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SPANISH VERSION OF THE ARCI (49-ITEM SHORT FORM): RESPONSE PATTERNS UNDER DIFFERENT DRUG CONDITIONS

J. Cami, X. Lamas, M. T. Teran, and M. Farre

The objective of this study was to evaluate the pattern of changes induced by different drugs on the scores of the five subscales (PCAG, MBG, LSD, BG, A) included on a Spanish version of ARCI-49 item short form. In a previous work, was demonstrated that the Spanish version used was sensitive to the simulated effects of different drugs (Lamas *et al.,* 1994).

METHODS: In the present research, the questionnaire was evaluated during the course of four clinical trials that included the administration of different doses of benzodiazepines (triazolam, flunitrazepam, diazepam), morphine, pentazocine, naloxone, alcohol and snorted cocaine. The drugs were administered under double-blind, randomized and placebo controlled conditions. In order to compare the results and to assess the specificity of the score changes, other measures of subjective effects were collected (*e.g.* visual analog scales of high, drunken, good effects or sick), together with a battery of objective measures of drug effect (*e.g.* pulse, pupil diameter or performance abilities).

RESULTS: The results showed appropriate responses to the different subscales (PCAG, MBG, LSD, BG) after drugs, being the pattern similar to that described in the scientific literature and the questionnaire manual. The responses to ARCI agree with the other measures of subjective effects. These findings indicate that the Spanish version of the 49-item ARCI used could be a useful instrument in the assessment of the subjective effects produced by drugs in Spaniard-speaking populations.

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Lamas, X.; Farre, M.; LLorente, M.; and Cami, J. Spanish version of the 49-item short form of the Addiction Research Center Inventory (ARCI). Drug Alcohol Depend 35: 203-209, 1994.

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STANDARD SPANISH VERSION OF THE ADDICTION RESEARCH CENTER INVENTORY (ARCI) IN A U.S. HISPANIC POPULATION

D. J. Geyen, E. G. Singleton, and J. E. Henningfield

A pilot study was conducted using the Spanish Version of the Addiction Research Center Inventory (ARCI) Short Form to assess the instrument's overall relevance for literate and Spanish speaking adults from Houston, Texas with a reported history of polysubstance abuse. Results of the administration according to the "standard instruction" format are presented together with demographic and social data pertinent to the findings. Perceptual reactions to the inventory are identified and their influence on future research with the population are discussed. The frequent misunderstanding of instructions and terms shows that it is a mistake for addiction researchers and clinicians to assume that all members of the Hispanic culture are homogenous as well as monolingual. Specifically, there are variations in the manner in which the Spanish language is spoken, written, and understood among this population, and the various subgroups that make up the Hispanic population in the United States differ in their demographic make up as well as in the specific social problems faced by each group.

AFFILIATION:

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A CROSS-VALIDATION OF THE ADDICTION RESEARCH CENTER DRUG EXPECTANCY QUESTIONNAIRE (ARCDEQ)

C J. Wong, D. B. Newlin, and E. G. Singleton

The ARCDEQ consists of 36 items per drug and asks about nicotine, alcohol, marijuana, cocaine, and heroin self-reports of the anticipated effects of drug use. The initial validation sample consisted of 122 nonusers, “chippers”, and heavy and addicted users of a wide range of drugs. The cross validation sample contained 114 subjects with comparable drug use histories who participated at least six months subsequent to the initial study. Each sample was subjected to separate factor analytic procedures to develop scales specific to each drug type. Only items that were stable across both samples were retained to assure stability of factor structure. Some factor structures were similar, but for the most part, the factor structures differed markedly between drugs. In many instances, the differences in factor structures were attributable to the known differences in subjective drug effects.

AFFILIATION:

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MEASURING DRUG-INDUCED BEHAVIORAL IMPAIRMENT: CONSTRUCT VALIDITY

R. C. Taylor, S. J. Heishman, and E. G. Singleton

Human performance encompasses a wide range of behaviors, including sensory, motor, attentional, and cognitive abilities. The impairing effect of drugs of abuse on performance has been viewed as one component of a drug's abuse liability profile, and numerous laboratory tests have been developed to measure drug-induced impairment on the various aspects of human performance. However, across studies, there is not general agreement concerning what constitutes drug-induced behavioral impairment and how it should be measured. In this study, we attempted to validate, under controlled laboratory conditions, a behavioral evaluation designed to assess drug-induced impairment.

Research volunteers (n=18) with a current history of moderate ethanol, cocaine, and marijuana use participated in nine experimental sessions separated by at least 48 hours. At each session, subjects were administered a single dose of oral ethanol (0, .28, .52 g/kg), smoked marijuana (0, 1.8, 3.6% THC), or intranasal cocaine (4. 48. 96 mg/70 kg) under double-blind conditions using a triple-dummy procedure. At 15 minutes after drug administration, subjects were tested by trained observers on the behavioral evaluation, measuring physiological and pupillary indices, psychomotor coordination, and general behavioral and physical state. Other physiological, subjective, and performance measures were assessed periodically during the session. Subjects were discharged in the afternoon after drug effects had dissipated.

Data from the behavioral evaluation were subjected to a stepwise discriminant analysis that resulted in a mathematical model (or discriminant function) consisting of a subset of variables that were the best predictors of the presence and absence of each of the three study drugs. The best-predictor subset of variables for each drug was then subjected to a discriminant function analysis that determined which variables discriminated between each drug and placebo and among ethanol, cocaine, marijuana and placebo. The discriminant function of each drug was then used to predict whether subjects were dosed or not dosed with that particular drug. Predictive accuracy was measured in terms of efficiency, the percentage of all true results.

Results indicated that, in most cases, the behavioral evaluation was more efficient in predicting placebo than active drug conditions, especially when simultaneously comparing placebo, low, and high drug doses. The evaluation was equally efficient in differentiating among placebo and all drugs. The evaluation was least efficient in predicting low drug doses and low and high cocaine doses.

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MEASURING DRUG-INDUCED BEHAVIORAL IMPAIRMENT: CRITERION-RELATED VALIDITY

S. J. Heishman, E. G. Singleton, J. M. Lutz, and J. E. Henningfield

Human performance encompasses a wide range of behaviors, including sensory, motor, attentional, and cognitive abilities. The impairing effect of drugs of abuse on performance has been viewed as one component of a drug's abuse liability profile, and numerous laboratory tests have been developed to measure drug-induced impairment on the various aspects of human performance. However, across studies, there is not general agreement concerning what constitutes drug-induced behavioral impairment and how it should be measured. In this study, we attempted to validate, under controlled laboratory conditions, a behavioral evaluation designed to assess drug-induced impairment.

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Criterion-related validity of the behavioral evaluation was determined by examination of the correlational matrix for each drug that contained variables from the behavioral evaluation and several criterion-related measures of impairment. These measures included observer ratings of impairment, subjective reports, digit-symbol substitution test (DSST) performance, and drug dose.

Results indicated that most of the criterion measures showed orderly dose-related changes for each drug; however, only marijuana significantly slowed DSST performance. Percentage of observer ratings of impairment increased with dose for ethanol and marijuana, but not for cocaine. More of the behavioral evaluation variables were significantly correlated with observer ratings of impairment than with any other criterion measure. The fewest variables of the evaluation were correlated with subjective reports. More variables were correlated with marijuana dose than with ethanol or cocaine.

Variables in the evaluation were differentially related to the criterion measures of impairment. Thus, the determination of drug-induced impairment relies primarily on what criterion is used as the "gold-standard" of behavioral impairment.

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DRUGS AS CONDITIONED REINFORCERS IN HUMANS

A. J. Mattox, C. R. Schuster, and C. E. Johanson

Although the primary reinforcing effects of drugs have been widely studied, the process by which drugs acquire conditioned reinforcing effects has not. This process may be important in drug addiction because drugs are frequently used/abused in a context in which many powerful social reinforcers are available. These conditioned reinforcing effects may compliment the primary reinforcing effects in maintaining drug-seeking behavior. These studies are designed to evaluate the role of conditioned reinforcement in drug-seeking behavior. Participants were told that they would be receiving sedatives, stimulants, tranquilizing drugs or placebo. They were also told that they could earn money based on their performance on two computer tasks (delayed matching-to-sample and stimulus tracking tasks). In fact, all capsules contained dextrose and the computer tasks were designed such that administration of one capsule color was associated with a low pay-off (X=$6.00) and administration of the other capsule color was associated with a high pay-off (X=$24.00). The pay-off was independent of the subjects actual performance but the tasks were sufficiently complex that the subjects were unaware of this. Capsule color/reinforcement magnitude pairings (low or high) were counter balanced across participants. In experiment #1 (n=12) there were two alternating sessions of Drug A and Drug B administration and three drug choice sessions during which participants chose either Drug A or Drug B. In experiment #2 (n=12) there were three alternating sessions of Drug A and Drug B administration and two random assignment sessions during which participants were given either Drug A or Drug B. During all sessions heart rate, temperature and respiration were monitored continuously while blood pressure and behavioral measures (POMS, drug identification, certainty and liking) were taken at 15 minutes before, and 30, 60, 90 and 120 after capsule administration. Participants showed decreases in Elation and Positive Mood and increases in Confusion scale scores on the POMS relative to baseline after the administration of capsule color associated with a low density of reinforcement. In contrast, there were increases in Elation and Positive Mood and slight decreases in Confusion scale scores on the POMS relative to baseline after the administration of capsule color associated with a high density of reinforcement. During choice sessions, participants primarily selected the capsule color associated with high density reinforcement, indicating that this capsule color had acquired conditioned reinforcing properties. However, during the random assignment of capsule ingestion, there was no evidence for conditioned mood changes. Thus, these colored capsules had acquired conditioned reinforcing properties because of their association with monetary reinforcement. However, under the conditions of these experiments, there is no evidence that the conditioning of mood states, *i.e.,* ingestion of the different colored capsules, in the absence of the monetary pay off did not engender mood changes.

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CARD SORTING: A METHOD TO EVALUATE PERFORMANCE EFFECTS OF ABUSED DRUGS

M. Butschky, J. Nichels, N. Snidow, and W.B. Pickworth

Computer controlled tasks measuring cognitive and motor components of drug-induced performance changes require expensive hardware. programming sophistication and extensive subject training. Three card sorting tasks and a motor control task using 32 well-shuffled playing cards were evaluated for ease of administration, performance stability and drug sensitivity. Task complexity was systematically increased as follows (Berry *et al.,* 1965):

TASK	PILES	INFORMATION BITS
A	2	1 (color)
B	4	2 (color, suit)
C	8	3 (color, suit, value)
D	2	0 (motor control)

Card sorting occurred before and at 30, 105, 180 and 300 min after drug administration. The dependent measure was the time to complete the tasks. Drugs (ethanol 0.3, 1 gm/kg; marijuana 1.3, 3.9% THC; d-amphetamine 10, 30 mg; pentobarbital 150, 450 mg; hydromorphone 1, 3 mg; placebo 2 occasions) were administered to eight male residential volunteers in a double-blind, triple dummy within-subject experiment. Subjects quickly learned the tasks and performance was stable throughout the 30 day study. Sorting time significantly differed as a function of task complexity averaging 23, 31 and 40 seconds for Tasks A, B, and C, respectively. Time for completion of the motor control task averaged 13 seconds . Only pentobarbital (450 mg) impaired motor performance; however, the high doses of ethanol, marijuana and pentobarbital slowed sorting to 122%. 109% and 130% of baseline levels. Amphetamine (30 mg) tended to increase speed (91% of baseline) on the difficult task (C). Low doses of the drugs had smaller performance effects that were generally not significant. Simple card sorting tasks can be used to evaluate systematically the effects of drugs on cognitive performance. However, these data do not support the concept that drug-impaired performance is a function task complexity.

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COGNITIVE FUNCTION IN DUALLY-DEPENDENT OPIATE AND COCAINE USERS BEFORE AND AFTER BUPRENORPHINE OR PLACEBO TREATMENT: AN N400 ERP STUDY

E. M. Kouri, S. E. Lukas, and J. H. Mendelson

The present study was conducted to assess psycholinguistic cognitive function following heroin and cocaine detoxification and to investigate whether buprenorphine treatment improves the disruptive effects of detoxification. Fifteen male volunteers between the ages of 25-40 who met DSM-IIIR criteria for concurrent opiate and cocaine dependence provided informed consent to participate in this study. Subjects were admitted to an inpatient treatment unit and were tested before, after 12 days of detoxification and then on the 15th day of either buprenorphine (12 mg/day, s.l.) or placebo treatment. Testing consisted of a visual N400 psycholinguistic task involving semantic anomalies. There were no significant differences in N400 amplitude, latency, or topographic distribution between the drug-dependent subjects and matched controls. Following detoxification there was a significant decrease in N400 amplitude in the drug-dependent group when compared to controls. During this second visit, self-reported signs of withdrawal were minimal. Buprenorphine treatment significantly reversed the N400 amplitude decrement following detoxification while placebo-treated subjects continued to show depressed N400 amplitudes. These data demonstrate that buprenorphine treatment is effective in eliminating detoxification-induced impairments in one measure of psycholinguistic cognitive ability.

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LONG-TERM EFFECTS OF BUPRENORPHINE FOR TREATMENT OF COMBINED HEROIN AND COCAINE DEPENDENCE

D. R. Gastfriend, J. H. Mendelson, N. K. Mello, S. K. Teoh, S. Reif, and S. L. Baker

Buprenorphine (BPN) reduces opiate and cocaine use in animal and human drug dependence studies, but long term efficacy and dose-response characteristics have not been determined. In two phases of outpatient trials, sublingual BPN was administered in men with concurrent heroin and cocaine dependence to determine its long-term safety and effectiveness for these disorders. In the first phase, subjects received BPN, either 4 mg or 8 mg, in single blind fashion (Gastfriend *et al.,* 1993). In the second phase, subjects received either BPN 12 mg or placebo, in double-blind fashion. After inpatient induction onto the study drug, subjects volunteered for up to 48 weeks of daily outpatient treatment.

Results: Randomization resulted in no significant differences among the phase I or phase II groups in demographics or drug use. Dropout by placebo subjects was four times greater than by BPN subjects (35% vs. 8%; X^2 = 11.03, p<.001). Less than half as many placebo subjects entered outpatient study treatment as did BPN subjects (23% vs. 55%). The BPN treatment groups consisted of 12, 12 and 7 subjects maintained at 4, 8 or 12 mg, respectively.

For BPN treated groups, 68% of subjects were retained for a mean of 30 weeks. Urine screens were negative 39% of the time for opiates and 48% of the time for cocaine. Opiate use decreased by 76% (6.9 to 1.7 days per week) overall. Lower doses of BPN were associated with less frequent opiate positive urines and days of use although these differences did not reach significance. There was no loss of efficacy over 48 weeks. Cocaine use decreased by 62% (5.1 to 1.9 days per week). Lower BPN dose was associated with fewer cocaine positive urines (ANOVA F=3.45, p=.03). Also, lower doses of BPN were associated with fewer days of cocaine use (ANOVA f=4.31, p=.01), although this was partially accounted for by a trend for greater baseline cocaine use in the 12 mg group. For the 4 and 8 mg doses of BPN, there was no loss of efficacy over 48 weeks. Craving data also indicated a dose effect of BPN (4 mg better than 12 mg) although these differences did not achieve significance.

Conclusions: BPN was more effective than placebo at stabilizing subjects in treatment with minimal adverse effects. A dose effect may exist for BPN in which higher doses may be less effective. Further work is needed to determine optimal dose characteristics, however, BPN maintenance appears safe and beneficial for the treatment of concurrent heroin and cocaine dependence.

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A CONTINGENCY MANAGEMENT PROCEDURE FOR OPIOID/COCAINE ABSTINENCE IN METHADONE-MAINTAINED COCAINE ABUSERS: A PILOT STUDY

A. H. Oliveto, R. Schottenfeld, T. R. Kosten, and J. Falcioni

Cocaine use is prevalent among methadone-maintained individuals and can lead to leaving treatment prematurely. Thus, it is important to develop treatment strategies aimed at facilitating cocaine abstinence in methadone-maintained individuals. The present pilot study examined the clinical effectiveness of a contingency management procedure in methadone-maintained cocaine abusers. Six volunteers (1 male/5 female/2 white/3 black/l Hispanic, mean age 40 yrs, none employed) were recruited for this five-week study from the APT Foundation's Legion Avenue Methadone Maintenance Program. The contingency management procedure consisted of monetary incentives administered for documented opioid- and cocaine-free urines. During week one, each submitted urine earned a voucher worth $5.00, regardless of toxicology results (to contact subjects with the incentives). Subsequently, every drug-free urine earned a monetary voucher worth $20.00 during week two, $15.00 during week three, $10.00 during week four, and $5.00 during week five. Supervised urine samples were obtained thrice weekly (MWF) and missed urines were counted as positive. At baseline, 73.3% (+/- 6.7) of the ten most recent urines obtained prior to study entry were positive for cocaine and/or opiates. In contrast, during weeks 2-5 of the study, 44.5% (+/- 12.0) of urine samples were positive (Student's t ratio=2.78; $p<0.05$). In addition, the self-reported number of days in which cocaine was used decreased and self-reported control over urge to use cocaine increased in a linear, dose-related manner across weeks one through five ($F=7.81$, $p<0.05$ and $F=10.24$, $p<0.05$, respectively). The number of dimes and dollar value of cocaine used also showed trends toward dose-related decreases across weeks one through five ($F=5.98$, $p=0.07$ and $F=5.47$, $p=0.08$, respectively). Since the conclusion of this study, urine samples obtained on a random basis in five of six subjects were 61.7% (+/-13.7) positive, which was not significantly different from baseline (Student's t ratio=0.64, $p>0.1$). These findings suggest that significant reductions in cocaine and opiate use can be facilitated using monetary incentives under a contingency management procedure, but that a short-term intervention does not promote sustained abstinence.

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EFFECTS OF PRE-TREATMENT OF DIAZEPAM ON METHADONE SELF-ADMINISTRATION

R. Spiga, S. Rafieha, J. Grabowski, P. B. Silverman, and R. A. Meisch

The effects of acute doses of diazepam on self-administration of methadone were examined. Methadone-maintained patients with a history of benzodiazepine use were recruited as subjects. Forty-five minutes prior to the methadone self-administration session the subjects received an oral pre-treatment dose of 0 (placebo), 5, 10 or 20 mg of diazepam. Subjects maintained on 80 mg of methadone were permitted to self-administer 0.054 mg/ml (0.54 mg per delivery) in a 60 minute session. During the methadone self-administration session 10 ml of methadone or vehicle (deionized water) was delivered contingent on completion of 128 button A or B presses (FR 128). Subjective measures were collected before and 5, 30, 60, 90 and 150 minutes after the methadone self-administration session. Preliminary results suggest that the diazepam pre-treatment decreased methadone self-administration. The 10 and 20 mg pm-treatment doses of diazepam in combination with approximately 10 to 15 mg of self-administered methadone reliably increased reports of the subjective effects “strong”, “like”, “good” and “high” relative to placebo and self-administration of 20 to 25 mg of methadone.

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TIME COURSE OF COCAINE WITHDRAWAL SYMPTOMS IN COCAINE-ABUSING METHADONE-MAINTAINED PATIENTS

A. Margolin, S. K. Avants, and T. R. Kosten

A phasic model of cocaine withdrawal has not been supported in studies conducted with cocaine abusing inpatients, suggesting that factors such as social context and cue-elicited craving may play a role in the experience of "withdrawal" symptoms. Because cocaine abuse is a major problem among methadone-maintained outpatients, we sought to determine whether methadone-maintained patients who abuse cocaine experience cocaine withdrawal symptoms, and to characterize the time-course of these symptoms. One hundred cocaine-abusing methadone-maintained individuals completed an anonymous questionnaire asking them to rate the intensity of 18 symptoms at six time points from 30 minutes to two weeks post-cocaine use. The symptoms were drawn from various sources, including proposed DSM-IV criteria for cocaine dependence, the Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM), and the Gawin and Kleber model of cocaine withdrawal. We found that in general cocaine "withdrawal" symptoms reported by our subjects tended to be mild to moderate in intensity and short-lived. Dysphoric symptoms were most intense between 30 minutes and three hours post-binge and tended to subside within 24 hours. Thirty minutes and three hours post-binge symptoms of "dysphoric agitation", such as anxiety, restlessness, irritability, tachycardia, and cocaine craving, predominated; 24 hours post-binge, and thereafter, a need for sleep and food predominated. Intensity of symptoms was unrelated to amount of cocaine used, length of binge, or history of cocaine abuse, but was related to route of cocaine administration and sex of user -- intravenous cocaine users and males reported more intensely dysphoric symptoms.

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CLINICAL USE OF BUSPIRONE IN COCAINE DEPENDENT HIV-INFECTED PATIENTS IN MMT

M. D. Herbst, N. Nanda, and S. L. Batki

OBJECTIVE: The authors conducted a retrospective analysis of the open clinical use of buspirone among HIV-infected cocaine dependent subjects in methadone maintenance treatment (MMT).

METHODS: Clinic records were reviewed for a one year period and revealed six subjects in MMT who met DSM III-R criteria for cocaine dependence who had been given buspirone in open clinical use with daily dispensing of buspirone with methadone. Mean daily dispensing of buspirone with methadone. Mean daily dose of buspirone was 45 mg. Mean methadone dose was 60 mg. Random drug urinalyses obtained in the course of routine clinical monitoring and clinic attendance were the outcome measure and were compared for 60 day periods before and after initiation of buspirone.

RESULTS: Mean proportion cocaine positive drug urinalyses was 77% in the 60 day period prior to initiation of buspirone and 26% in the first 60 days after initiation of buspirone. ($p > .05$ Wilcoxon). Mean proportion morphine positive urine drug tests fell from 24% to 14%. (NS-Wilcoxon). Mean number of missed clinic days was 1.8 in the 60 days prior to initiation of buspirone and 1.2 in the 60 days after. (NS-Wilcoxon). None of the patients discontinued buspirone due to side effects.

CONCLUSIONS: This retrospective analysis of the open clinical use of buspirone in mixed opiate-cocaine dependent patients in MMT suggests that buspirone was well tolerated and may have potential benefit as a pharmacological treatment for mixed opiate-cocaine dependence. Prospective controlled trials may clarify the role of buspirone in the pharmacotherapy of cocaine dependence.

