on morphine 100 mg/day (subcutaneously) for 1 to 8 days. Morphine was then discontinued and lofexidine was administered daily for 5 or 10 days followed by no medication for 2 days. Five subjects took lofexidine in the 1.6 mg/day dosage group, 23 in the 2.4 mg/day group, 12 in the 3.2 mg/day group and 3 in the 4.0 mg/day group. There were transient, orthostatic systolic BP changes with the systolic BP < 85 mmHg: 1.6 mg (n = 2), 2.4 mg (n = 19), 3.2 mg (n = 7), 4.0 mg (n = 3). There were also apparent dose-dependent decreases in the Modified Himmelsbach Opiate Withdrawal Scale. The Himmelsbach opiate withdrawal mean scores were: 1.6 mg = 30.3, 2.4 mg = 22.0, 3.2 mg = 18.3, 4.0 mg = 15.7. No serious adverse events were observed.

Overall, lofexidine appeared to have minimal hypotensive effects up to 4.0 mg/day and clinically attenuated opiate withdrawal signs and symptoms.

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754 THE NEUROPEPTIDE SUBSTANCE P IMPARTS VULNERABILITY TO METHAMPHETAMINE NEUROTOXICITY AND CELL DEATH

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Methamphetamine (METH) is an addictive substance that also causes extensive neural degeneration in the central nervous system. We determined the role of the NK-1 receptor in METH-induced neurotoxicity, we tested the effects of the selective NK-1 receptor antagonists WIN-51,708 and L-733,060 on markers of dopaminergic terminal toxicity in the mouse striatum. Male mice received four I.P. injections of METH (5 or 10 mg/kg) at 2 h intervals and were sacrificed three days after the treatment. Exposure to METH resulted in severe depletion of dopamine transporters, tissue dopamine content, and tyrosine hydroxylase in the striatum. METH treatment also induced the expression of glial fibrillary acidic protein in striatal tissue. Administration of either NK-1 receptor antagonist 30 min prior to the 1st and 4th injection of METH prevented the loss of dopamine transporters assessed by autoradiography with [123I]RT-121 and Western blotting. Pre-treatment with either neurokinin-1 receptor antagonist prevented METH-induced loss of tissue dopamine and of tyrosine hydroxylase. Pre-treatment with NK-1 receptor antagonists had no effect on METH-induced hyperthermia. Pre-exposure of mice to either of the neurokinin-1 receptor antagonist alone was without effect on all of these neurochemical markers. NK-1 receptor antagonists prevented METH-induced apoptosis in the striatum. These results provide the first evidence that tachykinins, particularly substance P acting through NK-1 receptors, play a crucial role in the pathogenesis of nigrostriatal dopaminergic terminal degeneration induced by METH.

755 ‘BINGE’ COCAINE ADMINISTRATION INDUCES AN INCREASE OF SOMATOSTATIN RECEPTOR2 mRNA LEVELS IN THE RAT CAUDATE PUTAMEN

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Background: Changes in gene expression in the rat caudate putamen after acute and subacute ‘binge’ cocaine administration were examined by two methods, Affymetrix oligonucleotide microarray analysis with verification by RNaSe protection assay. Method: Adult male Fischer rats had received ‘binge’ pattern cocaine administration (3 × 15 mg/kg, ip, at hourly intervals) or saline in the same pattern, for 1 or 3 days, and they were sacrificed 30 min after the last injection. Pooled RNA extracts of the caudate putamen for each group were used in both the microarray analysis and, for genes of interest, in the quantitative solution hybridization RNaSe protection assay. Results: Over twenty genes were identified as having cocaine-induced changes in level of mRNA using the stringent criterion of an at least two-fold difference between treatment and control groups. One was of particular interest, the somatostatin receptor 2 gene (SSTR2), since local administration of SSTR ligands has been shown to induce increased levels of dopamine and glutamate in the striatum as well as significant increases in locomotor activity (Raynor et al., 1993; Hathaway et al., 1998). The increase in SSTR2 gene expression found by microarray was corroborated by the RNaSe protection assay, with a 30% increase after 1 day ‘binge’ cocaine administration and a 13% increase after 3 days over...
the levels of the respective control groups. Conclusion: This novel finding of increased SSTR2 gene expression after ‘binge’ cocaine administration, taken together with the earlier reports of increased dopamine and locomotor activity following ligand-induced activation of SSTRs, suggests that somatostatinergic tone may play an important role in producing the effects of cocaine.