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ACUPUNCTURE FOR THE TREATMENT OF COCAINE ABUSE IN HIV-POSITIVE METHADONE-MAINTAINED PATIENTS

S. K. Avants, A. Margolin, P. Chang, and T. R. Kosten

We conducted a single-blind clinical trial of acupuncture for the treatment of cocaine dependence in HIV-positive and negative methadone-maintained patients. Forty DSM-III-R cocaine-dependent patients maintained on a stable dose of methadone were stratified by HIV status and randomized to receive acupuncture in sites commonly used for the treatment of drug addiction ("Type I" acupuncture) or to receive control needle insertion in sites located within 2 mm of Type I sites ("Type II" acupuncture). Subjects received treatment daily (Monday-Friday) for six weeks. The primary outcome measures were retention in treatment and cocaine use, assessed by twice weekly urine screens. Other measures included Beck Depression Inventory, Addiction Severity Index, SCL-90, Neurological Impairment Screen, and weekly self-reported cocaine use and craving. Seventy-eight percent of subjects completed the study, receiving an average of three treatments per week. There was a trend for HIV-positive patients to respond better to treatment in percent of urines positive for cocaine, self-reported amount and frequency of cocaine use, self-reported craving for cocaine, and ASI drug composite scores. There were also decreases in Beck depression scores, neurological impairment scores, and a number of SCL-90 symptoms. Subjects receiving Type I acupuncture reported significantly less cocaine craving, and marginally less cocaine use than subjects receiving Type II acupuncture. Data from this study suggest that acupuncture may show promise for the treatment of cocaine dependence in HIV-positive methadone-maintained patients. However, in the absence of a control for the possible non-specific relaxation effects of acupuncture treatments, no firm conclusion can be drawn.

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A COMPARISON OF COCAINE DEPENDENT PATIENTS WITH AND WITHOUT A COEXISTING OPIOID USE DISORDER

R. D. Weiss, J. Martinez-Raga, M. L. Griffin, and C. Hufford

The authors studied 90 patients hospitalized for the treatment of cocaine dependence in order to determine the clinical significance of a co-existing opioid use disorder in this population. Thirty-two patients (36%) had a diagnosis of opioid abuse or dependence, while 58 (64%) did not. The two groups were compared on sociodemographic characteristics, substance use histories, measures of psychopathology, severity of drug-related problems, and three-month cocaine use outcome. The authors found that patients with an opioid diagnosis were more likely to also have current major depression, antisocial personality disorder, and other concurrent substance use disorders. They also had higher composite scores on the Medical and Drug sections of the addiction Severity Index, and had a longer history of cocaine use. Nonetheless, three-month cocaine use outcome was similar for the two groups. Interestingly, the patients with an opioid use disorder engaged in more treatment during the three months after discharge. These results suggest that individuals with a coexisting opioid use disorder may constitute a subgroup of cocaine dependent patients with worse prognostic characteristics. However, differential treatment for this population may improve their outcome.

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PATTERN OF COCAINE USE IN METHADONE-MAINTAINED INDIVIDUALS

F. R. Levin, R. W. Foltin, and M. W. Fischman

The rapid rise of cocaine use among methadone-maintained patients has greatly concerned clinicians working within methadone treatment settings. Understanding the pattern of cocaine use may provide clues regarding both the manner in which methadone and cocaine interact and potential treatment strategies. Methadone-maintained individuals seeking admission into an intravenous cocaine study were interviewed using a pattern of drug use assessment. Sample characteristics included: 94% male, 94% Caucasian, 37±5 mean years of age, 13 ± 1 mean years of education, and 84% unemployed. Average methadone dose was 82 ± 20 mg. During the 28 days prior to evaluation, 63% of the applicants used cocaine on more than 20 days, and fewer than 50% missed any of their methadone doses. Although 74% of the applicants had used heroin in the past 28 days, only two of the applicants used heroin for ten or more days. Subjects reported weekly cocaine use in either grams or dollars worth. Average weekly amounts were 5.3 ± 3 grams or $298 ± 413. All but one subject received their methadone in the morning, and more than 45% of subjects began using intravenous cocaine within three hours of receiving their methadone. Although the number of cocaine injections ranged from 2 to 20 each day, 7 of 11 subjects injected at least five times per day. Possible explanations for consistent combined cocaine and methadone use include: 1) an intensified subjective response to methadone and/or cocaine, 2) a novel subjective response to methadone and/or cocaine, and 3) a modulation of drug-induced effects (*e.g.*. cocaine-induced jitteriness decreased by methadone). “Binge” cocaine use does not appear to be a typical pattern of use among methadone patients. However, during daily periods of cocaine use, multiple repeated injections of large amounts of cocaine are taken and these may place patients at substantial risk for medical complications. These findings emphasize the importance of detecting cocaine use among methadone patients and developing novel treatment strategies to treat these dually-addicted individuals.

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COCAINE ABUSE IS DECREASED WITH EFFECTIVE METHADONE MAINTENANCE TREATMENT AT AN URBAN DEPARTMENT OF VETERANS AFFAIRS (DVA) PROGRAM

L. Borg, D. M. Broe, A. Ho, and M. J. Kreek

Cocaine abuse is a serious problem in the United States today and can be associated with illicit opioid use. Effective long-term treatment of heroin addiction with methadone maintenance may be associated with diminished cocaine abuse. In a single clinic, 109 patients were studied over a 12 month period as they entered or continued treatment at an urban DVA methadone program. During the study period, 30 patients entered the program, 10 patients left, and 74 patients were in treatment continuously. Subject race/ethnic distribution was 69.7% African-American, 24.8% non-Hispanic white, and 5.5% Hispanic; 38% of the patients were anti-HIV-l seronegative, 31% were anti-HIV-l seropositive and 31% had unknown HIV status. Supervised weekly urine specimens were assessed for the presence of opioids and cocaine with gas liquid chromatography. Urine toxicology data were analyzed for each patient's last month in treatment following the treatment intervals used by Ball and Ross (1991). and these data were compared to admission drug use status.

The mean methadone dose in the DVA program was 67.4 ± 2.1 mg. Of the 18 patients in treatment < six months, 33.3% abused cocaine and 50.0% abused opioids. In the 47 patients treated for 6 to 53 months, 34.8% abused cocaine and 23.4% abused opioids. Of those in treatment for > 53 months (n = 44). 2.3% were positive for cocaine and 4.5% positive for opioids. Opioid abuse was progressively reduced across all three treatment intervals. Of the 89 patients for whom admission data were available, the number with cocaine abuse also decreased in all treatment intervals: by 25.0%. by 29.3% and by 34.4% respectively. The overall retention rate in the DVA program under study was 90.8%. The retention rate for the patients admitted during the 12 month study was 86.7%. versus 92.4% for those already in treatment. The significantly lower mean daily dose of the eight patients who left treatment compared to that of patients in treatment at the end of the study year (50 ± 7 *vs* 69 ± 2 mg, t = 2.34, df = 105, $p < 0.05$, one-tailed), suggests that an adequate methadone dose plays a role in retention in treatment.

These data demonstrate that with effective methadone maintenance treatment for heroin addiction, cocaine abuse is also decreased.

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NICOTINE AND COCAINE DYNAMICS: PATTERNS AND CONSEQUENCES. PRELIMINARY FINDINGS

M. E. Khalsa, M. D. Anglin, and F. H. Gawin

There are severe health consequences related to tobacco smoking and to cocaine smoking. Furthermore, cocaine and tobacco use are teratogenic. Because of the high prevalence of tobacco smoking among crack cocaine smokers, tobacco cessation programs need to be integrated into treatment for crack cocaine addicts. The objectives of this study were to explore the dynamic links between tobacco and crack cocaine smoking: to gather information about motivation of crack cocaine addicts to quit smoking; and to formulate recommendations concerning optimal timing of smoking cessation efforts and smoking cessation methods appropriate for this group. A total of 120 male cigarette smokers meeting DSM III-R criteria for crack cocaine dependence (and not for any other drug or alcohol), were studied. A longitudinal retrospective Natural History methodology was used to collect information on drug use patterns. Data are available from 80 subjects (mean age 40 years; 88% African-American). Ninety-one percent smoked tobacco within the month prior to the interview (mean cigarettes/day=11; 76% smoked high nicotine content cigarettes) and 53% reported waking up craving a cigarette more than once a week. The most frequently reported methods used when subjects have tried to quit cigarettes were: “cold turkey”; “gradual reduction”; and “candy or chewing gum”. Prochaska and DiClemente groups were: long-term quitters, 8%; short-term quitters, 4%; action group, 14%; contemplation group, 28%; and pre-contemplation group, 48%. Forty percent reported at least one period of tobacco abstinence of at least one month. All subjects (abstinent and never abstinent) concurred that, in general, smoking crack cocaine did/would make it more difficult to quit cigarettes. The majority of the subjects reported crack cocaine abstinence facilitated cigarette abstinence. However, duration of crack abstinence (>1 month) in those cigarette abstinent (12%) was only half as long (10 months) as in those who smoked (88%). Pre-contemplators endorsed the highest proportion of tobacco smoking pros on the Prochaska Pros and Cons of Smoking Scale. Short-term Quitters had the highest values on all three Confidence subscales. Habit/Addiction was the lowest scored temptation measure by all groups. These data are complex, further time series analyses to study the dynamics between patterns of nicotine and crack cocaine smoking are underway.

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RELATIONSHIP OF PSYCHOPATHOLOGY TO COCAINE VERSUS COCAINE AND ALCOHOL ABUSE

R. C. McMahon, R. M. Malow, and S. J. Ireland

INTRODUCTION: The use of cocaine and alcohol in combination produces a potent active metabolite, cocaethylene, that may produce biochemical, physiological and psychological effects exceeding those of either drug ingested alone. Alcohol and cocaine are frequently used concurrently, resulting in increased mortality and morbidity. The current study evaluates background, personality, symptom, and substance use differences between males who reported only cocaine use and those who reported cocaine and alcohol use to intoxication in the month prior to admission to drug treatment.

METHODS: Cocaine dependent males reporting only cocaine use (n=110) and reporting both cocaine and alcohol use (n=56) were drawn from admissions (N=304) to two residential treatment programs. Following informed consent, subjects completed the Addiction Severity Index (ASI) and Millon Clinical Multiaxial Inventory-II (MCMI-II). A discriminant analysis was conducted using age, education, number of previous treatment attempts, program currently attended, and the pathological personality and clinical symptom syndrome scales of the MCMI-II to differentiate between the groups.

RESULTS: A single discriminant function (Wilks' Lambda = 68, p=.0003) was derived. The structure matrix revealed that, in addition to the treatment program attended, the MCMI-II Alcohol Abuse, Anxiety, and Dysthymic scales contributed significantly to discrimination between the groups. Follow-up univariate tests revealed that the group which used both alcohol and cocaine scored higher on the Alcohol Abuse ($F[1,164]=29.57$, $p<.00001$), Anxiety ($F[1,164]=5.83$, $p=.016$), and Dysthymic ($F[1,164]=5.80$, $p=.017$) scales of the MCMI-II, and were more likely to attend a county-funded than a private, non-profit facility than the group reporting only cocaine use.

DISCUSSION: These results are consistent with previous findings that the concomitant use of cocaine and alcohol is associated with higher levels of anxiety and depression than cocaine use only. These findings suggest that subtyping substance abusers according to drug use patterns may provide a basis for designing specific therapeutic interventions and for investigating treatment outcome.

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ALCOHOL AND COCAINE INTERACTIONS IN HUMANS: HORMONAL AND PHARMACOKINETIC PROFILE

M. Farre, R. de la Torre, M. T. Teran, M. L. Gonzalez, E. Menoyo, J. Ortuno, P. N. Roset, J. Segura, and J. Cami

In a previous work, we studied the interactions between alcohol and cocaine on subjective, physiological, psychomotor performance and pharmacokinetic parameters (Farre *et al.,* 1993). The present investigation was designed to assess the effects of the drug combination on hormonal aspects.

METHODS: Eight experienced-non dependent healthy male volunteers were included in the study. They participated as out-patients in seven experimental days: three training sessions and four study sessions. Oral ethanol 0.8 g/kg (E) was administered as a beverage containing vodka, tonic water and lemon. Cocaine HCl 100 mg (C) was snorted. The study sessions were carried out as a double-blind, double-dummy, randomized, cross-over and controlled clinical trial. The four drug conditions were: placebo E-placebo C, E-placebo C, E-C, placebo E-C. Drug effects were evaluated measuring vitals, subjective effects (VAS, ARCI-49 item). Blood samples were obtained to determine cocaine, cocaethylene and metabolites (GC/MS), ethanol (GC/FID). prolactin (MEIA) and cortisol (FPIA).

RESULTS: Active drugs produced its characteristics effects on vitals, VAS and ARCI. The drug combination decreased significantly the scores of 'drunk', and increased the 'high' scores in comparison to E or C. Cocaine concentrations were higher in the combination condition, appearing also cocaethylene. Plasma prolactin levels were higher in the two conditions that included alcohol. C alone induced a decrease in prolactinemia. Plasma cortisol concentrations were almost two fold higher in the conditions that included cocaine. E and placebo had similar effects in this hormone.

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NEUROPSYCHOLOGICAL RECOVERY IN ALCOHOLICS AND COCAINE USERS

M. J. Selby, M. Quiroga, S. J. Ireland, R. M. Malow, and R. L. Azrin

Introduction. Neuropsychological (**NP**) deficits, particularly memory and executive functions, have been documented in chronic abusers of alcohol and cocaine. However, recovery from substance-related cognitive dysfunction following abstinence is less well understood. The present study compared NP functioning among alcohol and cocaine abusers with varying levels of abstinence to explore recovery of cognitive functioning with increased abstinence.

Methods. A pool of incarcerated males completed a comprehensive NP battery. Using DSM-III-R diagnostic criteria and duration of abstinence (<6 months and >6 months), subjects were classified into one of five subgroups: 1) alcohol abusers with short-term abstinence (**AS**); 2) alcohol abusers with long-term abstinence (**AL**); 3) cocaine abusers with short-term abstinence (**CS**); 4) cocaine abusers with long-term abstinence (**CL**); and 5) an incarcerated control group with no history of alcohol or drug abuse (n=50).

Results. The groups did not significantly differ on age, education, ethnicity, and IQ. A MANOVA revealed a significant group by time interaction ($F=1.5$, $p<.03$). as well as group ($F=1.4$, $p<.05$) and time ($F=4.6$, $p<.001$) main effects. Post-hoc tests revealed significant differences only on the Stroop, RAVLT trial 5, and Trails A and B. However, ALs subjects performed better than ASs on 12 of 14 measures. CLs performed better than CSs on 11 of 14 measures. Controls performed better than ASs on all 14 measures and CSs on 8 of 14 measures. ALs performed worse than controls on 3 of 14 measures while CLs performed better than controls on 12 of 14 measures. Both CSs and CLs performed better than comparably abstinent alcohol abusers on 12 of 14 measures.

Discussion. In this sample, alcohol abusers were more impaired on NP functioning than cocaine abusers. Cocaine abusers were minimally impaired even at the shorter abstinence interval. Longer periods of abstinence from both cocaine and alcohol appear to be associated with better performance on a majority of the NP measures. Although using a cross-sectional design, the present study suggests that NP recovery occurs in both alcohol and cocaine abusers with increasing abstinence.

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TREATMENT INTENSITY PREDICTS ABSTINENCE AND REDUCTION IN DRUG USE FOR COCAINE-DEPENDENT METHADONE PATIENTS

S. Magura, A. Rosenblum, M. Palij, M. Lovejoy, J. Foote, L. Handelsman, and B. Stimmel

This study identified predictors of recovery among cocaine-using methadone patients who received up to six months of intensive cognitive-behavioral outpatient treatment. The major hypothesis was that treatment intensity should predict changes in cocaine use. Subjects (N = 77) met DSM-III-R criteria for current cocaine dependence (by the SCID) and attended up to five individual and group sessions per week. Patient intake characteristics: male (53%); mean age = 36 years; Hispanic (64%); African-American (31%); unemployed (77%); more than ten years of regular cocaine use (49%); current depression/mood disorder (42%); current anxiety disorder (26%); current multiple drug dependence (55%); mean daily methadone dose = 68 mg; completed study treatment (61%); session attendance rate (55%). Paired comparisons between subjects, intake, and six-month self-reports of drug use during the past 30 days, showed reductions in cocaine use frequency (18 days versus 12 days) and drug injection (3.6 days vs. 2.2 days) [both $p < .05$]. Weekly urinalysis showed that 32% of treatment completers were abstinent from cocaine at 37 to 48 weeks after treatment admission vs. only 9% of treatment non-completers. In bivariate analysis, younger age, lower cocaine use at baseline, and more treatment sessions attended were associated with less cocaine use at follow-up. Quartiles of sessions attended were recoded as dummy variables (to model non-linearity) and entered into a hierarchical multiple regression equation, along with variables which had significant bivariate correlations with cocaine use frequency at baseline, with cocaine use frequency at follow-up, or with sessions attended. Attending more than 20 sessions independently explained 13% of the variance in cocaine use at follow-up. The effect was strongest for patients attending the most sessions (85-133); this group reduced cocaine use an average of 60%. The results indicate that there is a dose-response relationship between increased treatment intensity and reduction in cocaine use. These cocaine-dependent patients present severe psychiatric and interpersonal deficits and have been considered resistant to psychotherapy. The study suggests that innovative psychotherapy which is structured, intensive, coherent and emphasizes positive reinforcement can successfully engage, retain, and treat many such problematic patients.

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RETENTION IN HIGH INTENSITY TREATMENT FOR COCAINE USE

A. Rosenblum, S. Magura, M. Palij, M. Lovejoy, J. Foote, L. Handelsman, and B. Stimmel

This study identified predictors of treatment retention among methadone patients enrolled in experimental treatment for cocaine dependence. Subjects (N = 141) were randomly assigned to either (1) high-intensity treatment (5 x weekly individual and group psychotherapy for six months); (2) high-intensity treatment plus a five week, placebo-controlled, bromocriptine medication trial, or (3) low-intensity treatment (1 x weekly group for six months). Due to pregnancy concerns only males were included in the medication trial. Subjects met DSM-III-R criteria for cocaine dependence and had been stabilized on methadone. Subjects were 55% male, 45% female; 55% Hispanic, 35% Black, 9% White. No differences in study treatment completion were found for patient/therapist matching based on ethnicity or gender ($p > .10$). Nor were there any main effects for patients' age, gender, cocaine use frequency, receiving bromocriptine or placebo, or psychological distress as measured by the Brief Symptom Inventory (BSI). Using hierarchical regression, retention (number of days in treatment) was regressed upon: 1) variables significantly associated with either retention (ethnicity and employment) or treatment condition (BSI and excessive alcohol use), 2) two dummy variables representing the three treatment conditions, and 3) the interaction between treatment condition and BSI scores. Non-Hispanics and subjects in high-intensity treatment without medication were more likely to be retained than other subjects. Two treatment by BSI interactions were identified: High BSI scores among low-intensity medication subjects. high BSI scores predicted treatment retention.

Enhanced strategies are needed to improve engagement of Hispanic drug-using patients. Intensive psychotherapy appears to increase retention rates among patients with elevated psychopathology. The demands of a medication trial (blood work, increased urine testing, frequent interviews. uncertainty about medication) may be contributing to drop out rates.

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SOCIAL IDENTITIES AND TREATMENT OUTCOMES AMONG ALCOHOL AND COCAINE USERS IN PRIVATE TREATMENT

C. Weisz

Treatment response may depend, in part, on substance abusers' social identities. This study examined the relationships between social identities, social support, and treatment outcomes. Major predictions were that better outcomes would be associated with: 1) a greater number of positively valued social identities at treatment entry and follow-up, and 2) higher levels of conflict between substance use and valued identities at treatment entry.

This interim report involves 40 cocaine and/or alcohol users in private treatment. Interviews were conducted at treatment entry and 12 weeks after starting treatment. The social identity questionnaire asked Ss about their social roles, relationships, and category memberships. The identity score was the number of identities that Ss indicated as descriptive, positive, and important. Separate scales measured these dimensions for each identity category. The 11 identities were: spouse/romantic partner; family member; friend;worker/homemaker/student; group member; person with a hobby; member of ethnic/racial group; religious person; spiritual person; political person; active/physically fit person. In addition, for each identity, Ss rated how much their alcohol or drug use "interfered with being a_____" during the month before starting treatment. The conflict score was the sum of the conflict ratings for identities that Ss indicated were descriptive, positive, and important. Measures of perceived emotional, tangible, and abstinence-specific support were also included. Abstinence status, based on self-report and urine screens completed as part of treatment, indicated whether Ss were continuously abstinent from alcohol and cocaine, 1) between treatment entry and follow-up and, 2) within the last 30 days of the follow-up interview.

Identity scores increased from treatment entry to follow-up. The expected main effect of abstinence status on identity scores was not present for either outcome variable. There was an unexpected interaction between time and abstinence status for the full follow-up period Baseline identity scores were not related to abstinence status; however, at follow-up, abstinent Ss had *lower* identity scores than nonabstinent subjects. The relationship between conflict scores and abstinence was in the predicted direction but not significant. Perceived emotional support correlated positively with identity scores at baseline and follow-up, and with conflict scores at treatment entry. The social identity perspective may provide a useful tool for understanding behavior change and developing treatment strategies that foster identities associated with abstinence.

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EFFECTS OF DESIPRAMINE, AMANTADINE, OR FLUOXETINE ON COCAINE AND OPIOID USE IN BUPRENORPHINE-MAINTAINED PATIENTS: A PILOT STUDY

A. Oliveto, T. R. Kosten, R. Schottenfeld, and D. Ziedonis

This study determined the efficacy of administering promising cocaine anti-craving medications in combination with buprenorphine to decrease cocaine and opioid use among cocaine-abusing opioid-dependent patients. Eighteen cocaine-abusing opioid addicts, who presented a urine sample positive for both cocaine and opioids, were enrolled in a double-blind 12-week trial in which they received on a daily basis 8 mg s.l. of buprenorphine plus one of the following: desipramine at 150 mg (DMI, N=6), amantadine at 300 mg (AMA, N=6), or fluoxetine at 60 mg (FLX, N=6). Urine samples were obtained one to three times per week. The order of greatest patient retention across the 12 weeks was DMI (5/6) > AMA (4/6) > FLX (l/5).

During week one, the mean percentage of opioid-free urines in each group was 16.7±16.7 (DMI), 6.7±6.7 (AMA), and 20.8±12.5 (FLX). The mean percentage of cocaine-free urines was 8.5±8.3 (DMI), 20.0±12.2 (AMA), and 50.0±28.9 (FLX). After the first two weeks during which patients were stabilized on the medications, the percentage of opioid-free urines increased by a mean of 20.6±14.1 in the DMI group and 5.9±4.8 in the AMA group, but decreased by 5.2±9.8 in the FLX group. The percentage of cocaine-free urines increased by a mean of 16.9±10.8 and 8.92±12.1 in the DMI and AMA groups, respectively, and decreased by 13.9±13.9 in the FLX group. These results suggest the BUP/DMI group showed the greatest retention. Although baseline rates differ, the DMI and AMA groups tended to show greater opioid and cocaine abstinence than the FLX group.

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DRUG TREATMENT DELIVERY: STAFFING PATTERN, SERVICE PROVISION AND PERCEPTION OF QUALITY

M. L. Polinsky and Y. I. Hser

A mail survey was recently conducted of all programs in Los Angeles County that treat adult clients with drug problems. The survey included questions covering the major areas of organizational structure, staffing patterns, services, program philosophy and intensity, intake, treatment planning, and discharge. Questions were also asked about who completed the booklet (e.g.. demographics, years of experience) and respondents were asked to rate the quality of their program in various service areas. An 83% return rate represented 294 of 354 programs identified as eligible for the study.

Ratings of "excellent" were given to overall program effectiveness by 66% of the respondents, to overall treatment staff effectiveness by 64%. to quality of counseling services by 63%. to quality of referral services by 54%, to quality of medical care by 37%, and to quality of psychiatric care by 26% of the respondents. Ratings of "below average" or "average" were given to medical care by 16% of the respondents, to psychiatric care by 13%, to referral services by 11%, to treatment staff effectiveness and overall program effectiveness by 4%, and to counseling services by 3%.

The preliminary analysis presented examines the relationship of perceived overall program effectiveness with the reported staffing pattern (number of staff, qualifications, caseload) and service provision (type and intensity). The results may suggest specific areas for improvement in the current drug treatment delivery system.

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ORGANIZATIONAL FACTORS RELATED TO THE DIFFERENTIAL PROVISION OF SERVICES IN 17 DRUG TREATMENT PROGRAMS

T. A. Hagan, J. C. Ball, A. T. McLellan, K. Meyers, and M. Randall

This exploratory study demonstrated that current organizational theory can be applied to substance abuse treatment milieus; that program milieus can be quantified; that organizational characteristics can be categorized into six structural elements; and that these structural elements are significantly associated with service delivery. Although future scaling work on the structural element measures is required, the primary findings of the study are the following: 1) substance abuse treatment programs do not readily fit into open, closed, or proactive systems; 2) "centralization of authority" within an organization is positively correlated with traditional treatment services (i.e., individual, group, and crisis interventions) ($r = .27$, $p = .008$) as is "formalization" ($r = .22$; $p = .02$); and 4) "communication" within an organization is positively correlated with enhanced services ($r = .30$, $p = .005$) as is "participation in decision making processes" ($r = .21$, $p = .03$). The quantitative methodology developed in this study will allow future investigation of how client outcomes are related to program structures and processes.

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DRUG TREATMENT PROGRAM AND CLIENT RETENTION: A HIERARCHICAL LINEAR MODEL

C.-P. Chou and Y.-I. Hser

The impacts of program characteristics on client outcome have received substantial attention in substance abuse treatment research. Program characteristics usually involve modality, service provision, staff pattern and qualification, and policy. Client characteristics may include race, gender, age, and prior drug use history. One important client outcome is treatment retention. To adequately investigate the impacts of group, or macro, level characteristics on individual, or micro, level outcome, it is critical that the multi-level structure is incorporated in the statistical analyses. This study applied a newly developed statistical approach, Hierarchical Linear Model (HLM), to investigate the interaction effects of program and client characteristics on client's retention in the treatment. Conventional approaches have depended solely on detecting differences on mean levels to investigate group effects. The HLM also allows the application of both means and slopes as outcomes. It, therefore, provides a more appropriate mechanism to represent the complexity of the multi-level data and a more adequate model specification to test the impacts of social contexts.

This study involved merging of two data sets. Program level data were recently collected by a mail survey, the Treatment Referral Network Survey (TRNS), of drug treatment programs in Los Angeles County. Client level data include admissions to these programs in 1992 and were reported to the California Alcohol and Drug Data System (CADDS). Three types of program level data selected in this preliminary study are program modality, amount of services provision, and counselor's characteristics. Four client level variables are chosen as predictors: ethnicity, gender, level of prior substance use, and length of substance use before entering the treatment program. The results indicated that characteristics of treatment programs have effects not only on the length of treatment retention but also on altering the relationship between level of substance use and client treatment retention. The amount of services provided by the treatment program may weaken the relationship between prior substance use and length of retention.

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MEASURING PARTICIPATION IN OUTPATIENT DRUG TREATMENT

J. M. Hawke

This analysis explores measures of client participation in outpatient drug treatment programs, using a sample of probationers mandated to drug treatment in New York City. Using monthly attendance data, 426 probationers who were sentenced to probation between September, 1991 and September, 1992 and referred to drug treatment by the CPU were identified. Probationers in the sample were predominately male (8.5%) and minority (43% African American and 32% Latino). Five measures of client participation were examined: (1) length of time in treatment; (2) scheduled treatment intensity; (3) actual treatment intensity; (4) participation in therapeutic treatment; (5) participation in educational activities.

The average length of time probationers stayed in treatment was four months. However, only 4% stayed the full 12 months of contracted treatment. Because the client's attendance and the scheduling of treatment sessions by the programs impacts client participation in outpatient drug treatment programs, other measures of client participation were used. Scheduled and actual treatment intensity was measured the number of "full treatment days," and two indices of participation in treatment (PIT and EPIT) were derived from factorial analysis of the clients' attendance. Descriptive analyses show how these measures of participation vary by length of time in treatment. Findings suggested that length of time in treatment, when used alone. inadequately reflects client participation in outpatient treatment.

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REFERRING LEGALLY MANDATED CLIENTS TO DRUG ABUSE TREATMENT PROGRAMS: THE NEW YORK CITY EXPERIENCE

M. Natarajan and G. P. Falkin

In 1989. the New York City Department of Probation established Substance Abuse Verification and Enforcement units (SAVE) to provide enhanced supervision for high-risk probationers involved in cocaine and crack use and to refer them to appropriate drug treatment programs. Probationers are classified in one of four risk levels on the basis of their age, prior criminal record and employment status at the time of a pre-sentence investigation. This study examined whether cocaine/crack use is a suitable indicator for differentiating cases in terms of drug severity and assigning high-risk probationers to enhanced supervision. Data are derived from a subset of Probation Department's Management Information System (MIS) containing of all who were sentenced to probation between September 1991 and September 1992 (N = 19,621). For our analysis, data reported in the probation drug assessment done at the time of the pre-sentences investigation was mapped onto the Offender Profile Index's (OPI) Drug Severity Index. It was found that drug severity scores calculated in this way, can help differentiate high-risk drug abusing probationers for matching them both to appropriate for intensities of supervision and intensities of drug treatment. This finding has possible implications for the treatment referral process for high-risk drug abusing probationers such as developing a drug assessment scoring scheme, contracting with more residential drug treatment programs, and testing various hypothesis about probation classification and the referral process to treatment programs.

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AFFILIATION:

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MMPI-2 PSYCHOPATHOLOGY IN ADDICTED WOMEN REPORTING CHILDHOOD SEXUAL ABUSE

S. B. Barker, J. S. Knisely, K. S. Ingersoll, and D. L. Haller

Substance abusing women in treatment with and without histories of sexual abuse may present with differing diagnoses and treatment needs. The purpose of the present study was to describe MMPI-2 profiles and to evaluate the ability of the MMPI-2 to discriminate women with addictions who reported positive and negative histories for childhood abuse.

Subjects were 133 pregnant or recently postpartum women admitted to an intensive outpatient treatment program. Upon admission, the MMPI-2 was administered and a comprehensive intake form was used to assess chemical use, psychosocial, psychiatric, and medical histories. This form included three childhood abuse questions (verbal, physical, and sexual abuse) that required a "yes" or "no" response. MMPI-2 profiles of those subjects reporting histories of childhood sexual abuse (n = 24) were compared with subjects not reporting sexual abuse histories (n = 69) using a two-sided t-test for each scale. Also, a discriminant analysis was performed on the validity. k-corrected subscales. and Ps and Pk scores (post traumatic stress disorder scales). Data from those subjects who did not respond to the sexual abuse history question or with invalid MMPI-2 profiles were not included in the analyses.

Most of the women were single, unemployed, African-American poly-substance users. Twenty-seven percent reported histories of childhood sexual abuse. Sixty-four percent of the sexual abuse survivors also reported physical abuse, and 61% also reported both physical and verbal abuse. The MMPI-2 profile of mean scale scores for the sexual abuse group was more elevated than those not reporting abuse, although both groups generated a 4-8 profile type. Mean scores were significantly higher for the sexual abuse group for the validity scale F ($p = .0124$) and clinical scales 1 (Hs, $p = .006$), 2 (D, $p = .006$), 3 (Hy, $p = .0006$), 4 (Pd, $p = .0003$), 6 (Pa, $p = .015$), 7 (Pt, $p = .017$), and 8 (Sc, $p = .003$). The discriminant analysis yielded a linear function of L, F, 3,5, 8, and Pk that correctly categorized 75% of the sexual abuse survivors and 76.8% of the non-sexual abuse subjects. These findings lend further support to the need to identify abuse survivors among addicted women and also suggest that the MMPI-2 may be useful with patients to treatment.

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ANTEPARTUM HEPATITIS B VACCINATION IN HIGH RISK PATIENTS: IS IT FEASIBLE?

M. J. Dinsmoor, E. R. Spear, M. E. Willis, and M. R. Escobar

Percutaneous drug users (PDU) are at high risk for acquiring hepatitis B infection. Historically, it has been difficult to complete the hepatitis vaccine series in susceptible PDU, primarily as a result of vaccine refusal and poor compliance with follow-up visits. We postulated that initiating the vaccine series during pregnancy would be more likely to be successful, given the frequent visits required for prenatal care.

All pregnant patients who were recent PDU (within the last two years), were not hepatitis B immune, and were $\leq$ 28 weeks gestation were eligible for enrollment following informed consent. All patients were seen in a specialty clinic by a single provider, charts were flagged, and the vaccine schedule was placed in the front of the hospital chart. Vaccine was available at all hours through the obstetric emergency department, and attempts were made to contact patients to remind them of subsequent injections.

Between July 1, 1991, and April 30, 1994, 52 patients were evaluated for enrollment. Of these, 21 (40%) were hepatitis immune (surface or core antibody positive), 10 (19%) were of advanced gestational age, six (12%) were lost to follow-up prior to enrollment and two (4%) refused vaccination. Thirteen patients were enrolled, two were HIV antibody-positive. Five (38%) completed the vaccine series and six (46%) received two injections. In general, patients were unlikely to return following completion of their pregnancy. Three of 11 (27%) patients evaluated had a serologic response following one injection, and one of three (33%) had a response following two injections, for a cumulative seroconversion rate of 67% (four of six).

We conclude that although exposure to hepatitis B is common in these high-risk women, it remains difficult to successfully vaccinate them against hepatitis B. Despite an intensive vaccination effort, less than half of the patients completed the vaccine series. Because some patients had a serological response following partial immunization, attempts to vaccinate PDU pregnant women should continue, beginning as soon after the first trimester as possible.

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PERINATAL ADDICTED WOMEN: EFFECTS OF HOSTILITY ON RELAPSE RATES IN SHORT-TERM OUTPATIENT TREATMENT

C. W. Motley, J. S. Knisely and S. Schnoll

Critical to the efficacy of outpatient substance abuse treatment is an understanding of variables associated with high risk of relapse. Hostility is defined as a broad psychological construct encompassing various cognitive, emotional, and behavioral features of a person's negative orientation to interpersonal exchanges (Barefoot, Dodge, Peterson, Dahlstrom & Williams, 1989). The purpose of the present study was to investigate the relationship of hostility (measured by the Cook-Medley Hostility scale derived from the MMPI-2) and relapse in a sample of perinatal addicted women. It was hypothesized that women evidencing High Hostility scores would show higher relapse rates when compared to women with Low Hostility scores. 96 perinatal addicted women (8 1% African American; 17% Caucasian; 1% American Indian) who were enrolled in a comprehensive outpatient treatment program comprised the sample. The mean age was 27 and less than 50% completed high school. 83% of the sample was polysubstance abusers. The primary drug of choice was cocaine (82%), alcohol (7%), heroine (6%), cannabis (2%) or hallucinogens (1%). Subjects were administered the MMPI-2 as part of a larger study at intake. The Cook-Medley Hostility scale and its subscales (cynical hostility, aggressive responding, hostile affect, social avoidance, and hostile attributions) were evaluated for their efficacy in predicting relapse episodes based upon urine toxicology screens positive for alcohol and illicit drug metabolites twice weekly during treatment. Logistic regression was chosen to assess the effect of hostility on relapse. Depression, length of stay in treatment, and socioeconomic status were treated as potential covariates and showed no significant relationship to the hostility variables. Results indicate that scores on the Cook-Medley Hostility scales and its subscales were not related to relapse rates among this sample of perinatal addicted women. Contrary to the typically accepted tenet which assumes that hostile addiction treatment participants are at higher risk for relapse and negative consequences which impede treatment efficacy, this study demonstrated that hostility alone is not a strong predictor of relapse. Rather, hostility may interact with other attitudinal constructs to influence relapse episodes. This project was supported by NIDA Grant DA06094.

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ANGER MANAGEMENT IN SUBSTANCE ABUSE TREATMENT PATIENTS

P. M. Reilly, H. W. Clark, M. S. Shopshire, D. J. Sorensen and E. W. Lewis

The treatment of substance abuse is often complicated by a high incidence of anger and violence. In this presentation, we described the components of a 12-week cognitive-behavioral anger-management intervention, and examined its efficacy in a sample of 36 volunteer substance abusers who self-identified themselves as having anger control problems.

All participants were enrolled in treatment at the San Francisco Veteran Affairs Medical Center. Measures of self-reported anger and violent behavior were taken on the first, sixth, and twelfth week of treatment. Self-reported anger was measured with the State-Trait Anger Expression Inventory and the anger subscale of the Profile of Mood States. Self-reported violent behavior was measured with a behavior checklist with items ranging from direct threats (*e.g.,* threatened to throw something at another person) to extremely violent behavior (*e.g.,* used a gun or knife against another person). State-anger decreased significantly ($p < .05$) during the first six weeks of treatment, but did not decrease thereafter. Trait anger, in contrast, did not decrease during the first six weeks of treatment, but decreased significantly ($p < .05$) during the final weeks of treatment. In addition, less than 5% of the patients classified as violent at the start of treatment were classified as violent at the end of treatment.

These findings suggest that our anger management intervention may produce improved treatment outcomes by reducing anger and violence in substance abusers whose treatment is complicated by a high incidence of anger and violence.

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VALIDITY OF THE SCID IN SUBSTANCE ABUSE PATIENTS

H. Kranzler, B. Rounsaville, and H. Tennen

Background: Structured interviews, including the SCID, are widely used to maximize the reliability and validity of psychiatric diagnoses. Though the reliability of such interviews appears adequate, there has been little effort to evaluate their validity. The present study was conducted to determine the following questions: 1. How well do diagnoses obtained from substance abuse patients by a research technician using a semi-structured interview compare with those made by an expert clinician, and 2. Using a standard test validation approach, can valid substance use and comorbid psychiatric diagnoses be obtained with the SCID?

Methods: In a sample of 100 substance abuse patients (59% female, 56% white, mean age = 32.4 yr). we evaluated the procedural, concurrent and predictive validity of SCID substance use and common comorbid diagnoses. Procedural validity was assessed by measuring the sensitivity and specificity of SCID diagnoses using as a criterion diagnoses made through a Longitudinal, Expert, All Data ("LEAD") procedure. Concurrent validity was assessed using measures obtained at the time of treatment. Predictive validity was assessed using measures obtained during the six months post-treatment.

Results: The procedural validity of current and lifetime substance use disorders was significantly better than that of comorbid disorders. The concurrent validity for substance use diagnoses was excellent, while for comorbid diagnoses it varied from good (for major depression and antisocial personality disorder) to poor (for anxiety disorders). The predictive validity for substance use disorders was good, while for comorbid diagnoses it was poor.

Conclusions: Can a research technician using the SCID obtain valid psychiatric diagnoses in substance abuse patients? The answer is a qualified "yes". The validity of SCID diagnoses was significantly better for substance use disorders than for comorbid disorders. These findings are consistent with other reports that the diagnosis of comorbid disorders in substance abuse patients is fraught with difficulty.

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IMPACT OF SUBSTANCE ABUSE ON THE DIAGNOSIS OF AXIS II DISORDERS

A. Apter, H. Kranzler, V. Klinghoffer, and B. Rounsaville

To evaluate the impact of substance use on the prevalence and stability of personality disorder diagnoses, we interviewed 95 inpatients (mean age = 32 yr, 62% female, 12th grade education) from a two-week rehabilitation program using the SCID II. Current substance abuse/dependence diagnoses at baseline were: cocaine (63%), opioid (42%) and alcohol (32%). At intake, 83.2% of subjects received one or more Axis II diagnoses (M = 3.36). Patients were asked to differentiate enduring traits from those related principally to substance use. When substance-induced traits were excluded, 75.8% of patients received one or more diagnoses (M = 2.46). Both the proportion of patients who received a diagnosis and the mean number of diagnoses declined significantly ($p < .01$) when the organic exclusion was applied. The following personality disorders were most prevalent: borderline (36.8%). avoidant (31.6%). antisocial (36.8%), histrionic (26.3%). and paranoid (24.2%). Eighty-one patients (85.3%) were re-interviewed one month after discharge. Of this group, 72.8% received one or more Axis II diagnoses (M = 2.10). Comparing Axis II disorders at the two time points, there was a significant decrease ($p<.05$) in the percentage of diagnosis-positive patients and in the mean number of diagnoses. During the follow-up period, there was also a significant decrease (compared with pretreatment) in use of heroin, cocaine and alcohol ($p<.01$).

Although we found decreases both in substance use and Axis II disorders from baseline to follow-up, there was no correlation between these measures. This suggests that the decline in Axis II diagnoses is not due to generalized under-reporting of symptoms. It also suggests that the relationship between substance use and Axis II disorders is complicated by additional features, which we will examine in future analyses.

We conclude that substance-induced personality features complicate the diagnosis of personality disorders in substance abuse patients. Careful questioning in a cross-sectional interview makes it possible to exclude some of the false-positive diagnoses. Following treatment, however, an additional decline in personality disorder diagnoses may occur. Unrecognized, these effects may lead to over diagnosis of personality disorders in substance abuse patients.

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DIAGNOSING MENTAL DISORDERS IN SUBSTANCE ABUSERS: TEST-RETEST RELIABILITY OF TWO INTERVIEWS

H. E. Ross, R. Swinson, S. Doumani, and E. Larkin

This study investigates the test-retest reliability of two standardized interviews (computer- and clinician-administered) in diagnosing DSM-III-R lifetime mental disorders in treated substance abusers. The Structured Clinical Interview for DSM-III-R (SCID) and the Computerized Diagnostic Interview Schedule (C-DIS) were each administered to 173 substance abusers in treatment who were randomly assigned to one of two groups. One to two weeks later, subjects in one group repeated the C-DIS and subjects in the other group were re-interviewed by a different clinician who was blind to the results of the initial interviews. Both instruments demonstrated fair or good to excellent reliability for psychoactive substance use disorders, with kappas ranging from .50 to .89 for individual disorders. The reliability of comorbid mental disorders was considerably worse on both instruments. C-DIS kappas ranged from -.05 for generalized anxiety to .70 for simple phobia. SCID kappas ranged from .31 for panic disorder to .83 for antisocial personality disorder. Anxiety disorders, as a group, some phobic disorders, and antisocial personality disorder showed adequate levels of test-retest reliability on both instruments. There was a trend for threshold cases to account for some of the disagreement on the C-DIS. Differences of opinion between clinicians on organicity rule-outs explained some of the disagreements on panic disorder and major depression. The C-DIS, unlike the SCID, tended to diagnose more disorders at initial interviews, perhaps a result of its tedious probe structure which subjects may learn to avoid on repeat interviews. These results suggest that a single interview does not provide a reliable lifetime diagnostic profile of comorbidity in substance abusers. They support conclusions regarding the limitations of retrospective self-report data in current substance abusers.

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MODIFIED THERAPEUTIC COMMUNITY FOR HOMELESS MICAs PROFILES

S. Sacks and K. Foster, Sr.

This poster describes the profiles of homeless mentally ill chemical abusers (MICAs) in three New York City community residences, as part of a live-year project evaluating the efficacy of modified therapeutic communities for this population. The study design consists of three treatment conditions: modified therapeutic community, enhanced community residence, and wait-list treatment-as-usual control group. Study subjects are referred from shelters and psychiatric care facilities and after an initial stabilization period, are given an extensive interview, consisting of a standardized questionnaire and a psychological battery. Data collection includes demographics, substance abuse, and psychiatric diagnosis.

Preliminary analysis (N=88) has generated several descriptive (profile) findings. First, the typical client is a Black or Hispanic male in his early thirties who is unemployed, did not complete high school and has low scores on standardized IQ tests. Second, substance abuse (usually crack or alcohol) and criminal behavior in the past year are reported by almost all clients. Third, clients are accurately described as homeless MICAs in view of the following: a) the majority have been homeless for periods ranging from one month to more than ten years and have had two or more episodes of homelessness, b) results of the Diagnostic Interview Schedule (DIS) show 64% with an Axis I diagnosis for Schizophrenia, Mania or Major Depression, and c) 84% have a DIS Axis I diagnosis of Substance Abuse/Dependency. Planned analyses include describing client profiles for a large sample and providing profile comparisons between treatment conditions. This study provides comprehensive client profiles of homeless, mentally ill, chemical abusers entering different types of community residence treatment programs.