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756 Abuse liability assessment of oral oxycodone in healthy volunteers

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Oxycodone (OXY), is an opioid widely prescribed to patients in ambulatory settings for moderate-to-severe pain. There is clear evidence from several epidemiological databases that OXY is also abused. No studies have examined the abuse liability of OXY in either drug abusers or non-drug-abusing volunteers. In an ongoing study, six males and five females (mean age + S.D.: 24.7 + 2.8 years) with no histories of drug abuse participated in a randomized, double-blind, crossover trial in which they ingested OXY (10, 20, 30 mg) and placebo; a standard abuse liability testing regimen was used in which measures were collected before and for 5 h after capsule administration, as well as after the sessions were completed. OXY had a number of euphoric effects: peak ARCI MBG scores, and peak VAS ratings of feel good, having pleasant bodily sensations, drug liking, and ‘want to take drug again’ were higher in the 20 and/or 30 mg OXY conditions than in the placebo condition (all P’s < 0.05). However, post-session (end of session and 24 h later) measures of overall drug liking and wanting were no different than that of placebo and were due to a substantial proportion of subjects who reported euphoric effects during OXY sessions having after-session liking ratings that were similar or substantially lower (indicating disliking of the drug) than those of placebo. Taking both within and after-session ratings into account, acute administration of OXY appears to have modest abuse liability in people without histories of drug abuse.

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757 Mu opioid receptor agonist reinforcement in an operant runway: Effects of route of administration, pharmacokinetics, and experimental design

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The positive as well as the negative reinforcing effect of intravenously administered drugs of abuse have been successfully demonstrated by Ettenberg and colleagues in an operant runway, a bona fide operant conditioning paradigm that avoids confounding drug effects on motor performance and drug accumulation. We assessed the reinforcing effect of subcutaneously administered opioids. Neither morphine nor remifentanil, a very-short-acting mu opioid receptor agonist, could consistently be established as positive reinforcer when administered subcutaneously. However, remifentanil proved to be a reliable reinforcer if given intravenously. In the course of the experiments, the following shortcomings of the runway paradigm became apparent: The first trial (run) of the day consistently resulted in short runtimes regardless of the previous training. Experimenter expectations resulted in immediate behavioral changes in the tested rats, rendering experimenter-blind conditions obligatory. The subcutaneous injections themselves proved to be negatively reinforcing, an effect that was expressed in continuously increasing runtimes when the inter-trial interval was 24 h and became also grossly observable when the inter-trial interval was reduced to 30 min.

758 Effects of scopolamine on schedule-induced polydipsia in rats


Schedule-induced polydipsia (SIP) is characterized by behavioral indulgence. In consideration of its compulsive component, SIP might have similarities compared with other addictive behavior, and share some common neurobiological mechanisms. Numerous researches have been conducted to elucidate the underlying neurobiological processes. In this study we used cholinergic muscarinic receptor antagonist scopolamine to investigate the roles of cholinergic muscarinic system in mediating initiation and maintenance of SIP in rats. SIP was induced when food-deprived rats were subjected to a fixed time (60s) feeding schedule for 3 h daily. Results showed that established SIP were significantly attenuated by 15min pre-session treatment with scopolamine (0.35, 1.0 mg/kg, i.p.) for 7 consecutive days (P < 0.05, n = 6/C). After 7 days withdrawal of scopolamine, the attenuating effect of scopolamine on SIP was decreased. When scopolamine (0.35 mg/kg, i.p.) were given from the first SIP training session for 7 consecutive days, no statistically significant effect was found on water intake during test sessions compared with control, however, SIP were significantly lowered after withdrawal of scopolamine for 7 days, and enhanced by scopolamine re-treatment (P < 0.05, n = 6/C). These results suggested that cholinergic muscarinic system underlie the mediation of schedule-induced polydipsia. Different effects of scopolamine on initiation and maintenance of SIP implied that these two processes might involve different mechanisms.