The modified TC has the potential to provide an innovative model for the treatment of MICA clients and to guide future policy decisions regarding MICA clients and their treatment in the mental health system. Future directions in the field include: 1) documentation of existing models for different dual disorder populations in different settings; 2) evaluation of the comparative effectiveness of existing treatment models for the full range of dual disorders; and 3) the development of effective treatment and services systems that are comprehensive and integrated.

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COMMUNITY BASED TREATMENT PROGRAMS FOR MICAs: A TYPOLOGY OF DIFFERENT TREATMENT ENVIRONMENTS

J. Collins, J. J. Rivera, and M. Rahav

The high prevalene of the psychiatric/substance abuse dual disorder has called attention to the question of where and how to treat those who are mentally ill chemical abusers (MICA's). The aim of this paper is to describe two community based treatment approaches for MICA's: the therapeutic community (TC) approach and the community residence (CR) approach. The TC is a residential treatment program for substance abusers and has historically been based in the drug treatment system. The CR is a residential care program that provides housing supports and rehabilitation services for the mentally ill. As part of a longitudinal study that aims to compare different, community based treatment modalities for MICA's, one TC program and two CR programs have been modified to allow their treatment of MICA's The three programs are all located in New York City in economically depressed neighborhoods, characterized by disproportionally high residency of people of African-American and Hispanic ethnic origin, crime, family dissolution and welfare dependency.

Data were gathered through multiple sources: including existing documentation; key informative interviews, and environmental rating scales. The information gathered from these sources was organized into a typology reflecting multiple dimensions of program operation, philosophy and structure and is available from the authors.

The articulation of a program model is a difficult task. There are some themes, however, which have emerged in the process of developing the typology. In the CR, clients are given the supports they need to function in the community and they are gradually engaged into a process of recovery and rehabilitation. There are fewer demands on clients and consequently, there are more modest goals for treatment. The TC has a mandate to transform its participants into productive members of society. It has higher expectations for its clients and places greater demands on them. Given the radically different philosophies and assumptions behind the treatment programs, it is remarkable how much they have in common. This similarity may have emerged, in part, from the need to adapt to the overwhelming difficulties in working with mentally ill chemical abusers.

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CORRELATES OF TREATMENT RETENTION FOR MICAs: A REPORT ON A NEW DROPOUT MEASUREMENT INSTRUMENT

M. Rahav, L. Nuttbrock, J. J. Rivera, and D. Ng-Mak

Dropout from treatment is, probably, the single most important obstacle in treating mentally ill, chemical abusers (MICA's). Most MICA's who enroll in community based residential treatment drop out before completing treatment. The main sources of information on dropout are, obviously. the clients who dropped out themselves- the "Splittees" or "Leavers". However, by the time dropout occurs, the splittees are not available to give any information. In order to address this problem, an instrument, the Dropout Questionnaire (DQ) has been developed to allow the collection of information from clients in treatment, pertaining to their possible dropout from treatment, before it actually occurs.

The DQ consists of four scales, measuring the following: a) satisfaction with the program environment; b) craving for drugs/alcohol and old habits; c) missing family members; and d) reasons for staying. Items of all four scales (47 items all together) are scored on a five point Likert scale. The questionnaire was administered to 207 homeless, MICA men in treatment in a number of different community based, residential treatment programs around New York City. The treatment programs represent two types of treatment approaches: the therapeutic community approach, and the community residence approach for which differential patterns of dropout might be expected. The DQ was administered repeatedly, at various points of times in the course of treatment, attempting to capture attitudes towards and inclinations to drop out. Testing the scales and the correlations of key items with other measures showed the scales to be reliable and valid.

Despite the sound psychometric properties of the DQ, it did not correlate very strongly with dropout and retention. Other variables did not correlate with retention either. This tentative finding seems to suggest that dropout is NOT an event that is preceded by feelings of dissatisfaction with the various amenities of the treatment program, nor with a natural tendency or long brewing desire to split. Further investigation is needed to determine if there are other correlates of dropout need or to test an alternative hypothesis that dropout is an impulsive behavior triggered by situational events and not at all correlated with clients' characteristics or their feelings about their treatment programs.

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COMORBIDITY AMONG ADOLESCENTS IN THERAPEUTIC COMMUNITY TREATMENT

N. Jainchill, G. Bhattacharya, and J. Yagelka

Increasingly, adolescents are being admitted to residential therapeutic communities (TCs) for treatment of substance abuse disorders and related social and psychological / psychiatric problems. Little is known about adolescents who enter treatment, or the effectiveness of the TC modality for these clients. There is almost no information on the prevalence or types of non-substance, psychiatric disorders among adolescents with substance abuse problems. This study assessed comorbidity among adolescents in treatment for problems of drug abuse in six residential TCs in the United States and Canada. DSM-III-R diagnoses were obtained with the Diagnostic Interview for Children and Adolescents (DICA-R) on over 800 clients. Adolescents were interviewed within the first two weeks of being admitted to treatment. Psychiatric disturbance (e.g., types of disorders, number of positive diagnoses) were examined in relation to demography, primary drug of abuse, client motivation and readiness to change, and retention in treatment.

The findings reveal the extent of comorbidity among adolescents in treatment for problems of drug abuse. A large majority, 86%, had at least one non-substance, DSM-III-R psychiatric diagnosis. Most received more than one diagnosis. The most commonly occurring diagnoses in order of frequency arc: Conduct Disorder; Oppositional Defiant Disorder; Separation Anxiety; Obsessive Compulsive Disorder; Attention-Deficit Hyperactivity; Overanxious Disorder; Major Depression-Current; and Dysthymia. Females yield a higher total number of diagnoses than males; proportionately more females than males yield positive diagnoses irrespective of diagnostic category, *i.e.,* behavior disorders as well as affective disorders. Blacks yield the lowest total number of diagnoses among the ethnic groups. Differences by disorder vary. There is no relationship between age and total number of diagnoses. Among the primary drug of abuse groups, crack/cocaine abusers yield a significantly higher total number of diagnoses than marijuana abusers. Adolescents who remain in treatment at least 90 days have a lower number of diagnoses than those who leave treatment prior to 90 days. Most notably, the relationship between the CMRS score (measuring Circumstances prior to entry into treatment, Motivation and Readiness for treatment, and perceived Suitability of the program) and number of diagnoses is significant and linear. Future analyses will examine the interactions among these factors to further clarify the relationship among psychiatric disturbance and client-treatment interactions.

The prevalence of psychiatric disturbance, and the spectrum of disorders which is reflected among the adolescents admissions to the therapeutic communities involved in the present study, highlight the urgent need for comprehensive treatment approaches which will address problems other than substance abuse.

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THE RELIABILITY OF THE ASI AMONG CLIENTS WITH SEVERE MENTAL ILLNESS AND SUBSTANCE ABUSE PROBLEMS

D. Zanis, A. T. McLellan, M. Burke, and M. Randall

This study examined the reliability and utility of the Addiction Severity Index (ASI) as administered to clients with severe mental illness (SMI) and secondary substance abuse disorders enrolled in a publicly-funded community mental health center. A total of 62 clients with SMI volunteered to participate in the reliability study of the ASI. Ninety percent of the clients had a primarily diagnosis of schizophrenia and all clients had been diagnosed as a substance abuser in their lifetime. We conducted both interobserver and test-retest methods of reliability. All interviewers had at least one year of ASI experience, but had little experience interviewing clients with severe mental illness. All interviewers participated in a one week training program that addressed issues common among interviewing psychiatric clients.

Overall 19% of the ASI composite scores could not be calculated due to missing data and 31% of the clients misunderstood or misrepresented responses in at least one of the seven ASI domains. As a whole, the interobserver reliability of the ASI was satisfactory to highly acceptable with Pearson coefficient correlations ranging from .78 to 1.00. However, when a test-retest method of reliability was conducted, the variability among the reliability coefficients was rather large across the seven composite scores. Four ASI domains (medical, alcohol, drug and family) had composite score reliability coefficients below .65 providing evidence that the stability of ASI composite scores over a three to five day time interval resulted in unacceptable reliability coefficients. Further, the ASI severity ratings demonstrated considerably less reliability than the composite scors under similar testing conditions.

The main finding of this study was the lack of utility of the ASI composite scores due to missing data. Further, we found that both the characteristics of the client population and the circumstances of the interview process appeared to account for much of the measurement error. Evidence suggests that while the ASI has a number of limitations in assessing the problems of severe mentally ill substance abusers, it is likely that other similar self-report instruments would encounter some of the same limitations.

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CLIENT TREATMENT NEEDS ASSESSMENT INSTRUMENT

Y. I. Hser and M. L. Polinsky

As part of a larger study on matching drug users with treatment programs, an instrument is being developed for client assessment and treatment referral. The objectives of this instrument are to screen and identify users who need drug treatment, to decide on and rank "appropriate" treatment programs for the client, and to identify predictors of referral and treatment outcome. The instrument contains three main areas of assessment: (1) drug use (frequency and severity as indications of need for treatment); (2) problems in other psychosocial domains (e.g.. legal status, medical status, employment, alcohol use, family/social and psychiatric status), which may indicate the need for treatment to prevent escalation of drug use or affect the client's ability to successfully participate in a treatment program; and (3) client preferences with regard to program characteristics and services provisions. Besides the client background information, seven problem areas assessed in the Addiction Severity Index (ASI) are covered by questions adapted from that instrument. Items for client preferences include questions about the client's past treatment program experiences as well as ratings of need for specific services, specific program components, geographic location of the program, etc.

This instrument will eventually be computerized and used in conjunction with a treatment provider database to facilitate efficient treatment referral. This presentation reports on the initial investigation of the psychometric properties of the instrument, including test-retest administration of the instrument to several samples/populations, internal consistency of several constructs, and comparisons of observed severity index with results reported by the Philadelphia group that designed the ASI (McLellan *et.al.,* 1992).

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DEPRESSION IN DRUG AND ALCOHOL DEPENDENCY

A. Eriksen, N. S. Miller, M. S. Gold, and N. G. Hoffman

INTRODUCTION: The purpose of this study is to evaluate the association of major depression in alcoholics and drug addicts in abstinence-based treatment programs.

METHODS: Six thousand, three hundred and fifty-five patients from 41 treatment sites received a structured CATOR interview on admission and were followed up at six and 12 months.

RESULTS: In the total sample of 6355, the rate of lifetime diagnosis of major depression was 43.7%. The abstinence rate for one year was 55.4% and no differences were found between those with and those without a lifetime diagnosis of major depression. Alcohol dependence was associated with depression significantly less than other drug dependencies. The association of a lifetime diagnosis of major depression was greatest for opiate [62.9% in males ("M"); 68.5% in females ("F")], prescription (62.2% in M; 76.0% in F), and stimulant (60.6% in M; 79.0% in F) dependence.

There was a significant association between the number of drugs used and frequency of drug use with a lifetime diagnosis of major depression. Daily drug users showed the greatest rate of depression. The rates of depression were significantly greater for females (65.6%) than males (56.2%). Depressed females and depressed males began drinking at an earlier age (before age 14) and were more likely to be multiple drug users. Outpatients were less likely to be depressed than inpatients (29.5% vs 40.4%).

CONCLUSION: A lifetime diagnosis of major depression was significantly associated with drug use and multiple drug (including alcohol) dependence.

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ANALYSES OF DEPRESSION AND ADDICTION SEVERITY CONTROLLING FOR SOCIAL SUPPORT

M. Chan, J. Guydish, B. Tajima, and D. Werdegar

METHODOLOGY:

Newly enrolled (<30 days) clients (N=256), in a community based substance abuse intensive day treatment or traditional residential therapeutic community, were interviewed with regard to demographics, substance abuse, education and employment, social support, and psychiatric characteristics. Instruments administered included the Addiction Severity Index (ASI) and the Beck Depression Inventory (BDI). Social support was measured using the Social Support Evaluation instrument developed by colleagues at the University of California, San Francisco, for use with similar populations.

RESULTS AND DISCUSSION:

Population (N=256) characteristics included the following: Mean age 33 years; 25% female; mean education, 12 years; ethnicity: African-American 58%. white 24%. Hispanic 14%, and Asian-American 3%. Thirty-three percent of the population registered moderate to extremely severe BDI scores. BDI scores were significantly correlated to addiction severity for drug abuse ($r=.18$, $p<.005$) and alcohol abuse ($r=.19$, $p<.005$) as measured by the ASI composite scores. In addition, a negative correlation was observed between BDI scores and total social support scores - which include practical, emotional, and self esteem components ($r=-.48$, $p<.001$). Although total social support scores were not correlated to drug or alcohol severity, scores for the self esteem component of social support showed an inverse correlation to both drug ($r=-.13$, $p<.05$) and alcohol ($r=-.13$, $p<.05$) severity as well as to BDI scores ($r=-.44$, $p<.001$).

Many clients newly enrolled in drug abuse treatment were found to have moderate to extremely severe levels of current depression as measured by the BDI. Depression was correlated with both drug and alcohol addiction severity, and inversely correlated with Total Social Support. Depression scores as well as drug and alcohol severity were inversely correlated to self esteem, suggesting the possibility of a dynamic interaction among the three. The findings suggest that screening drug treatment clients for depression and social support, especially self esteem, may expose conditions that would benefit from special intervention. Programs that include opportunities for strengthening social support and self esteem may also ameliorate some forms of depression, and thereby improve the effectiveness of treatment.

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OUTCOMES FOR DRUG USERS IN A DAY TREATMENT PROGRAM

J. Guydish, A. Razban, A. Acampora, and D. Werdegar

Day treatment models of care have been used extensively in mental health services, in the care of the frail elderly, and in the treatment of alcoholism. With respect to drug abuse, however, the day treatment modality has a shadowy identity, and such programs are infrequently reported in the literature. This paper reports outcomes for clients entering an intensive drug abuse day treatment program.

METHODS:

Clients entering a newly established intensive day treatment program, and remaining in treatment approximately 14 days, were asked to participate in the study. Those entering the cohort (N=66) completed a baseline interview from 14 to 30 days after admission, and were tracked for follow-up interview after six months. Each interview included the Addiction Severity Index (ASI), the Beck Depression Inventory (BDI), and the Symptom Checklist-90 (SCL-90).

RESULTS AND DISCUSSION:

Retention in day treatment ranged from 13 to 321 days, with a median of 35. Many clients later transferred to a residential treatment program operated by the same agency, reflecting a staff preference for moving clients into the residential program. Total time in treatment for the sample (day treatment plus any residential treatment) ranged from 14 to 467 days, with a median of 128. Those clients located and interviewed at follow-up (n=38) showed significant treatment gains over baseline. Specifically, mean ASI composite scores in four areas (alcohol, drug, legal, and social) were significantly lower on follow-up, as were mean scores for the BDI and SCL-90. Gains associated with day treatment are confounded because many clients (64%) received both day treatment and residential treatment during the follow-up period. Nevertheless, all clients in the sample received at least two weeks of day treatment, median retention in day treatment was over one month, and a substantial minority (21%) remained in day treatment for over two months. Further research is needed to assess the effectiveness of day treatment in comparison with other modalities.

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PSYCHIATRIC COMORBIDITY IN COCAINE ADDICTION

D. B. Marlowe, S. D. Husband, R. J. Lamb, K. C. Kirby, M. Y. Iguchi, and J. J. Platt

One-hundred consecutive admissions to an intensive outpatient cocaine treatment clinic in Camden, NJ were assigned DSM-III-R diagnoses using the SCID. Subjects were 68% male; 91% African-American, 8% Caucasion; 65% single, 23% divorced or separated; 90% unemployed; 25% homeless. The mean age was 32.19 years (SD = 6.81); average education = 11.78 years (SD = 1.70); and median adjusted annual income = $1,071. Subjects were administered the SCID ten days post-intake as part of a standard sequence of research assessments. All interviews were administered by or under the supervision of the senior author. No inter-rater reliability data are available.

Ninety-one subjects received at least one lifetime DSM-III-R diagnosis in addition to cocaine dependence or abuse. Comorbid alcohol dependence (30% current, 37% lifetime) and cannabis dependence (14% current, 23% lifetime) were common, and a significant number of subjects had a past history of opiate (11%) or amphetamine (10%) addiction. A significant minority were diagnosed with clinical depression (8% current, 10% lifetime) or anxiety (8% current and lifetime). Bipolar, psychotic, somatoform, and eating disorders were identified in 1% to 3% of subjects. By far the most prevalent diagnoses were on Axis II (73% of subjects), with over one-third of subjects receiving more than one personality disorder diagnosis, frequently crossing DSM-III-R “clusters.” The most frequent diagnoses were in Cluster B (53%). Antisocial (23%). borderline (22%). paranoid (21%) and narcissistic (17%) personality disorder were identified most often. Males were diagnosed significantly more often than females with lifetime alcohol and stimulant dependence, and with antisocial and narcissistic personality disorder. Females were diagnosed significantly more often with secondary dysthymia and borderline personality disorder. Three central findings emerged from this study. First, unlike most prior reports on alcoholics and opiate addicts, rates of non-substance use Axis I disorders were substantially equivalent to population base rates. Second, there was a wide range of severe Axis II pathology having important implications for the clinical management and treatment of these patients. Finally, there were certain gender differences in the distribution of psychopathology. Cocaine treatment might benefit from the integration of collateral therapies for personality disorders which, for example, assist clinicians to set effective limits, maintain appropriate boundaries, and assist patients to manage triggers for impulsivity and negative mood states. There is also some support for the implementation of topical groups dealing with gender-specific issues.

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THE IMPORTANCE OF EVALUATING EARLY ONSET ANXIETY DISORDERS IN A COCAINE DEPENDENT POPULATION: A REPLICATION

D. B. Dewart, R. A. Roemer, P. Jackson, and A. Cornwell

This study extends studies evaluating the age of onset of anxiety disorders in a cocaine dependent population. Age of meeting criteria for the first anxiety disorder was characteristically in childhood or early adolescence and predated cocaine dependence. Ninety-seven cocaine dependent patients were evaluated using the SCID-P. Exclusionary criteria included psychotic disorders *e.g.,* schizophrenia, HIV+ status, or conditions attributed to a general medical condition, e.g., hypothyroidism.

Fourty-six percent (45 of 97) were diagnosed with early onset anxiety disorder. It was found that only one patient had been previously asked about anxiety disorders prior to our evaluation. Individuals with anxiety disorders used marijuana longer, used more alcohol, and met criteria for cocaine dependence later than those without anxiety disorders.

Fourty-seven percent (46 of 97) met the criteria for mood disorder of which 41 (48%) were diagnosed with major depression, and five with bipolar disorder, depressed. The remaining 51 of 97 received no diagnosis of mood disorder. Careful examination of the age of meeting criteria for mood disorder revealed a history of mood disorder prior to cocaine dependence. For all 46 patients with mood disorder, the first major episode (age 18.8 years) followed age at which patients met criteria for anxiety disorder (9 years) and preceded any cocaine dependence (25 years). This is particularly important inasmuch as there were four patients evaluated prior to seven days of cocaine abstinence. Thus, onset of anxiety disorder and mood disorder preceded cocaine dependence and continued to re-occur regardless of abstinence from cocaine.

We confirm the importance of evaluating the relationship between early onset anxiety disorder and mood disorders in a cocaine dependent population. We use a time line method of evaluation which identifies age of meeting criteria for anxiety disorder, mood disorder and substance dependence. This documents the existence of early onset anxiety disorders in a cocaine-dependent population.

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EARLY DECLINE IN SELF-REPORTED DYSPHORIA IN INNER-CITY COCAINE ADDICTS BEGINNING TREATMENT

M. Y. Iguchi, S. D. Husband, D. B. Marlowe, K. C. Kirby, R. J. Lamb, and J. J. Platt

Introduction. Previous reports have described high rates of comorbidity between addictive disorders and mood or anxiety disorders (Weissman 1988; Weissman *et al.,* 1976). One difficulty with such studies is that mood is usually assessed at or immediately following intake, a time when substance users' self-reported mood may be subject to large fluctuations (Brown and Schuckit 1988; Gibson and Becker 1973; Strain *et al.,* 1991). The current study examines this issue in new admissions to drug-free, outpatient treatment for cocaine abusers. **Method.** Subjects were 82 consecutive admissions to intensive outpatient treatment for cocaine abuse on whom complete data were available. Data on depression, anxiety, and hopelessness were collected at intake, and at four weekly intervals post-intake, using the Beck scales for depression (BDI), anxiety (BAI) and hopelessness (BHS). Mean scores and prevalence of clinically significant mood disturbance were compared over time using one-way analyses of variance, and the Scheffe test for between-group differences (significance level: $p<.05$). **Results.** Trends in self-reported mood showed a significant decrease in mean scores on the BDI and BAI between intake and week one (from 17.6 to 8.3 and from 15.2 to 7.0, respectively; $p<.0001$), and no further significant changes in scores from weeks one through four. Similar drops in the rate of clinically significant BDI and BAI scores (>18) were also observed (from 54% to 19% and from 35% to 12%, respectively, $p<.0001$). In contrast, BHS scores showed no significant changes over the study period. By week four, rates of clinically significant depression, anxiety, and hopelessness were at similar levels (17%, 13%, and 16%. respectively). **Discussion.** The findings suggest that the assessment of depression and anxiety in this population may be confounded by short-term changes in self-reported mood over the first days of treatment, due either to nonspecific effects of the intake process or to a practice effect of the scales used in assessment. These findings suggest that the USC of the BDI and BAI to assess mood in this population should be postponed at least one week after intake, but that the BHS may be more reliable at intake. The results also suggest that intake levels of self-reported mood may be inappropriate as baseline measures of mood when evaluating the effects of treatment; instead, baseline should be determined after mood has stabilized in treatment.

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HIV RISK BEHAVIORS IN PERINATAL AND INPATIENT DRUG ADDICTS

K. S. Ingersoll, D. L. Haller, and K. S. Dawson

This study examined HIV risks related to drug behavior, sexual behavior, and physical illnesses in substance abusers in treatment from an outpatient perinatal program and a chemical dependency inpatient hospital unit. Subjects were 161 female perinatal outpatients, 533 female inpatients, and 549 male inpatients. Most were African-American, but a larger proportion of male inpatients were white. Cocaine was the preferred drug of 83% perinatal addicts and 46% of female inpatients; 56% of men preferred alcohol. Over 94% of each group reported exclusively heterosexual behavior.

Measures: Questions relevant to HIV risk were extracted from a structured Comprehensive Intake Interview during the first week of treatment.

Results: Injection risk; 37% of men reported injecting drugs, compared to 31% of female inpatients and 22% of perinatal addicts. Among those who injected, most shared needles within the past week. Sex-related risk: Only 8% of perinatal, 15.5% of female inpatient, and 14% of male inpatient addicts always used birth control; 55% of perinatal, 64% of female inpatient, and 55% of male inpatients used no birth control. Only 13% of women and 42% of men used condoms as a primary birth control method. Number of sexual partners in 2 yrs. ranged from 0-99+ for all groups, and a third of each group endorsed sex with an HIV+ partner. Relatively few subjects reported their significant other to be a drug user, but most had sex with partners other than a steady partner. Health-related risk: Less than 10% of subjects had active TB or +PPD; slightly more subjects had hepatitis. None of the perinatal, 8% of the female inpatient, and 14% of the male inpatient addicts were HIV+. 41% of perinatal, 13% of female inpatient, and 9% of male inpatient subjects had other STDs. These differences probably reflect increased detection of the perinatal group's illnesses due to increased medical surveillance as part of their treatment program.

Conclusions: Among all three addicted populations, multiple risk factors for HIV emerged. Heterosexual substance abusers report many behaviors which put them at increased risk for HIV transmission. However, the pattern of risk differs, with perinatal addicts and inpatient women having more sex-related risk, and men having more injection-related risk. These differences are likely related to drug of choice and the corresponding route of administration. Women from both treatment programs resembled each other more than men in drug and sexual patterns. Risk reduction curricula should be tailored to emphasize preventive strategies which are gender-specific.

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PSYCHOSOCIAL CORRELATES OF HIV RISK AMONG PREGNANT DRUG ABUSERS

R. M. Malow, S. J. Ireland, M. Quiroga, and F. J. Penedo

Introduction: AIDS has reached epidemic proportions among substance abusing women. However, the determinants of HIV risk among drug using women is under-studied. The purpose of this study was to identify substance abusing and psychopathology correlates of HIV risk among socio-economically disadvantaged, drug-dependent women.

Methods: A sample of heterosexual, HIV seronegative, pregnant women (n=81) meeting inclusion criteria (e.g., not psychotic) were selected from consecutive female admissions (n=200) to a publicly funded drug treatment program. The Addiction Severity Index was administered to assess drug use and the Risk Behavior Assessment to measure HIV risk behaviors. A multifactorial HIV risk behavior index was constructed using: 1) number of sexual partners, 2) condom use, 3) prostitution, and 4) injection drug use. Subjects were categorized into a Low Risk (LR; n=34) and High Risk (HR; n=47) groups and compared using Chi-Square, and correlational analyses.

Results: The LR and HR groups did not significantly differ in age, education, income, employment, and marital status. Significant associations were shown between drug use and high levels of HIV risk behavior. Although subjects in both groups did not differ in psychopathology, subjects in the HR group reported receiving more money from illicit activities ($p<.01$) and a higher incidence ($p<.02$) of problems with their partners. With respect to substance abuse, HR subjects displayed greater levels of alcohol intoxication ($p=.01$), alcohol abuse ($p=.001$), cocaine abuse ($p=.008$). and polysubstance abuse ($p=.04$) in the 30 days prior to admission. HR subjects also reported a higher lifetime incidence of alcohol intoxication ($p=.03$), cocaine abuse ($p=.003$), polysubstance abuse ($p=.04$), and heroin abuse ($p=.04$).

Discussion: For this sample of treatment-seeking, pregnant, substance abusing women, a greater severity of drug abuse and dependence was associated with higher levels of HIV risk behavior. The prevalence of illegal activities found in the HR group supports previous findings of an association between antisocial symptoms and the level of HIV risk behavior. Drug dependence subtypes were identified to better understand the relationships among the use of specific drugs, patterns of use, psychopathology, and HIV risk.

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HIV RISK AND DRUG USE AMONG COLLEGE WOMEN

M. Leik, R. Malow, S. Ireland, L. Porter, and J. Lewis

Introduction: Heterosexual contact has recently surpassed injection drug use as the predominant mode for HIV exposure among U.S. women. Because college women often engage in sexual experimentation, it is critical to identify substance use and other psychosocial correlates of safer sex.

Methods: Subjects were 112 unmarried, heterosexual, college women using the student health clinic. Ethnicity was 47% white, non-Hispanic; 27% Hispanic; 12% African-American; and 15% Other. Subjects anonymously completed a 76-item questionnaire to assess HIV-related knowledge, attitudes, and sexual risk behavior.

Results: Approximately 75% of these students were at some risk for HIV due to inconsistent or no condom use. Use of alcohol and/or drugs before or during sex at some time in their lifetime was reported by 58% of the women. The number of lifetime partners was significantly correlated with alcohol and/or drugs use before or during sex ($r=.35$, $p<.001$). The primary partner's attitude toward condoms ($r=.47$, $p<.001$) was significantly associated with condom use ($r=-.46$, $p<.002$), while the woman's own attitudes toward condom use were not. Sexual communication with the primary sex partner was negatively correlated with having a partner who was an injection drug using, gay, and/or bisexual male ($r=-.46$, $p<.01$). Multiple regression analyses of the ARRM variables showed that knowledge of safer sex guidelines ($p<.02$), knowledge of high-risk sexual practices ($p<.03$) and the primary sex partner's attitudes toward condoms ($p<.001$) significantly predicted condom use (adjusted $R^2=.31$, $F=5.26$, $p<.001$).

Discussion: Results indicate these college women were more likely to use condoms if they possess greater HIV knowledge and their sexual partners held more positive attitudes toward using condoms. Women with better sexual communicative skill were less likely to have partners at high risk for HIV. Although factual knowledge significantly predicted condom use among college women, the most important determinant was the male partner's attitudes toward condoms. This suggests the need to include male partners in HIV prevention interventions with college women and to focus on eroticizing condom use for men. Future research should focus on preventing high-risk behavior by improving knowledge, altering the male partner's attitudes toward condoms, and enhancing communication and negotiation skills. Due to the relationship between drug and/or alcohol use before or during sex and having more partners, college students need to be encouraged to avoid alcohol/drug use as a prelude to sex.

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AIDS-RELATED RISK FACTORS AMONG SOUTHERN COLLEGE STUDENTS

E. J. Brown

OBJECTIVE: Protected sexual activity is crucial in reducing the risk of contracting human immunodeficiency virus (HIV) among college students. The purpose of this study was to document AIDS risk perceptions, measure level of AIDS knowledge, determine self-reported AIDS-related risk behaviors and determine which variables best explained the variance in AIDS-related risk behavior.

METHODS: A convenience sample of 18-21 year old college students from North Central Florida completed in class an AIDS Self-Efficacy Survey (which included a perception of AIDS risk question), an Adapted AIDS Awareness Test, and a Relative AIDS Risk Index.

FINDINGS: The sample was comprised of 28 1 females and 126 males, mean age 19.3 years. Of the 407 students, 90% viewed their risk of contracting AIDS as nil or small, 70% appraised their AIDS self-efficacy strength as moderate or high, and 62% scored between 85-100% on the AIDS knowledge test. Yet, by self-report, 60% of the total sample engaged in unprotected sexual intercourse and 59.4% engaged in sex while under the influence of alcohol. No discernible difference in these variables existed by gender, ethnicity, or SES. The significant variables perception of AIDS risk and AIDS self-efficacy explained 20% of the variance in AIDS-related risk behavior.

CONCLUSIONS: The results indicate that college students may be at risk of contracting HIV because they tend to engage in sex without condoms use and drink alcohol prior to or during sex. In spite of these behaviors, the majority of the students did not think they were at risk of acquiring HIV. This suggests the need for interventions among college students to enhance more congruent appraisal of personal AIDS risk. Recommended is small group discussions with college students about the relationship between behavior and actual AIDS risk.

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A TEST OF THE AIDS RISK REDUCTION MODEL WITH INDIGENT, COCAINE ABUSING WOMEN

S. J. Ireland, R. M. Malow, L. Alberga, F. Penedo, and J. Lewis

Introduction: This study examined the predictive validity of the AIDS Risk Reduction Model (ARRM) for indigent, crack cocaine abusing women, who are showing an alarming increase in AIDS. The ARRM postulates several important mediating variables (e.g., self-efficacy) and three hierarchical stages of HIV risk reduction behavior: 1) labeling one's sexual behavior as risky, 2) making a commitment to modifying behavior to reduce risk, and 3) enactment of safer sexual practices.

Methods: HIV seronegative, heterosexual women at high risk for HIV (N=114) attending a publicly-funded inpatient drug treatment program completed the ASI, an AIDS risk questionnaire, and the Beck Depression Inventory. The sample was mostly African American (72%).

Results: Compared to most subjects (67%) who failed to label their behavior as risky (i.e., were at a pre-labeling stage; **PLs**), subjects who accurately labeled (ALs) themselves at risk reported less sexual self-efficacy ($t=2.0$, $p<.05$), a greater likelihood of engaging in unsafe sex following treatment ($t=3.7$, $p<.001$), and less confidence in avoiding unwanted sex ($t=2.0$, $p<.05$). The ARRM variables were less predictive than for a comparative male sample, and contextual factors served as more significant mediators of risk perception. Regression analysis showed that having greater problems with employment and depression, more lifetime sexual partners and STDs, and a lower likelihood of having a primary sex partner predicted labeling of HIV risk (adj. $R^2=.35$, $F=17.7$, $p<.0001$).

Discussion: Data suggest that for this sample: 1) contextual factors are more predictive of perceived and actual HIV risk than ARRM variables, and 2) ALs and PLs represent conceptually meaningful subgroups requiring different HIV prevention interventions. For the AL group, which reported greater psychosocial dysfunction, interventions might address contextual factors (*e.g.,* employment), enhance interpersonal skills, and ameliorate psychopathology (*e.g.,* depression) that may impede adopting safer sex behaviors. For PLs, who were more likely to have a primary sexual partner and exhibited an "optimistic bias" concerning HIV risk, interventions might include couple counseling to increase risk perceptions and enhance motivation to adopt condoms with their primary sex partners.

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OPIATE DEPENDENCE, GAMBLING AND HIV RISK IN A LOW INCOME POPULATION

L. Roehrich, J. L. Sorenson, and P. Good

This study examined the prevalence of problem gambling and HIV risk behaviors in a sample of 94 admissions to outpatient opiate detoxification at a county hospital. It was hypothesized that subjects with a dual diagnosis of opiate dependence and pathological gambling may be more likely to exhibit other sensation seeking behaviors. Subjects completed a standard gambling problem measure (Lesieur & Blume, 1987; SOGS), the Addiction Severity Index (McLellan *et al.,* 1980), and an HIV risk measure (Delucchi & Hall, 1991). The sample included 62 males (66%) and 32 females (34%), and 21 subjects met criteria for a past or current gambling problem. African Americans (37.1%) and Hispanic/Latino (26.7%) clients were significantly (p = .02, Mann-Whitney U) more likely to have a past or current gambling problem, as compared to whites (8.3%) and others (12.5%).

Stepwise multiple regression techniques and ANOVAs were used to explore the relationship between gambling behavior, demographic variables, and HIV risk variables. Higher gambling scores (SOGS) did tend to be related to higher levels of needle sharing (p = .08), unprotected sexual activity (p = .07), and perceived AIDS risk (p = .13); these three variables accounted for about 20% of the total variance. These data suggest that minority substance users may be at higher risk for the development of gambling problems, as compared to the general population. The combined risk behaviors of injection drug use and gambling activities did not appear to be strongly related to a higher incidence of HIV-related behaviors. Both gamblers and non-gamblers were most likely to engage in the following behaviors: sharing cookers and/or cottons, and unprotected sexual activity.

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ANTISOCIAL PERSONALITY DISORDER AND AIDS RELATED RISK BEHAVIORS

J. J. Rivera, M. Rahav, and L. Nuttbrock

Antisocial personality disorder has been found to be a factor in predicting the likelihood of engaging in behaviors that create a high risk for contracting the HIV virus. Homeless men with a history of mental illness and chemical abuse (HMICA) present with a host of personal, behavioral, and environmental problems that make them vulnerable to contracting the HIV virus. Many of these problems are related to the criteria used to determine the presence of an antisocial personality disorder. Among HMICA men, however, it is often difficult to distinguish whether antisocial behavior reflects enviornmental or situational forces or actual pathology of the personality. The aim of this study is to explore the relationship between antisocial personality disorder and AIDS related risk taking behavior.

The sample used in this investigation consists of 217 homeless, mentally ill, chemical abusing men recruited for long term residential treatment. These men have all had two or more psychiatric hospitalizations, a DSM-III-R Axis I diagnosis and a history of chronic substance abuse. Subjects were interviewed using the antisocial personality section of the Diagnostic Interview Schedule (DIS) and the AIDS Risk Factors Interview-(ARFI), a self report inventory assessing past and present intravenous drug use, past and present sexual activity and perceptions of the AIDS related risks that may be involved with these activities.

No relationship was found with risk behavior and seropositivity. In general there was little or no relationship between conduct disorder and adult risk behaviors. The overall level of adult pathology as measured by the total number of symptoms and the criterion of three or more adult symptoms was correlated with risk behavior. The diagnosis of antisocial personality disorder, which requires the presence of conduct disorder as well as adult symptoms, was not related with risk behaviors. This finding suggests that the antisocial behavior pattern or lifestyle, which in the HMICA sample is not unique to those with the personality disorder, may be more important than the presence or absence of the disorder itself which requires the enduring presence of these behaviors beginning in childhood.

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ATTITUDES AND PERCEPTIONS REGARDING THE RISK OF AIDS AMONG MENTALLY ILL, CHEMICAL ABUSING, HOMELESS MEN

L. Nuttbrock, M. Rahav, and J. J. Rivera

Homeless, mentally ill, chemical abusing (HMICA) men often evoke the image of people who have lost all touch with main stream society, who live and sleep on the streets, and who are totally oblivious and indifferent to their well being and health. Three major problems and disorders converge on these men: homelessness, mental illness and chemical abuse. For the most part, these HMICA men lack the minimal amenities needed to live in main stream society. They also have serious psychiatric problems, a high prevalence of depression, suicidal ideation and suicide attempts, and chronic drug and/or alcohol abuse problems. The aims of this study are to explore AIDS related risk taking behavior and risk perception among HMICA men in order to assess what aspect of the HMICA syndrome constitutes the greatest risk in contracting the HIV.

The sample used in this investigation consists of 99 homeless, mentally ill, chemical abusing (HMICA) men recruited for treatment in community based MICA programs in the New York City Metropolitan area. All of the men in our sample have had two or more psychiatric hospitalizations, a DSM-III-R Axis I diagnosis and a history of chronic substance abuse. Subjects were interviewed using a number of self report measures to assess psychopathology. history of substance abuse, criminal involvement, HIV infection status and the AIDS Risk Factors Interview (ARFI), a self report inventory assessing past and present intravenous drug use, past and present sexual activity and perceptions of the AIDS related risks that may be involved with these activities.

Eleven HMICA men were reported to have been seropositive. Seropositivity was found to be most associated with sex with partners who were IVDU's themselves and with prolonged homelessness. Whether they were IVDU's themselves or not, the majority of the respondents showed keen awareness of the AIDS related risk of IVDU and motivation to prevent such risks. This was not, however the case with AIDS related risks of sex activities. A large number reported sex with IVDU's. with strangers, and while "high" on drugs or alcohol. The results suggest that the greatest AIDS related risk for HMICA's may not be their psychiatric or drug abuse morbidity, but rather their unsafe sexual practices resulting from prolonged homelessness and poverty.

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DRUG USE AND HIV-RISK BEHAVIOR AMONG NON-INJECTING FEMALE SEX PARTNERS OF INJECTING DRUG USERS IN NEWARK AND JERSEY CITY, NJ

V. Lidz, M. Y. Iguchi, J. F. French, and J. J. Platt

The AIDS Community Outreach Demonstration Projects of Newark and Jersey City interviewed 547 female sex partners (SPs) of injecting drug users (IDUs) between April 1989 and January 1992, using the AIDS Initial Assessment, v. 8.0 (AIA) questionnaire. SPs were subjects who had current sexual relationships with IDUs but had not injected drugs themselves during the previous six months. 237 SPs (43%) were re-interviewed with the AIDS Follow-Up Assessment (AFA) six months later. Overall, 16% of SPs were HIV positive at baseline, as compared with 42% of approximately 4,379 IDUs recruited in the same cities (Iguchi. *et. al.,* 1994). Earlier histories of injected drug use, as reported on the AIA, were moderate among SPs: 11% had injected heroin, 10% cocaine, and 8% speedball. Histories of non-injected drug use were less moderate: 42% had used heroin; 70% cocaine; and 21% speedball. Twenty-eight percent were currently using heroin, 46% cocaine, and 8% speedball, with half of current use less frequent than weekly. Mean years of drug use was 12.45. Sixteen percent had received at least one detoxification and 15% had attended NA. suggesting drug use at problematic levels. Rates of HIV infection were high among the subgroup with IDU histories and among those with drug treatment histories. The SP subjects with IDU histories had HIV risk behavior and infection rate profiles similar to the project's IDU subjects (Iguchi, *et. al,.* 1992). The SPs had a mean of 2.2 sex partners (SD= 3.9). but HIV positive SPs had a mean of 1.6 sex partners (SD=1.7). Fourty-four percent reported some use of condoms, but consistent use was rare. Subjects who were followed-up had higher rate of HIV positivity than subjects not followed up (18% vs. 14%), but lower mean years of injection drug use (5.4 vs 7.1) and lower mean number of sex partners (1.9 vs. 2.2). At follow-up, 5.4% reported injecting drugs since baseline; 20% stopping or decreasing non-injection use; and 6.3% starting or increasing non-injection use. Thirteen percent received some form of drug abuse treatment since baseline. One hundred and ninety-nine reported having sex since baseline, 104 with the same partner as at baseline. Because these partners were all IDUs as a matter of the SPs' qualification to enter the study, and because HIV infection rates are high among IDUs in the two cities, these SPs remain at substantial risk of infection. Fifty-six reported sexual relations with multiple partners since baseline. Only 27% indicated having used a condom, with most reporting infrequent use, disturbing findings for subjects whose sexual relationships place them at considerable risk of infection. In sum, preliminary analyses suggest that drug use overall decreased but some subjects initiated or re-initiated injection drug use. Moreover, risks of sexual exposure to HIV continued to be substantial and use of condoms inconsistent even among high risk subjects.

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THE AIDS RISK REDUCTION MODEL AND CONDOM USE AMONG INJECTION DRUG USERS

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INTRODUCTION AND METHODS:

The AIDS Risk Reduction Model (ARRM) (Catania *et al.,* 1990) hypothesizes that behavior change is a three-stage process involving: 1) labeling a behavior as problematic (perceiving a personal risk); 2) committing to changing the behavior; and 3) acting to accomplish the change. A variety of factors influence movement from one stage to the next. Our analysis uses the ARRM to assess behavioral change with regard to condom use in a sample of injection drug users (IDUs). We collected survey data from injection drug users in Los Angeles at two time points one year apart. The current study analyzes data from those who reported having sex with at least one partner at baseline (N=315). Demographics: 145 men, 170 women, 118 Anglos (37.5%), 88 African-Americans (27.9%). 106 Hispanics (33.7%). and three Asians (1%). Items from the questionnaire were factor analyzed. Once the measurement model was confirmed, a path model based upon the stages in the ARRM.

FINDINGS:

Our Stage Two construct, intentions to use a condom at baseline, negatively predicted unsafe sex our Stage Three outcome, having sex without a condom in our follow-up data. Our Stage One construct, perceived susceptibility to HIV infection, predicted intentions to use a condom and indirectly predicts behavior change. At baseline, subjects who were at risk of HIV due to high risk sex practices perceived their susceptibility to HIV. Our findings provide limited support, for the predictive power of the ARRM in our sample of IDUs.

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RECENT SEXUAL ACTIVITY AND CONDOM USE IN OPIOID DRUG ABUSERS ENTERING METHADONE MAINTENANCE TREATMENT

V. L. King, R. K. Brooner, M. Kidorf, and G. E. Bigelow

HIV sexual risk reduction in IVDAs is a pressing public health concern. Several reports show some reduction in high risk sexual behaviors in IVDAs, though the magnitude of changes remains modest. The present study examined the relationship between recent (past 30 days) sexual activity, substance use and other psychiatric disorders, HIV knowledge, condom knowledge and attitudes, and a behavioral measure of intent to use condoms. Study participants were 88 new admissions to a methadone substitution therapy drug abuse treatment program. Comprehensive sexual behavior data for the 30 days prior to admission was obtained from each patient. All patients received a single HIV-l group education session with a pre-test of HIV knowledge and attitudes about condom use. Further, patients were given coupons at the end of the group that could be redeemed for further information about STDs as well as condoms and dental dams and another coupon that could be exchanged for additional condoms and information. A total of four coupons could be exchanged in this manner. Rates of coupon redemption for condoms and information were highest for the higher risk group (commercial sex, multiple partners, anal sex, inadequate use of condoms) versus the lower risk group (sexually abstinent, 100% condom use), and this trend continued through the four weeks of the study. There were no significant differences between groups for the HIV knowledge or condom attitude or condom knowledge surveys. Alcohol abuse/dependence (77% of higher vs 43% of lower) but no other substance (e.g., cocaine) was significantly greater in the higher risk group. The higher risk group also had a greater percentage of Axis I disorders (18% higher vs 7% lower) and Axis II disorders (26% higher vs 14% lower), but these differences were not statistically significant. In this population, attitudes toward condoms and knowledge of condoms and HIV were not correlated with sexual behavior in the recent past, though other psychiatric and substance use disorders were somewhat greater in the higher risk group. Factors other than education and knowledge of appropriate attitudes about sexual risk behavior may play a greater role in actual sexual risk behavior in opioid drug abusers entering methadone treatment.