759 Conditioned place preference after single doses or ‘binge’ cocaine in C57BL/6J and 129J mice

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The purpose of this study was to examine the rewarding effects of cocaine in C57BL/6J and 129J mouse strains. Numerous researchers have studied the development of conditioned place preference. Cocaine was administered to mice of both strains in a single daily dose of cocaine (2.5, 5, 10, 20 mg/kg, i.p.) or in a ‘binge’ pattern administration (15 mg/kg x 3, i.p., at hourly intervals). Conditioning sessions were conducted for 30 min immediately after each injection. Single daily injections of cocaine at doses 5–20 mg/kg induced conditioned place preference in each strain of mice. However, only C57BL/6J mice developed conditioned place preference after ‘binge’ pattern cocaine administration. Also, both strains showed a significantly greater locomotor activity in the conditioning chamber across the range of single-doses of cocaine and to ‘binge’ pattern cocaine administration compared to saline controls. When mice that had received single-dose cocaine administration at the 10mg/kg dose were retested 4 weeks later, time spent in the preferred side (drug-paired compartment) was significantly reduced compared to the initial test in the 129J mice, but not in the C57BL/6J mice. Thus, the persistence of conditioned place preference is strain dependent. The fact that 129J mice did not develop conditioned place preference after ‘binge’ cocaine administration, but did after a range of single doses,
suggests that the rewarding effects of cocaine are influenced by pattern of administration, a factor that may be relevant to the development of human cocaine addiction.

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**Spinal muscarinic receptor-nitric oxide mediates the expression of morphine withdrawal symptoms in the rat**

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The adaptation expression of muscarinic receptor m1–5 in spinal cord during morphine dependence had been observed in my lab. The present study is to characterize the role of muscarinic receptor subtypes m1–5 in mediating the morphine dependence and the effects of m1–5 antisense oligodeoxynucleotides on expression of neuronal nitric oxide synthase (nNOS) in spinal cord during morphine withdrawal. The intrathecal treatment with either m2 or m3 A-olig (1 nmol per rat) at 24 h prior to naltrexone challenge could block the morphine withdrawal symptoms including wet dog shaking, irritating, salivation, diarrhea and weight loss, and m1 A-olig only prevent the wet dog shaking and diarrhea and m4 A-olig only inhibit the irritation. The total ratings of morphine withdrawal symptoms were attenuated by intraventricular injection of m1 A-olig, however, other A-oligs for m2–5 and mismatch probes were inactive. The m1, m2 and m3 mRNA in spinal cord were down-regulated specifically by intrathecal injection with m1, m2 or m3 A-olig itself. The nNOS mRNA levels and protein expression in spinal cord were also down-regulated respectively by intrathecal injection of m1, m2 or m3 A-olig. The results provided the evidence that M1, M2 and M3 receptor coupled efficiently with nNOS in spinal cord, as a positive feedback whereby spinally released NO increases the acetylcholine, which initiated the expression of many signs of the withdrawal symptom precipitated by naloxone.