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RNA: RISK NETWORK ASSESSMENT FOR EPIDEMIOLOGIC RESEARCH ON DRUG ABUSE AND HIV

D. Taylor, R. K. Price, D. Mager, and L. B. Cottler

The Risk Network Assessment for Epidemiologic Research on Drug Abuse and HIV (RNA) was designed to rapidly assess characteristics and behavioral patterns of people who have jointly engaged in behaviors which put them at risk for HIV/AIDS. It was developed primarily for the St. Louis site (Each-One-Teach-One Study, DA08324) of the NIDA Cooperative Agreement Project aimed at nationwide implementation of HIV surveillance and intervention targeted at out-of-treatment drug abusers. The RNA focuses specifically on HIV-transmittable relations.

We analyzed data from the first waves of RNA interviews conducted between January and April 1994. A total of 267 alters (network members) were named by 57 probands (index subjects) solicited through three questions: injection, crack smoking and sex, jointly engaged during the last 30 days. Expectedly, IDU probands injected drugs with the higher number of alters (mean=2.3) than crack-using probands, and crack using probands smoked crack with more alters (mean=5.2) than did IDU probands. However, while IDU probands reported more than two times as many crack-using alters than sex partners, crack-using probands reported six times as many sex partners than injecting partners. Injecting partners (as were IDU probands) were older and less likely to be living alone than crack-using partners. IDU probands reported knowing more than 50% of their injecting partners very well, compared to crack-using probands reporting 37% of crack partners. Probands reported more frequent sex in their crack-using network than in their sex network and the least in their injecting network (mean frequency of sex 7.9, 5.9, 3.1). In a one month period, an active injector had an 80% chance of injection with someone and an active crack user had an 86% chance of smoking crack with someone; suggesting usefulness of assessing HIV-risk networks. Further, for this sample, the RNA appears to have captured different patterns of overlap among injecting, crack and sexual networks between IDU and crack-using probands. Since joint crack smoking alone is not a HIV-transmittable behavior, an overlap of injecting and crack-using networks does not appear sufficient to create a transmission "bridge" to promiscuous heterosexuals who are non-IDUs. Such a pattern of risk network overlap may have contributed to a slow spread of HIV in the St. Louis drug-using population and their heterosexual counterpart. Obviously, a larger sample is needed to confirm this observation. Probands did not know HIV status of 27% of their risk-network alters, indicating a limited utility of network assessment for HIV based solely on probands. Direct assessment with network members through link tracing is recommended while taking into account cost containment needs.

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COCAINE AND CRACK USE AMONG HIGH-RISK ADDICTS IN AN ENHANCED METHADONE MAINTENANCE PROGRAM

M. D. Anglin, C. E. Grella, and S. E. Wugalter

This study examines cocaine and crack use among subjects admitted into a research demonstration project for addicts at high-risk of HIV infection.

METHOD: Discriminant function analysis was performed to determine the unique characteristics of 1) self-reported cocaine users compared with non-users and 2) crack users compared with non-crack cocaine users at treatment intake. Logistic regression analysis was performed to determine the predictors of cocaine and crack use after treatment admission.

RESULTS: Cocaine users reported more varied criminal activity, higher levels of depression and suicidality and were more likely to use alcohol. They were more likely to exchange sex for money or drugs, were less likely to report condom use, shared needles with a greater variety of partners, tended to use new needles less frequently, and were marginally more likely to be HIV-positive. Crack smokers were more likely to be African-American, to use alcohol, and to engage in more types of criminal activities. They were less likely to clean needles prior to injection and to use new needles, but reported fewer uses per needle. Individuals using cocaine or crack after treatment admission were more likely to be African-American, to use heroin at follow-up, to have used crack or spcedballs at intake, to use alcohol at follow-up, to be married or living with a partner, to report more sources of legal income, and marginally more likely to be depressed.

CONCLUSIONS: Cocaine users present a higher-risk profile at treatment intake than non-cocaine users; those who use crack are more at risk than non-crack cocaine users. Cocaine and crack use after treatment entry was unaffected by either participation in an enhanced treatment program or length of time in treatment.

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COCAINE USE AND HIV INFECTION IN METHADONE MAINTAINED AND UNTREATED INTRAVENOUS DRUG USERS

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We surveyed 424 intravenous drug users (IVDUs), 107 of whom were currently enrolled in a Methadone Maintenance Program (MMP) with a cumulative lifetime methadone treatment of 92 weeks (SD 174). Of the 317 subjects in no current treatment, 98 had a history of MMP with a cumulative treatment length of 131 weeks (SD 168). In this cohort we assessed risk factors for HIV infection and conducted HIV testing.

The entire cohort included 39% HIV zero-positives with no difference between genders. Of the HIV negatives, African Americans represented 44% of the untreated and 12.5% of the MMP subjects. Of the HIV positives, African Americans constituted 69% of the untreated and 51% of the MMP subjects ($p<0.0001$). There were no statistically significant differences in HIV rates by age, education and marital status.

Regarding risk behaviors, MMP subjects reported fewer drug injections in the last 30 days ($p<0.001$). a reduced speedball injection frequency ($p<0.05$), and reduced total cocaine ($p<0.001$) as well as injected cocaine ($p<0.01$) use frequency. HIV positives reported 20% more total cocaine use ($p<0.05$) and injected cocaine use frequency ($p<0.05$) than HIV negatives. In addition, while only 40% of the MMP subjects regardless of HIV status reported IV cocaine use, 64% of HIV negative and 78% of HIV positive out-of-treatment subjects reported IV cocaine use (chi square 6.5; $p<0.01$) MMP, therefore, significantly reduced the percentage of subjects injecting cocaine (chi square 19.7; $p<0.001$). Stratified analysis by race confirmed the increased use of cocaine by HIV positives only in African Americans and not in Caucasians and Hispanics. Reduced substance use including cocaine use rates in MMP subjects was found for all ethnic groups.

In summary, African Americans are over-represented in the HIV positive group and under-represented in the MMP group. Furthermore, IV cocaine use is a risk factor for HIV infection and participation in a MMP is associated with reducing this risk factor.

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VALIDITY OF SELF-REPORT DATA ON RISK BEHAVIORS FROM HEROIN ADDICTS ENTERING FREE METHADONE TREATMENT

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This study reports on a validity check of self-reported risk behavior used to assess eligibility for free methadone treatment in a demonstration project.

METHOD: Prospective subjects were assessed for membership in at least one of four designated high-risk target groups. The validity check assessed the consistency in self-reported risk behaviors at eligibility, intake, and follow-up interviews. Admitted and suspected liars were compared with non-liars on psychological measures, needle and sex risk behaviors, self-reported drug use, urinalysis results, economic status, treatment motivation, and demographics.

RESULTS: Of the 500 subjects admitted, 32% either admitted to lying or were strongly suspected of lying in the eligibility assessment. Of the four target groups: 1% falsely claimed to be HIV-positive; 14% falsely claimed they were gay or bisexual males; 23% falsely claimed to be sex workers [prostitutes]; and 8% falsely claimed to be a sex partner of a high-risk IDU. Liars were more likely to be older males compared with non-liars or undetected liars. They reported less income in the 12 months prior to entering treatment and hence may have had more economic incentive to enter a free treatment program. Liars did not differ in their psychological characteristics, criminal behavior, treatment motivation, needle use, and frequency of condom use. Liars had a higher rate of inconsistency between self-reported cocaine use and results of urinalysis at intake, but a lower rate of inconsistency in self-reported bensodiazapilne use at follow-up.

CONCLUSIONS: Eligibility criteria exclusively based on sex risk may exclude older male addicts who otherwise face risk of HIV infection through needle use and unprotected sex. Individuals who previously admit to lying in order to gain project admission may be less likely to falsify self-reported drug use at follow-up, after their treatment status is assured.

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AN AUTOMATED VERSION OF THE RISK ASSESSMENT BATTERY (RAB): RELIABILITY, VALIDITY, AND SUBJECT ACCEPTANCE

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INTRODUCTION: Over the past two decades, advances in computer technology have led to the development of many automated psychological assessments. Advantages of computerized assessments include reduced cost and time required for data entry, improved quality control during data collection, and the possibility that subjects may feel more comfortable reporting sensitive information to a computer. In an effort to improve cost-effectiveness and quality of data processing, we have developed an automated version of the RAB; a self-administered HIV risk assessment instrument that yields drug, sex, and total risk scores. The goals of this study were to ascertain the reliability of the computerized RAB (C-RAB), and to gauge subject reaction. An additional objective was to determine if there were less inconsistent responses and missing data on the C-RAB.

METHODS: Subjects were 86 male veterans enrolled in a methadone maintenance clinic. Both the paper & pencil and automated RAB were completed within one hour. The order of administration was counter-balanced. After subjects completed both versions of the assessment, a short interview was conducted to assess their opinions and preferences.

RESULTS: Correlations of drug, sex , and total risk scores between the two versions were .92, .93, and .93 respectively. Furthermore, percent exact agreement of the items comprising the risk scores ranged from 93 to 98 percent. Seventy percent of subjects preferred the C-RAB. while only 6% preferred the RAB. There was a total of 8 unanswered questions on the RAB, but only one on the C-RAB. Likewise, no subjects recorded inconsistent responses on the C-RAB, while one subject had five inconsistent answers on the RAB. There were no significant differences between the RAB and C-RAB in the amount of sensitive information reported. However, more subjects felt that the C-RAB (43%) protected confidentiality better than the RAB (11%).

CONCLUSION: The magnitude of the risk score correlations and the level of item agreement suggest that the C-RAB can be reliably used to collect data. The results of the opinion survey also indicate that subjects' reaction to the C-RAB was extremely positive. While there was no evidence of enhanced self-reporting on the C-RAB, there was a reduced number of missing items and inconsistent responses.

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FACTORS ASSOCIATED WITH UNSAFE NEEDLE INJECTION IN DENVER

R. E. Booth and S. K. Koester

To assess predictors of unsafe needle injection, we studied 378 out of treatment drug injectors in Denver, Colorado. Respondents were asked about their needle hygiene practices during the 30 day period prior to the interview. Unsafe needle hygiene, defined as injecting with previously used, non-disinfected needles, was reported by more than a third of those interviewed. Factors associated with unsafe needle practices were: injecting heroin, perceived likely chance of getting AIDS, and lack of exposure to AIDS interventions in the community. Heroin injection, as a risk factor, is inconsistent with previous research where cocaine injection was associated with needle risk and HIV. The high percentage reporting unsafe needle practices within a 30 day interval, in spite of their perceived chance of getting infected, points to the grave risk AIDS continues to pose for drug users. We conclude that the apparent success of exposure to AIDS intervention efforts in changing needle practices shows promise for prevention programs targeting drug injectors.

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TRAINING IN INTERPERSONAL PROBLEM-SOLVING FOR INJECTION DRUG USERS: AIDS-EDUCATION AND HIV-RISK REDUCTION

J. J. Platt, M. Y. Iguchi, V. Lidz, and D. Mathis

To lower risks of HIV infection among IDUs, drug treatment programs often include special interventions to reduce HIV-risk behavior. While interventions focusing on interpersonal cognitive problem-solving skills have, (a) increased the addict's ability to cope with daily problems and, (b) enhanced treatment outcome, their usefulness for reducing HIV-risk behaviors has not been explored. The present study utilizes an AIDS-Education Training in Interpersonal Problem-Solving (TIPS) program. The underlying hypothesis was that IDUs who understand the risk of HIV infection may not behave in ways consistent with their knowledge because they lack necessary social-interpersonal skills.. The study was conducted as part of the AIDS Community Outreach Demonstration Projects of Newark and Jersey City, NJ, as part of NIDA's National AIDS Demonstration research project. Of 2544 subjects interviewed from 5/90 to 7/91, 569 were recruited for this substudy. Data are presented for 376 active IDUs not enrolled in drug abuse treatment for at least six months. Subjects were randomly assigned to either the TIPS intervention (N=210) or a contact-control group (N=166). Eight sessions were conducted 2X/wk for four weeks. The intervention reduced two important types of HIV-risk behavior: needle sharing and obtaining used needles. But these reductions were significant only among those who attended relatively few sessions. The same subjects had also engaged in more frequent risk-taking at the study's outset than subjects who attended more sessions. Thus, although the TIPS intervention seems to decrease important components of HIV-risk behavior, it proved most effective with high-risk IDUs who attended relatively few group sessions. The results suggest that a brief skills intervention would be effective for high-risk individuals while increasing rates of participation.

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INDIRECT SHARING: INJECTION-ASSOCIATED HIV RISKS

S. K. Koester and R. E. Booth

This study examines the process of drug injection among active injection drug users (IDU's) in Denver. Results indicate that a series of behaviors associated with drug injection may facilitate the transmission of HIV, even when injectors use separate syringes. These "indirect sharing" practices occur when participants in an injection episode contaminate "shared" injection paraphernalia, and when they divide a "shared" or jointly purchased drug in the process of preparing it for injection. In this latter case, one injector uses their syringe to pull up water to mix the drug into a liquid. Then, using the calibrations on the syringe, the drug is divided into individual doses. These doses are then transferred (squirted) into the barrels of the other participants' syringes (backloading). These practices are "indirect" only because the risk they present is less directly apparent. Risk is obscured because contamination occurs during intermediate steps in the injection process. In these practices, the syringe itself is not shared, only its contents are. These behaviors have been infrequently reported and remain only partially understood. Data from direct observations of injection episodes, semi-focused, open-ended interviews with IDU's, and a survey suggest these "indirect sharing" behaviors are frequent and routinized practices within a larger drug preparation and injection process. Findings also indicate that many IDUs are unaware of the potential risk associated with these behaviors. These findings have important implications for HIV prevention and illustrate the benefits of combining qualitative and quantitative methods.

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ARE DRUG TREATMENT PROVIDERS WILLING TO PARTICIPATE IN HARM REDUCTION AND TO WHAT EXTENT?

P. E. Evans, H. W. Clark, G. Hughes, C. Hoyo, K. Robinson, M. Lodico, D. DePhilippis, and M. Shopshire

OBJECTIVE: To investigate and compare drug treatment providers' attitudes related to their participation in harm reduction in two San Francisco Bay area communities, San Francisco (SF) and San Jose (SJ).

METHODS: Recruitment: County drug and alcohol administrators contacted to inform them of the study, elicit their support and obtain names of public contract drug treatment programs in SF and SJ. Subjects: Eligible subjects were counselors, admissions staff, physicians nurses, etc. and administrators. Questionnaire: A 101 item forced-choice questionnaire was developed to assess AIDS knowledge, attitudes and beliefs and harm reduction. Follow-up: Drug treatment administrators were contacted four times. A total of 889 questionnaires were mailed with 499 returned for a response rate of 55%.

RESULTS: Drug treatment staff in SF were more comfortable telling clients about bleach compared to SJ (9% vs 16%, p=.04). However, no differences were noted in telling clients about clean needles (15% vs 21%, p=.13). Providers in SF were more comfortable giving clients bleach (23% vs 58%. p=.002) and clean needles (39% vs 49%, p=.04) compared to SJ. In SF 87% of providers agreed that needle exchange should be expanded to prevent the spread of HIV compared to 79% in SJ (p=.02).

CONCLUSIONS: There appears to be a philosophical difference in a passive instructional approach (telling clients) vs active participation (giving clients) to harm reduction. Drug treatment providers do support needle exchange programs. Additional strategies are needed to overcome barriers to acceptance of harm reduction among drug treatment staff. In the meantime, needle exchange programs need to be separate from drug treatment programs.

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ONE YEAR RETENTION IN METHADONE MAINTENANCE AND HIV RISK BEHAVIOR

E. A. Wells, D. A. Calsyn, A. J. Saxon, T. R. Jackson and L. L. Clark

Using initial and 12-month interviews from 353 injection drug users (IDUs) newly admitted to a methadone maintenance (MM) research and demonstration project, we sought to determine what dimensions of HIV risk behavior change are associated with retention in MM. Three dimensions of injection risk behavior were identified through factor and reliability analysis of the AIDS Initial Assessment (AIA) needle use questions: sharing injection equipment with sexual partner (initial α=.82, 12-month α=.84); sharing with others (α=.75;α=.64); and new needle use (α=.74;α=.81). Among the 257 IDUs who continued to inject drugs in the six months prior to a 12-month interview, only the sharing with others scale differentiated between Ss retained vs. those discharged prior to 12 months. Retained Ss obtained lower scores even when initial risk scale scores, injection frequency and other control variables were included ($F = 3.92$, $df = 1,229$, $p < .05$). This suggests MM is important in reducing risky needle sharing, independent of its effect on injection frequency.

Using reliable AIA measures of sexual risk behavior (Myers *et al.,* 1990) (number of IDU sexual partners; unprotected vaginal intercourse) we also examined associations between MM retention and changes in sexual risk. Initially it appeared as if Ss retained for one year reported lower risk on both measures, but the difference was not maintained when age was entered as a covariate. Older IDUs have better treatment retention and report less risky sexual behavior. There were no differences among Ss receiving minimal, standard or enhanced counseling services or between Ss receiving contingency contracting or no contracting, or interactions between counseling level and contingency contracting when injection frequency was controlled.

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RISK FOR HIV INFECTION IN DRUG USERS REFUSING CONFIDENTIAL HIV TESTING

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Little is known about the risk for HIV infection in drug users who refuse confidential HIV testing. HIV seroprevalence in this group may be different than in drug users accepting HIV testing. To describe the extent of the HIV epidemic among drug users, the overall HIV seroprevalence should be assessed. Understanding the predictors of HIV test refusal may help develop policies for HIV screening and prevention. Our study was aimed at assessing the overall rate of HIV infection among applicants to methadone treatment, determining the risk for HIV infection in those refusing testing and describing their characteristics. We analyzed the characteristics associated with a positive HIV status in patients who accepted HIV testing or acknowledged HIV seropositivity.

HIV testing was offered to 160 applicants to methadone treatment at the time of medical evaluation. If they acknowledged HIV seropositivity, their serum was not tested. If they accepted HIV testing, their serum was tested immediately with a number identifier. If they refused HIV testing, their serum was frozen, and tested later with no identifier. Socio-demographic characteristics were obtained from a structured medical interview. Substance abuse variables were collected from an automated data base (Substance Abuse Management Information System [SAMIS])

Of 151 patients with unknown HIV status, 124 accepted HIV testing (82%) of which 14 (11.2%) had a positive result. Of 27 patients refusing HIV testing, 4 (14.8%) had a positive result . The risk for HIV seropositivity did not differ significantly among those refusing testing. Overall incidence of HIV infection was 11.9%; overall prevalence was 19.9%. The only predictor for refusing HIV testing was having private health insurance: 33% patients with private versus 9.9% with public insurance refused HIV testing ($p<.05$). HIV seropositive patients were more likely to abuse cocaine, to administer it intravenously, to have a severe secondary drug abuse problem, and to have had prior drug abuse treatment. Whites and patients with minor children were less likely to be HIV seropositive.

Insurance status predicted HIV test acceptance but not seropositivity. Substance abuse variables predicted seropositivity but not HIV test acceptance. More than 80% applicants to methadone treatment accepted HIV testing; patients with private insurance were more likely to refuse HIV testing. HIV seropositivity was predicted by dual addiction to cocaine and prior drug abuse treatment, both of which may be indicators of a more severe drug abuse problem.

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VIOLENT AND OTHER DEATHS AMONG ST. LOUIS SUBSTANCE USERS AT HIGH RISK FOR HIV

M. Bidaut-Russell, L. B. Cottler, and W. M. Compton

Our NIDA funded studies are conducted in the midst of environmental adversity. For instance, St. Louis City had 274 homicides in 1993, the highest number since statistics have been documented. Loss of study subjects, through death or attrition, is one of the most difficult problems facing epidemiologists and clinical investigators. The goals of this study were to investigate cause of death as one reason for loss to follow-up and to look at various characteristics of both deceased and alive drug users. Our hypothesis was that drug users who were found to be deceased at follow-up and those who were still alive had different pattern of chug use and mental health history.

For the present study, we have been tracking deaths among subjects from the Substance Abuse and Risk for Aids (SARA) and Efforts to Reduce the Spread of AIDS (ERSA) studies. For the SARA study, interviews were collected from 514 drug users, and two waves of interviews took place between 1989 and 1991. For the ERSA study, which began in 1990 and ended in May 1994. 485 interviews were collected at baseline. A total of 17 probands (13 males and 4 females; 70% African-American) were found to have died at 18 month follow-up. The average age of those who died was 29.4 ± 6.2, and the mean number of years of stay in the study was 1.1 ± 0.8. Three different sources: death certificates (N = 9), family members [mothers (N = 3). wife (1). sister (1), and brother-in-law (1)], and the newspaper (N = 1) provided information about cause of death. For comparison, a sample consisting of 36 still alive drug users from the SARA and ERSA studies was selected after being matched with the deceased drug users for date of entry in the study (± 1 week), gender, age, and race. Lifetime psychiatric disorders and pattern of drug use were assessed at baseline, in the study subjects, using the NIMH-Diagnostic Interview Schedule (DIS) Version III-R (Robins *et. al.,* 1989).

Death rate was 11 per 1000 per year. Only two probands died from causes associated with HIV disease. The other 14 died from drug overdose (1 subject), homicide (6), renal failure (2), accidents (3), pulmonary embolism (1), and cancer (1). Cause of death was unknown for one subject. Out of the six subjects who had been murdered, three had acute ethanol intoxication at time of death. There was no significant differences in mean age, marital status, education, and employment status between deceased and still alive drug users. Deceased and still alive drug users had comparable drug use patterns. Cocaine, heroin and cannabis were the three drugs both deceased and alive drug users had used the most. Deceased and still alive drug users had comparable lifetime prevalence rates of drug abuse/dependence, major depression, antisocial personality disorder, and alcoholism abuse/ dependence.

In conclusion, although in our samples of deceased and still alive drug users drug use patterns and prevalence of lifetime psychiatric disorders were comparable, future studies including a larger number of probands are needed to confirm our results. Because of the high rate of death by homicide among deceased drug users (35%), information about exposure to violence should be collected routinely both at baseline and at follow-up.