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**Changes of HPA activity and mRNA levels of POMC and CRF-R1 in the hypothalamus and pituitary of the rat during withdrawal from chronic ‘binge’ cocaine**

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Tolerance to cocaine stimulatory effects on the HPA axis develops after chronic ‘binge’ cocaine (BC) in the rat. This blunting of HPA activity in response to cocaine is associated with reduced CRF mRNA levels in the hypothalamus. Little is known about the effects of withdrawal from chronic cocaine on HPA activity. The present studies were undertaken to determine levels of the HPA hormones across 10 days following chronic BC. Male Fischer rats showed significantly attenuated HPA responses on the 14th day of chronic BC (3.15 mg/kg/ day at hourly intervals), as reflected by plasma ACTH and corticosterone levels. About 1 day after the last BC (the 1st day withdrawal), significant elevations in plasma ACTH and corticosterone levels were found. The acute cocaine-withdrawal related elevations were also found on the 4th day of withdrawal and returned to control levels after 10 days of withdrawal. In the anterior pituitary, levels of both POMC and CRF-R1 mRNA were significantly increased on the 14th day of chronic BC. The elevations were also found on the 1st day of withdrawal and were at control levels on the 4th day of withdrawal. In the neurointermediate lobe, a sustained reduction in POMC mRNA levels was observed on the 3rd, 7th and 14th day of chronic BC, which remained reduced after the 1st day of withdrawal and was at control levels on the 4th day of withdrawal. In the hypothalamus, POMC mRNA levels showed a transient decrease on the 1st day BC with no change during chronic BC or its withdrawal. CRF mRNA levels in the hypothalamus were not different from saline controls during cocaine withdrawal. Taken together with our previous studies showing reduced hypothalamic CRF mRNA levels on the 14th day of chronic BC, the present results show that (1) there is an increase in HPA activity during acute cocaine withdrawal and (2) in addition to being associated with CRF input from the hypothalamus, the activation of the HPA axis by withdrawal from cocaine may be, at least in part, due to the increased POMC and CRF-R1 mRNA expression found in the anterior pituitary during and following chronic BC [DA-P50-05130 and DA-00049 (M.J.K.)].

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**The buprenorphine sublingual tablet dose-dependently decreases mu-opioid receptor availability in heroin-dependent volunteers**


We previously found that maintenance on 2 and 16 mg of the buprenorphine (BUP) sublingual liquid globally decreases mu-opioid receptor availability in vivo relative to placebo. Aims of this study were to confirm this relationship with the sublingual tablet over a wider dose range, and to correlate BUP concentration-effects in brain and peripheral compartments. Five opioid-dependent volunteers were maintained on 32, 16, 2 and 0 mg BUP (in that fixed order) under double-blind conditions. Measures of receptor availability were obtained with the mu-selective radioligand [11-C]carfentanil and PET (ECAT EXACT-47 scanner in 3-D mode) after subjects were maintained 12 days at each BUP dose level. Binding measures (Bmax/ Kd) were obtained on a voxel-by-voxel basis using Logan plots and occipital cortex as reference region. T1-weighted MRI was acquired and PET images were co-registered and warped to stereotactic atlas coordinates. Subjects were restricted to an inpatient unit (to enforce abstinence from illicit drugs) for the final 4 days prior to each scan. Scans took place 2 h after the daily dose. Volumes of interest (VOIs) (prefrontal cortex, anterior cingulate, caudate nucleus, nucleus accumbens, amygdala) were placed on the MRI images then transferred to the receptor maps, and whole brain values were calculated with automated routines. BUP plasma pharmacokinetics was assessed over a 24-h period. BUP significantly reduced mu-opioid receptor availability in a dose-dependent manner: Relative to placebo (i.e. 12-day BUP washout), mean global carfentanil binding decreased 41% at 2 mg (range across VOIs, 27–47%), 80% at 16 mg (range across VOIs, 85–91%), and 84% at 32 mg (range across VOIs, 93–98%). BUP produced significant dose-dependent changes in BUP plasma levels. For the 5 individual subjects, Pearson correlations (across the 4 BUP dose levels) between carfentanil binding and peak BUP plasma levels ranged from −0.70 to −0.96. The imperfect relationship between brain and plasma BUP concentrations is a topic for future studies

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