REFERENCE:

Available upon request of senior author.

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COMMUNITY-BASED HIV INTERVENTIONS TO DRUG-USING WOMEN

C. J. Reback and V. B. Brown

INTRODUCTION: This paper describes a community-based research and demonstration project for high-risk women. Target populations include women who are: injection drug users, non-injection drug users, sexual partners of drug users, those who exchange sex for money and/or drugs, and former drug users. All communities served are low-income, predominantly African-American and Latino, and within the inner-city neighborhoods in Los Angeles County.

METHODS: Respondents for the study are recruited by indigenous community outreach workers. After an initial screening and assessment interview, women are randomly assigned to either a standard or enhanced intervention. The standard intervention includes three individual counseling sessions, six unstructured groups. pre- and post-test counseling, HIV-antibody testing for women who choose to be tested, and referrals without advocacy to appropriate services. The enhanced model includes three individual counseling sessions, optional crisis intervention counseling from a social worker, six structured groups with specific topics and curricula, two pre- and post-test counseling sessions, HIV-antibody testing for those who choose to be tested, and referrals with advocacy to appropriate services.

RESULTS: Effective outreach strategies for hard-to-reach women must include codes that signify that the outreach worker identifies with the target population. These signifiers include continuity in the field; knowledge of "gatekeepers" in the community; up-to-date and culturally appropriate referrals to treatment centers, shelters, disaster relief programs and other agencies; sharing of personal experiences; and gift giving. Common barriers in the women's lives are drug use; past or current physical, emotional and/or sexual abuse; feelings of lack of control over their lives; psychological distress; few close friends; and intimate relationships that cause stress and problems. Programs must implement innovative interventions to overcome these barriers. Findings are useful in developing outreach/intervention designs to reach high-risk women.

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AFFILIATION:

PROTOTYPES, A Center for Innovation in Health, Mental Health and Social Services, Culver City, CA

COMPARISON OF HIV SEROPREVALENCE BETWEEN IV COCAINE AND HEROIN USERS

B. A. Beall, D. L. Frankenfield, C. S. Contoreggi, and W. R. Lange

One hundred and forty intravenous (IV) cocaine and heroin users recruited from the Baltimore metro area were stratified by stated drug of choice, gender, and race in order to determine the seroprevalence of selected viral markers, including human immunodeficiency virus (HIV), to ascertain whether certain risks may be more specifically defined in segments of this population, and to determine what health care interventions should be considered.

This population was 55% male, 47% white, 53% African-American, with an age range of 21-45 years. Most of this population was unemployed, single, and had less than a high school education; approximately 20% were either on probation, parole, or bond.

In the past month, most had shared needles and approximately 33% reported using shooting galleries. In the past year, more than 33% reported having multiple sex partners (>4).

Despite self-reported knowledge of harm reduction measures to reduce HIV transmission, 20% of this population was HIV seropositive; 11% was indeterminate. Most of this population was also seropositive for hepatitis B and C, which have similar epidemiologic profiles. The HIV infection rate was highest in African-American cocaine-preferring females.

The large number of HIV indeterminates warrants further investigation, as does the increased HIV seroprevalence in the African-American females who prefer cocaine. Consideration should also be given to providing innovative preventive health care interventions such as the distribution of sterile needles, and specifically targeted behavior modification education to this population in the context of one-stop health care delivery which would include comprehensive drug treatment services.

AFFILIATION:

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WESTERN BLOT CONFIRMATION OF URINE SCREENS FOR HIV

B. D. Johnson, M. Hossain, and J. Astone

A distinct need exists for an HIV screen which does not involve the collection of blood specimens and avoids possible exposure to blood-borne diseases. Calypte Biomedical has developed a technology for screening for HIV in urine which has been documented as having sensitivity and specificity equivalent to blood screens.

In this research, 361 urine specimens collected from anonymous arrestees in the Drug Use Forecasting Program were tested by the Calypte HIV urine screens, those testing positive were confirmed with Western Blot (WB) using urine. Preliminary results show that 84% of the specimens testing positive by Calypte were confirmed by Western Blot.

Calypte urine HIV screen has strong potential for being as accurate as, and more convenient than, current blood-based screens. Future analysis will include assessments of sensitivity and specificity of Calypte urine screen.

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AFFILIATION:

National Development and Research Institutes and Medical and Health Research Association of NYC, Inc., New York, NY

COMPREHENSIVE PRIMARY CARE FOR SUBSTANCE USERS: THE CENTRAL MEDICAL UNIT MODEL

J. M. Shi, S. P. Henry, S. I. Molde, and P. G. O'Connor

Substance users are a vulnerable population in need of medical care. In New Haven, the APT Foundation has developed Central Medical Unit (CMU) to provide primary health care for substance users in drug treatment. CMU offers comprehensive medical services, including longitudinal care for chronic illness, urgent care for acute medical problems and preventive health care. Tuberculosis screening, immunizations, substance abuse risk reduction, sexually transmitted disease/ HIV counseling, family planning and referral, women's health screening and establishment of primary care provider are the specific health maintenance services offered. HIV specific medical evaluation and treatment are available. During the period July 1992 to June 1993, 1283 patients enrolled in APT made 5052 visits at CMU. Four hundred and thirteen visits were for comprehensive medical evaluation, and 4640 visits were for ongoing primary care. One hundred and seventy-four HIV positive patients were identified, and they required 422 visits.

CMU has consistently been able to meet the State of Connecticut, Department of Health Services HIV care objectives which include T-cell testing, anti-retroviral and PCP prophylaxis, T.B., syphilis, hepatitis B (HB) screening and treatment, pneumovax and influenza vaccinations. In this group of 174 HIV+, 97% (169) had updated CD4: 29% (51) with CD4<200, 40% (69) with CD4 200-500. and 28% (49) with CD4>500. Ninety-seven percent of the 120 eligible clients (CD4<500) were offered anti-retroviral therapy, 92% of the 51 eligible clients (CD4<200) were offered PCP prophylaxis. Ninety percent (156) had T.B. screening. Twenty-three clients were PPD+, 72 PPD- and 53 anergic. Eight were screened by chest X-ray only. None had active T.B. by chest X-ray. Ninety-seven percent (168) had syphilis test. All nine RPR+/FTA+ had completed treatment. Ninety-eight percent (170) had HB screen. Nine of 14 eligible for HB vaccination (HBV serology negative) were offered vaccination. Ninety percent (156) had pneumovax. Fifty-one percent (89) had 92-93 influenza vaccine.

CMU also participates in research. The on-site research studies include outpatient opiate detoxification, HIV/HBV/HCV epidemiology, buprenorphine maintenance, and primary care/HIV initiatives. It also provides off-site medical support for other substance abuse research protocols. Finally, CMU serves as teaching site for medical and nursing students, and internal medicine residents from Yale University. It serves as a liasion with community agencies in regards to drug treatment prevention, referral and training.

CMU serves as a model to improve the availability and accessibility of health care and drug treatment for substance users. It also contributes to research and education in the fields of primary care and addiction.

AFFILIATION:

APT Foundation and Yale University, New Haven, CT

EVALUATION OF A POSSIBLE PHARMACOLOGIC INTERACTION BETWEEN RIFABUTIN (RIF) AND METHADONE (MET) IN HIV+ INJECTING DRUG USERS

L. S. Brown, Jr., R. C. Sawyer, P. K. Narang, and R. Li

Rifabutin is an antibiotic recently approved by the FDA for prophylaxis of Mycobacterium avium complex (MAC) in HIV infected patients. Since it is chemically related to rifampin, which enhances methadone clearance, it was thought necessary to assess its possible interactions. Twenty-four patients (63% African-American, 37% Hispanic, 83% male, mean age 44 years) were enrolled in the open-label, safety and tolerance study. After baseline plasma and urine measurements, patients took 300 mg/day Rifabutin for 13 days. No effects on methadone pharmacokinetics were detected by day 14. However, 17 of 23 evaluable patients reported one or more withdrawal symptoms. Most symptoms were mild, and only three patients required a methadone dosage increase. Rifabutin may interfere with methadone action by mechanisms not obvious in pharmacokinetics changes. Clinicians should be aware that prescription of Rifabutin may necessitate a methadone dosage increase.

AFFILIATION:

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HIV TESTING ON NIDA RESEARCH UNIT

R. Lee, F. Vocci, Jr., T. N. Alim, S. Kelly, and S. I. Deutsch

PURPOSE: The belief exists within the substance abuse/research community that if HIV testing were to be strongly recommended by staff, or required for specific protocols, recruitment of research subjects would be negatively affected. The experience of the NIDA research unit does not support this belief. Our experience is that required or strongly recommended HIV testing has had little or no impact on our ability to recruit research subjects.

PROCEDURE: The NIDA research unit at the Washington, D.C. V.A.M.C. is a 24 bed inpatient facility which conducts clinical pharmacology and pharmacokinetics studies of medications for the treatment of opiate and cocaine abuse. Unit policy prohibits HIV positive individuals from participating in research unless they are asymptomatic. have a CD4 count > 500 and require no medication. Prior to October, 1993 only IV heroin or other "high risk" populations were routinely tested. Beginning in October, 1993 HIV testing was strongly recommended for all patients. Pre- and post-test counseling is provided to all patients regardless of test results. Appropriate referrals are initiated for patients with positive results.

CONCLUSIONS: The requirement for HIV testing for all heroin protocol patients and the strong recommendation to all other patients has not had a negative impact on patient recruitment. NO patient declined to be admitted to a protocol based on the requirement for HIV testing.

When HIV testing was required by protocol, compliance was 100%; NO patient refused to participate because of this requirement.

When HIV testing was done only by patient-initiated request, compliance was 13% in 1992 and 43% from January to September, 1993.

When HIV testing was strongly encouraged for all patients, beginning in October, 1993, compliance rose to 93%.

AFFILIATIONS:

VA/NIDA Research Unit, VAMC Washington, DC, and Medications Development Division, NIDA, Rockville, MD

DRUG TREATMENT CLIENT AND STAFF ATTITUDES TOWARDS HIV TESTING

J. Astone

Large numbers of clients in drug treatment may have been exposed to HIV, yet the rates of seropositivity are not well documented for non-IVDU drug abusers, nor is HIV testing routinely available for these individuals. Clients who want to know their HIV status seek anonymous testing outside of their drug treatment program.

This study examined the attitudes of drug treatment clients and staff towards HIV testing within four different drug treatment modalitites: detoxification, residential, outpatient, and methadone maintenance at an urban hospital in New York.

A 19-item survey was administered to staff members (N = 148) and a modified 18-item survey was administered to clients (N = 423) over a five month period in 1990. Between-treatment and within-treatment setting comparisons were made.

Clients and staff from all treatment settings were in agreement with voluntary and mandatory HIV testing. Future research recommendations are discussed.

AFFILIATION:

Medical and Health Research Association of New York City, Inc./NDRI, New York, NY

ACOUAINTANCE WITH HIV-POSITIVE PERSONS AND AVOIDANCE OF HIV-INFECTED CLIENTS AMONG DRUG TREATMENT STAFF

M. A. Lodico, P. E. Evans, H. W. Clark, G. Hughes, and K. Robinson

OBJECTIVE: To identify correlates of preferring to avoid HIV+ clients among drug treatment staff in a low (San Jose, [SJ]) and high (San Francisco, [SF]) HIV prevalence area in the San Francisco Bay area.

METHOD: An anonymous mail survey of direct service drug treatment staff and administrators of publicly funded contract agencies in SF and SJ was conducted in 1993. The return rate was 55% (n = 499). A 101 item forced-choice survey assessed demographics, HIV casual transmission knowledge, and acquaintance with and attitudes towards HIV+ persons.

RESULTS: In SJ, 36% of respondents reported knowing a friend or family member infected with HIV contrasted with 69% in SF ($p < .001$). While 10% of those who personally knew an HIV positive person agreed that they would avoid caring for an HIV+ client, 24% of those without such acquaintance preferred to avoid HIV+ clients ($p < .001$). Moreover, of the 143 respondents who wrongly endorsed any casual transmission items, 25% would avoid an HIV+ client contrasted to 12% of those without misconceptions ($p < .001$). No bisexuals, only 4% of homosexuals but 19% of heterosexuals reported preferring to avoid HIV+ clients ($p < .001$). Interactions between sexual orientation and acquaintance and between sexual orientation and casual transmission misconceptions were identified. Of heterosexuals acquainted with an HIV+ person and holding no misconceptions, only 11% preferred to avoid, while 20% of those who either had some misconceptions or knew no HIV+ person preferred avoidance, but 34% of those who knew no HIV+ person and held misconceptions preferred to avoid HIV+ clients ($p = .001$). In contrast, among male gays, the 7% who preferred to avoid actually knew HIV+ persons and held no misconceptions; no lesbians reported a desire to avoid.

CONCLUSIONS: Presentations to staff, particularly heterosexual staff, by HIV+ persons should be promoted especially in low HIV prevalence areas as a way to decrease staff avoidance of HIV+ clients. Discussions regarding attitudes towards homosexuality should also be encouraged.

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AFFILIATIONS:

Multicultural Research Insitute, Bayview-Hunter's Point Foundation; Treatment Research Unit, University of California, San Francisco, CA, San Francisco Veteran's Administration Medical Center, CA

THE EFFECT OF KNOWLEDGE ON WILLINGNESS TO PARTICIPATE IN HIV VACCINE TRIALS

I. Fureman, K. Meyers, D. Metzger, G. Woody, A. T. McLellan, H. Navaline, T. Boney, and R. Kanter

Can intravenous drug users make truly informed decisions regarding their enrollment in preventive HIV vaccine trials, given the complexity of the issues and the desperate nature of their situation? In preparation for efficacy testing of preventive HIV vaccines, Project Jumpstart in Philadelphia asked potential trial participants how to best educate their peers about vaccines and vaccine trials. Based primarily on their input, a videotape was produced using a talk show format. A professional moderator facilitated a discussion about HIV vaccine trial issues between a studio audience filled with potential trial participants and a panel of experts. The panel included two representatives from NIH, two local Project Jumpstart representatives, and an individual who had actually participated in a Phase II vaccine trial. Two hundred sixty five individuals agreed to take part in a controlled study of the videotape's effectiveness at communicating facts about HIV vaccines and vaccine trials. Of those 265, 79 were excluded from analysis because they either assisted us in the creation of the materials, or were HIV positive and therefore ineligible for participating in a *preventive* vaccine trial. Of those remaining, 88 were randomly assigned to a group which received a pamphlet including information related to HIV vaccine trials and attended a brief question and answer session; 98 watched the videotape in addition to receiving the pamphlet and taking part in the question and answer session. Immediately prior to and following the education session, participants were given a brief questionnaire which assessed general knowledge about HIV vaccines, willingness to participate in an HIV vaccine trial, and trust in government. A higher percentage of the participants in both groups more fully understood key concepts such as vaccine-induced seroconversion and vaccine/placebo trials, after receiving the information. The group that viewed the videotape reported a reduction in government mistrust. Our examination of the relationship between HIV-vaccine knowledge, trust in government, and willingness to participate in the vaccine trial yielded interesting results. Regardless of the study group, knowledge about HIV vaccine trials as assessed in our quiz *was unrelated to willingness to participate in trials.* Willingness to participate in a preventive vaccine trial was related to trust in government both before and after the education session, in both study groups.

AFFILIATION:

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RETENTION OF INTRAVENOUS DRUG USERS FOR LONGITUDINAL ASSESSMENT IN HIV RESEARCH AND VACCINE TRIALS

T. Boney, M. Abrams, K. Meyers, F. Mulvaney, R. Incmikoski, D.. Metzger, J. Williams, S. Dyanick, P. Green, B. Davis, A. Johnson, and G. Woody

Historically, retention rates among injection drug users (IDUs) in research studies have been problematic due to relocation, disinterest, unstable living arrangements and death. However, maintaining high participant retention is vital to the collection of meaningful data. Therefore, it is essential that IDUs be retained and that factors associated with attrition be identified.

This paper explores retention rates among two cohorts of IDUs. One cohort was recruited in 1989 as part of the NIDA-funded *Risk Assessment Project* (RAP), a longitudinal study of HIV infection and risk behaviors among IDUs. One hundred fifty-two in-treatment (IT) and 103 out-of-treatment (OT) participants were enrolled. Using similar methods, 471 participants were recruited in 1992 for a NIAID sponsored *Vaccine Preparedness Initiative* (VPI).

For both cohorts, a variety of techniques are employed to insure retention. Correct and varied contact information is collected including phone numbers and addresses of family, friends, study participants, shelters or regular hangouts. An automated client tracking database schedules appointments months in advance. Participants are reminded of their appointment a number of times; letters are mailed one month and one week before the appointment and reminder calls are made to those noncompliant with visits. Incarcerated and out-of-town participants are visited or interviewed by telephone. One simple tactic that has received positive participant feedback is the sending of holiday and birthday greetings. Subjects also receive remuneration, health education and supportive counseling, free condoms and bleach kits, and for HIV positive participants, medical monitoring. Finally, project staff are genuinely interested in working with the participant population and have developed an excellent rapport with them.

Among the RAP cohort, 84% were retained for four years while 94% of the VPI cohort were retained through the one year follow-up. Only treatment status was associated with retention among the RAP cohort as significantly more of those IT at baseline were retained than those OT at baseline (88% vs 77%, $P < .05$). Among VPI participants, females had significantly higher rates of retention than males (98% retained: OR 4.3). and IT participants had significantly higher rate of retention than OT participants (96% retained: OR 2.5). Mortality in both cohorts was significant. Ten percent of the RAP cohort died during the four year follow-up period (3.39 / 100 person years) and 2% of the VPI cohort died within the one year follow-up period (2.04 / 100 person years). This data demonstrates that IDUs, especially females and those IT, can be retained in longitudinal research. Further study needs to examine other reasons for attrition. For example, do staff characteristics play a role in retention? Also, with mortality so high in this population, liaisons with public health departments may be useful in the identification of deceased participants.

AFFILIATIONS: University of Pennsylvania / Philadelphia Veterans' Affairs Medical Center, Center for Studies of Addiction, Philadelphia, PA

HIV SEROPREVALENCE AMONG IDUS: SOCIO-DEMOGRAPHIC AND TREATMENT-RELATED DIFFERENCES ACROSS TWO IN- AND OUT-OF-TREATMENT COHORTS

H. Navaline, D. Metzger, K. Meyers, T. Boney, A. Johnson-Wilson, J. Williams, S. Dyanick, F. Mulvaney, B. Davis, M. Abrams, P. Green, P. Oglesby, R. Davis, and G. Woody

The changing demographic characteristics of those most likely to become HIV infected has implications for the design of intervention and outreach efforts. Among injection drug users (IDUs). these changes may be mediated by treatment status. We address this issue by examining the *baseline* seroprevalence rates of two in- and out-of treatment cohorts of IDUs participating in the Risk Assessment Project, a NIDA-funded longitudinal study of HIV infection and risk behaviors.

METHODS: Recruitment of the first cohort of 255 participants began in 1989 and continued for nine months. Eligibility criteria included: age of 18 or older, history of regular injection opiate use and, for out-of-treatment (OT) recruits, no drug treatment during the past 10 months. In-treatment (IT) participants were recruited from an inner-city outpatient methadone program. Three hundred seventy-nine patients (86% of the clinic census) completed a questionnaire and 152 of these were randomly selected to participate in the longitudinal study. OT participants (n=103) were recruited through referrals from IT subjects and by community outreach near the clinic.

Three years later, in 1992, another cohort of 100 IT and 60 OT IDUs was recruited over a six month period. Recruitment methods and inclusion criteria matched those used to enroll the original cohort. Seventy-four percent (n=257) of clinic patients not already in the study agreed to complete a survey; 100 were randomly selected to participate in the longitudinal study. The new OT cohort was recruited via IT referrals and outreach in the community. Every six months, participants complete pre-test counseling, HIV testing and behavioral assessments such as the Risk Assessment Battery (RAB), a brief, self-report measure that surveys the extent of drug use and sexual behaviors.

RESULTS: The *new IT* cohort, as compared to the *original IT* cohort, had a significantly higher proportion of women (29% vs. 11%, $p < .05$), African-Americans (5% vs. 25%, $p < .001$) and participants older than 44 years of age (6% vs. 30%, $p < .05$) who were HIV positive at baseline. There were no such differences between the two OT cohorts. These findings suggest not only that these sub-groups may be at elevated risk of infection, but that treatment programs may need to target medical and support services to minority women and older patients. Baseline HIV seroprevalence for the *new IT* cohort (18%) matched the concurrent rate of the *original IT* cohort at its three year follow-up. However, baseline seroprevalence among *new OT* recruits was significantly lower than the concurrent rate among the *original OT* participants at their three year follow-up (23% vs. 39%, $p < .001$). This suggests that prevalence data from OT populations recruited using non-probability methods must be interpreted cautiously.

AFFILIATIONS: University of Pennsylvania/Philadelphia Veterans' Affairs Center for Studies of Addiction, Philadelphia, Pennsylvania.

CHANGES IN PSYCHOLOGICAL SYMPTOMATOLOGY AS A FUNCTION OF SEROSTATUS AND GENDER AMONG IDUS

R. Davis, D. S. Metzger, K. Meyers, F. D. Mulvaney, H. A. Navaline, and G. E. Woody

INTRODUCTION: Virtually all substance abuse treatment programs serving drug users have adopted the goal of reducing HIV risk behaviors and have implemented a variety of interventions. including AIDS education and HIV testing, to achieve this goal. While pre- and post-test HIV counseling are required, this is often limited to a single session. As the analyses presented herein suggest, it may be necessary to examine and respond to IDUs' reactions to their antibody status beyond the initial post-lest session. Unfortunately, however, little is known about IDUs' reactions to the HIV testing process or their serostatus. Since many IDUs are infected with HIV, treatment programs will need to identify whether psychological issues surround the testing and notification process and, if so, respond appropriately. Whether or not changes in psychological symptomatology among IDUs occurred during the 24 months after notification of HIV serostatus was examined: 163 lDUs completed the SCL-90, the Risk Assessment Battery (RAB), and the Psychiatric Status section of the Addiction Severity Index (ASI). **METHODS:** Changes in psychological symptomatology as a function of serostatus and gender were examined using the first 24 months of interview, questionnaire, and serologic data (collected at 6-month intervals) on 23 subjects who tested positive at the initial assessment and 140 subjects who remained negative throughout the first 24 months of the RAP project, a longitudinal study of HIV risk behaviors and infection among in- and out-of-treatment IDUs. The project is funded by NIDA and is in its fifth year of data collection. In order to be included in these analyses, all 163 subjects had to have complete data over the first two years of the study. All subjects were seen every six (6) months for ongoing serologic and behavioral assessments. At each scheduled six month appointment. subjects completed a battery of self-administered questionnaires, participated in a face-lo-face interview, received pre-HIV test counseling, and had their blood drawn for HIV antibody testing. Subjects were compensated $20 for participation in this data collection session. Subjects returned within two (2) weeks for serologic results and post-HIV test counseling. Subjects were compensated $10 for participation. HIV-positive subjects were scheduled for medical follow-up with the project's nurse practitioner.
RESULTS: Analyses of changes in SCL-90 symptom severity between seronegative and seropositive IDUs revealed significant differences between groups at 12 months post-notification. Seropositive IDUs reported greater levels of overall psychological distress ($p<.05$), anxiety ($p<.05$), hostility ($p<.05$), phobic anxiety ($p<.003$), and obsessive-compulsive symptomatology ($p<.05$) at 12-month follow-up. Psychoticism subscale scores were significant at the 12- ($p<.01$) *and* 18- ($p<.015$) month follow-up intervals for the seropositives, as measured by the SCL-90. Further analyses of symptom severity as a function of serostatus *and* gender revealed significant differences between seropositive females and the other groups. Seropositive females reported significantly greater levels of overall psychological distress ($p<.001$), anxiety ($p<.001$). psychoticism ($p<.001$). interpersonal sensitivity ($p<.001$), and somatization scores ($p<001$) at 12 months post-notification, as measured by the SCL-90. ASI psychiatric composite scores were also significantly higher for seropositive females ($p<.05$) at 12 months post-notification. **DISCUSSION:** These data suggest that greater levels of psychological symptomatology among seropositive IDUs post-notification, and especially among seropositive females, requires further study to uncover what may underlie a heightened vulnerability to symptomatology among this group and lo consider whether seropositive IDUs, and females in particular, require psychological treatment enhancement. The present analyses were performed with a small sample of seropositive females (N=4), therefore caution is advised in interpreting these results. Also, the significant differences between seronegative and sempositive subjects is accounted for by especially high scores among the seropositive females. Seropositive males "drop out" as a significant group once seropositive subjects are analyzed by gender. Follow-up over the course of this longitudinal study will provide further analyses and insight into the changes in psychological symptomatology as a function of serostatus and gender among IDUs.

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NOR-BINALTORPHIMINE: A VERY, VERY LONG ACTING KAPPA OPIOID ANTAGONIST IN PIGEONS

D. C. Jewett and J. H. Woods

Food-restricted pigeons were trained to peck a lit key under a fixed-ratio schedule of food reinforcement. Bremazocine decreased food-reinforced responding (ED_{50}= 0.03 mg/kg). Naltrexone (5.6 mg/kg) reduced the potency of bremazocine by one-third. Naltrexone's effect lasted less than 24 hours. The antagonist effects of nor-binaltorphimine (nor-BNI, 1.0 mg/kg). on the other hand, lasted over 100 days. A single injection of nor-BNI was given to four pigeons, and the time course of the amount of antagonism of bremazocine was measured. A cumulative dosing procedure was used to assess the potency of bremazocine in suppressing food-reinforced responding. Bremazocine's effects were measured every four to seven days. One hour after nor-BNI was given it was ineffective. Eight days later, it produced a 3-fold reduction in the potency of bremazocine. Between two and three weeks after nor-BNI, it reduced the potency of bremazocine by 10-fold. It continued to antagonize bremazocine for over two months; the control sensitivity returned after 112 days. Smaller doses of nor-BNI (0.01-0.1 mg/kg) did not antagonize bremazocine. This effect was not due to tolerance to bremazocine since no tolerance developed to bremazocine administered every four days. It would appear that nor-BNI has a long action in all species in which duration of antagonism has been measured [v.i.z., mice (Endoh *et al.,* 1990), pigeons and monkeys (Butelman *et al.,* 1993)]. Long duration of action is obtained by both central and systemic administration. The mechanism by which this unusual duration is brought about is unknown.

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EFFECTS OF NALTRINDOLE ON COCAINE'S SELF-ADMINISTRATION IN THE RAT

K. A. Menkens, E. J. Bilsky, E. D. French, F. Porreca, C. L. Hubbell, and L. D. Reid

INTRODUCTION: Previous work has shown that naltrindole (NTI), a δ selective opioid receptor antagonist, blocked cocaine-induced conditioned place preference and facilitation of rewarding intracranial stimulation (ICS) (Menkens *et al.,* 1992; Reid *et al.,* 1993). Here, we further assess NTI's effects on cocaine facilitation of ICS or cocaine self-administration. There were also tests for NTI's effects on MDMA- and morphine-induced facilitation of pressing for ICS.

METHODS: Intracranial self-stimulation: The rats of these procedures had chronically indwelling bipolar electrodes for ICS of the MFR. Each was trained to press for three different levels of ICS on a FR1 schedule. Subjects were given the opportunity to press for ICS daily at each intensity for ten minutes. After rates of pressing became stable, subjects were given placebo and then cocaine (5 mg/kg, *i.p.*), MDMA (2 mg/kg, *s.c.*) or morphine (4 mg/kg, *s.c.*). While continuing the daily administration of the drug, a dose of NTI was administered (10 mg/kg, *i.p.,* 20 min before the session). In one experiment, NTI was given for five days while rats were given cocaine. **Intravenous self-administration:** Each rat (n=9) was fixed with a chronically indwelling intravenous catheter. Rats were trained to bar-press for infusions of cocaine and then switched to a progressive ratio schedule. Rats were allowed to press for five hours during daily sessions until rates of responding were stable across days. Then, rats were given a dose of NTI before a day's opportunity to press for cocaine. Rats not responding on the lever over a one hour period are considered to have reached a break point, a major metric for assessing rats' avidity toward cocaine.

RESULTS: Intracranial self-stimulation: NTI blocked the enhancing effects of cocaine and MDMA at all intensities and on all days tested. NTI did not block the enhancing effects of morphine. **Cocaine self-administration:** NTI did not affect all rats similarly. NTI hardly modified some rats' rates of pressing for cocaine. Two of the rats, however, did not press for cocaine under the influence of NTI. Most (8 out of 9) rats reduced their break points under NTI. The mean break point on the day before NTI (all rats) was 19.2. the mean break point on the day when NTI was given (ail rats) was 13.1, $t(8)=2.3$, $p=.05$.

CONCLUSION: These data confirm previously presented data germane to cocaine. NTI blocks cocaine- and MDMA-induced enhancement of pressing for ICS. Further, NTI's effects seem to persist, at least, across a five day period without any obvious diminution of effect. NTI dramatically modifies some rat's propensity to self-administer cocaine. The results indicate that a further inspection of delta opioidergic processes in stimulant-reinforcement is warranted.

REFERENCES: Available upon request of senior author.

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DIFFERENTIAL ANTAGONISM OF RESPONSE RATE-DECREASING EFFECTS OF OPIOID AGONISTS BY BETA-FUNALTREXAMINE

J. P. West, D. Hapke, D. Morgan, R. C. Pitts, M. J. Picker, and L. A. Dykstra

Lever pressing by rats was maintained under a fixed-ratio 20 (FR 20) schedule of food presentation. Using a cumulative-dosing regimen, the effects of various doses of the *mu*-opioid agonist fentanyl, the mixed action opioids butorphanol and nalorphine, and the *kappa* agonist U50,488 were determined alone and in combination with various doses of ß-funaltrexamine (ß-FNA), a specific, irreversible *mu*-opioid antagonist. ß-FNA alkalates *mu*-opioid receptors, reducing the available pool. Dose related decreases in response rates were found when each drug was tested alone. The response rate decreasing effects of fentanyl and butorphanol both were antagonized by ß-FNA in a dose-dependent fashion; nalorphine was slightly antagonized, and the kappa agonist U50,488 was not antagonized by ß-FNA. The sensitivity of fentanyl and butorphanol to antagonism by ß-FNA, however, was quite different. A given dose of ß-FNA, for example 5.0 mg/kg, shifted the dose effect curve of fentanyl to the right approximately 0.5 log unit while it shifted the dose effect curve for butorphanol approximately 1 log unit to the right. Also, the time required for the dose effect curve of butorphanol to return to pre-ß-FNA levels was two weeks, one week longer than for fentanyl. These data indicate, therefore, that fentanyl is a full mu-agonist while butorphanol can be categorized as a partial *mu*-agonist. The effect of ß-FNA in combination with nalorphine is puzzling; the data suggest a *mu*-opioid receptor component in the effects of this drug. The rate decreasing effects of U50,488 were not antagonized by ß-FNA, suggesting that the *mu*-opioid receptor is not involved in mediating the effects of this drug.

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TOLERANCE AND CROSS-TOLERANCE TO EFFECTS OF VARIOUS *MU* OPIOIDS ON SCHEDULE-CONTROLLED RESPONDING OF MORPHINE-MAINTAINED SQUIRREL MONKEYS

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The purpose of the present experiment was to assess the response-rate-decreasing effects of various *mu* opioids prior to (pre-chronic), during (chronic) and after (post-chronic) daily administrations of morphine in squirrel monkeys. The *mu* opioids varied in terms of their relative intrinsic efficacy: etorphine, *l*-methadone, sufentanil (high intrinsic efficacy), morphine (intermediate intrinsic efficacy), buprenorphine, and meperidine (low intrinsic efficacy). Three squirrel monkeys' lever pressing was maintained by a fixed-ratio 30 schedule of food presentation. During the pre-chronic phase, buprenorphine, etorphine, meperidine, *l*-methadone. morphine, sufentanil, and the non-opioid pentobarbital dose-dependently decreased response rates with ED_{50}'s of 0.016, 0.0002, 2.84, 0.15, 0.65, 0.0006, and 5.05 mg/kg, respectively. The monkeys then were administered morphine twice daily, in a dose that increased gradually to 3.0 mg/kg, two hours before the experimental session and again 6-8 hours after the session. When response rates had stabilized under this chronic regimen, the effects of the compounds were redetermined. The morphine dose-effect curve was shifted to the right 0.97 log unit. Cross-tolerance was observed between morphine and buprenorphine (0.42 log unit shift), etorphine (0.58 log unit shift), *l*-methadone (0.47 log unit shift), and sufentanil (0.72 log unit shift). During daily administrations of morphine, meperidine completely suppressed response rates. The monkeys did not eat food when offerred, salivated, and showed visible body tremor. These effects were reversed by morphine in two of the three monkeys. No cross-tolerance was observed between morphine and pentobarbital's effects. Dose-effect curves generally returned to within 0.25 log unit when daily administrations of morphine were terminated. These results indicate that the degree of cross-tolerance between morphine and the other *mu* agonists did not vary as a function of intrinsic efficacy.

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WITHIN-SESSION ANALYSIS OF EFFECTS OF HALOPERIDOL AND MORPHINE ON BEHAVIOR MAINTAINED BY TIMEOUT FROM AVOIDANCE

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Concurrent performances were studied in rats under conditions where responses on one lever postponed shock on a free-operant avoidance schedule, and responses on another lever produced periods of signaled timeout from avoidance on a variable-ratio schedule. After responding had stabilized under these baseline conditions, the effects of haloperidol (.001-.1 mg/kg) and morphine (1-10 mg\kg) were evaluated and compared to the the effects of natural extinction produced by withholding reinforcement for responses on the timeout lever. Haloperidol produced gradual decreases in responding on both levers across the session that were similar to patterns produced by natural extinction. This finding indicated that the within-session decrements produced by haloperidol are not restricted to positive reinforcement situations. A difference between the effects of haloperidol and natural extinction was that extinction bursts (brief periods of high rate responding) occurred early in extinction sessions, but not during sessions preceded by haloperidol injections. Consistent with previous studies (*e.g.* Galizio, Ordronneau & Robinson 1994), morphine (1-10 mg\kg) selectively decreased responding on the timeout lever. However, these effects were apparent throughout the session. The absence of within-session decrements with morphine suggests that the rate decreases noted above are not produced by interference with negative reinforcement processes.

REFERENCE:

Galizio, M. Ordronneau, C. & Robinson, E. G. (1994). Opioid drugs and timeout from avoidance, Behavioural Pharmacology, 5, 125-130.

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CHRONIC NALBUPHINE TREATMENT MODIFIES THE RATE-DECREASING EFFECTS OF SOME OPIOIDS IN PIGEONS

L. R. Gerak and C. P. France

Nalbuphine is an opioid agonist which may produce its effects through actions at μ and κ receptors. In the present study, the response rate-decreasing effects for several compounds were determined in untreated pigeons and in pigeons treated chronically with nalbuphine (1.0-56.0 mg/kg/day). Prior to chronic treatment, dose-effect curves were determined for nalbuphine as well as several opioids and a non-opioid. All compounds produced dose-related decreases in response rates. Dose-effect curves for nalbuphine and naltrexone, determined at each of five nalbuphine treatment doses, were not different from control. Chronic nalbuphine (56.0 mg/kg/day) produced 5- to 10-fold shifts to the right in the dose-effect curves of the μ agonists morphine, fentanyl and etonitazene and the κ agonist enadoline, relative to control. When nalbuphine treatment was suspended for 52 hours, the dose-effect curves for morphine, fentanyl, etonitazene and enadoline remained shifted to the right of control curves; however, these shifts were 3-fold less, compared to dose-effect curves determined four hours after administration of nalbuphine, suggesting nalbuphine partially antagonized the rate-decreasing effects of morphine, fentanyl, etonitazene and enadoline. During chronic nalbuphine treatment, ketamine and nalorphine dose-effect curves were not different from control, suggesting that shifts in the morphine, fentanyl. etonitazene and enadoline dose-effect curves were not exclusively due to behavioral tolerance. In drug-naive pigeons, naltrexone did not antagonize nalbuphine; taken together with the lack of tolerance development in nalbuphine-treated pigeons, these data suggest the rate-decreasing effects of nalbuphine are not mediated by opioid receptors. Moreover, tolerance did not develop to nalbuphine but developed to morphine and to other drugs; this tolerance was not accompanied by a change in sensitivity to naltrexone, indicating tolerance developed in the absence of dependence. The absence of dependence, along with an apparent low efficacy, may contribute to the low abuse liability of nalbuphine.

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DISCRIMINATIVE STIMULUS EFFECTS OF C1-977 IN PIGEONS

M. R. Brandt and C. P. France

Drug discrimination studies have been used extensively to assess similarities and differences among a wide variety of drugs, including drugs of abuse. The drug discrimination procedure exhibits exquisite pharmacological selectivity, in that drug-associated responding occurs only after the administration of drugs that share other effects (*e.g.* mechanisms of action) with the training drug. The purposes of the current study were: 1) to establish the kappa opioid enadoline as a discriminative stimulus in pigeons; and 2) to characterize the selectivity of the enadoline discriminative stimulus by testing opioids and non-opioids for their ability to substitute for enadoline. Initially, subjects were trained to discriminate 0.1 mg/kg of enadoline (i.m.) from saline while responding under a fixed-ratio 20 schedule of food presentation in a single-cycle procedure. Enadoline produced dose dependent increases in drug key responding with a dose of 0.1 mg/kg producing ≥90% drug key responding. Animals were subsequently trained to discriminate 0.178 mg/kg enadoline from saline in a multiple-cycle procedure. Cumulative doses of enadoline produced dose dependent drug key responding. In time course studies, the discriminative stimulus effects of 0.32 mg/kg of enadoline lasted for one hour followed by a switch in responding to the saline key over a three hour period. Increasing doses of naltrexone (NTX) produced parallel rightward shifts in the discriminative stimulus dose effect curves of enadoline. Substitution tests using the selective kappa agonists spiradoline, U-50,488, and U-69,593 resulted in ≥90% drug key responding. Both nalorphine and the *kappa* selective opioid peptide dynorphin A(1-13) decreased response rates without producing drug key selection: up to rate decreasing doses, nalbuphine, morphine and ketamine also produced predominantly saline key responding. This study demonstrates that discriminative control can be established with enadoline in pigeons and that the magnitude of antagonism of this effect by NTX is consistent with kappa receptor mediation. In contrast to some purported *kappa* agonists which do not exert discriminative stimulus effects exclusively through *kappa* receptors in this species (*e.g.,* ethylketocyclazocine), the enadoline discriminative stimulus appears to result entirely from actions at *kappa* receptors. That dynorphin A(1-13) and nalorphine failed to substitute for enadoline, is consistent with the view that these compounds have low efficacy at *kappa* receptors.

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CHARACTERIZATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF KAPPA OPIOIDS AND MIXED-ACTION OPIOIDS: ROLE OF TRAINING DOSE AND INTRINSIC EFFICACY

M. A. Smith and M. J. Picker

In a two-choice drug discrimination procedure, rats were trained to discriminate either 0.056 (low dose) or 0.17 (high dose) mg/kg of the kappa-opioid bremazocine from saline. The kappa-agonists U50,488, EKC, spiradoline, CI-977, and U69,593 substituted completely ($\geq$ 80% bremazocine-appropriate responding) for the bremazocine stimulus in both training groups, a finding consistent with their high efficacy kappa profile. The mixed-action opioid (-)-cyclazocine substituted for the low training dose and produced intermediate levels of bremazocine-appropriate responding in the high training-dose group. In contrast, the mixed-action opioids butorphanol, nalorphine, nalbuphine, and levallorphan produced low to intermediate levels of bremazocine-appropriate responding in both groups of animals. When combined with the training stimulus, these drugs were capable of antagonizing the bremazocine stimulus in a dose-related manner in both groups of animals. In both training groups, naloxone and levallorphan produced dose-dependent rightward shifts in the bremazocine dose-effect curve. (-)-Cyclazocine potentiated the effects of lower doses of bremazocine while antagonizing higher doses, producing a general flattening of the bremazocine dose-effect curve in both groups. The kappa agonist U50,488 potentiated the effects of bremazocine producing a leftward and upward shift in the bremazocine dose-effect curve. The mu-opioid morphine neither substituted for nor antagonized the bremazocine stimulus in either training group. Collectively, these results suggest that the drug discrimination procedure can be used to effectively characterize the kappa agonist and antagonist properties of opioid compounds with different degrees of intrinsic efficacy at the kappa receptor.

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INDIVIDUAL DIFFERENCES IN THE DISCRIMINATIVE STIMULUS, RATE-DECREASING AND ANTINOCICEPTIVE EFFECTS OF HIGH AND LOW EFFICACY MU OPIOIDS

D. Morgan and M. J. Picker

This study examined individual differences in sensitivity to the stimulus, rate-decreasing and antinociceptive effects of high and low efficacy mu opioids. In rats trained to discriminate a 3.0 mg/kg dose of morphine from water, there was little evidence for individual differences in sensitivity to the stimulus effects of morphine; across rats, the lowest discriminable dose (LDD) of morphine varied by 0.5 log unit. In contrast, the LDD of nalbuphine and levallorphan varied by at least 3.0 and 2.25 log units, respectively. When these rats were tested in a tail-withdrawal procedure, the lowest dose of morphine that produced a maximal antinociceptive response varied across rats by 0.5 log unit, for nalbuphine by at least 1.5 log units, and over .75 log unit for levallorphan. Individual sensitivity to the stimulus effects of nalbuphine and levallorphan was a good predictor of sensitivity to its antinociceptive effects. There was little evidence for individual differences in sensitivity to the rate-decreasing effects of morphine, nalbuphine or levallorphan; for each opioid, the dose that suppressed responding did not vary across individual rats by more than 0.5 log unit.

In summary, there were no individual differences in sensitivity to the effects of morphine across three measures; however there was differential sensitivity to the stimulus and antinociceptive effects of nalbuphine and levallorphan. Furthermore, sensitivity to the stimulus effects of a low efficacy opioid was a good predictor of sensitivity to its antinociceptive effects.

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ANIMALS TRAINED TO DISCRIMINATE MORPHINE FROM NALOXONE GENERALIZE MORPHINE (BUT NOT NALOXONE) CONTROL TO NALORPHINE

S. Smurthwaite and A. L. Riley

Nalorphine has been reported to substitute for both the mu opiate agonist morphine and the mu opiate antagonist naloxone in animals trained to discriminate these compounds from vehicle, presumably due to nalorphine's intermediate efficacy at the mu receptor (*i.e.,* efficacy between that of naloxone (no efficacy) and morphine (high efficacy). In an assessment of the relative efficacy of nalorphine, in the present experiment six experimentally naive, Long-Evans female rats were trained to discriminate morphine from naloxone within the conditioned taste aversion baseline of drug discrimination learning and were then administered nalorphine (as well as other mu agonists and antagonists) to assess their ability to substitute for the training drug. Nalorphine (like the mu opiate agonists methadone and buprenorphine), substituted for morphine, whereas the opiate antagonists naltrexone and diprenorphine engendered naloxone-appropriate responding. That nalorphine substituted selectively for morphine following the morphine/naloxone discrimination suggests that in terms of its efficacy at the mu receptor, nalorphine lies closer to morphine than naloxone.

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INHIBITION OF CYP2D1 ENZYME ACTIVITY ALTERS HYDROCODONE METABOLISM BUT NOT DRUG DISCRIMINATION IN THE RAT

N. Joharchi, E. M. Sellers, T. A. Berns, S. V. Otton, and R. L. Balster

Hydrocodone (HC), a commonly prescribed opioid antitussive, is bioactivated to hydromorphone (HM) via cytochrome P450 2D6 (CYP2D6) enzyme. Active CYP2D6 enzyme is genetically absent in about 7% of Caucasians (designated poor metabolizers, PM). Deficient hydromorphone production after hydrocodone in poor metabolizers has been associated with decreased euphoric and increased dysphoric effects (Otton *et. al.,* 1993).

In order to establish the behavioral relevance of hydromorphone formation via CYP2D1 (the hepatic form of CYP2D6 in rats), drug discrimination of HM in rats in the presence and absence of enzyme inhibitors (quinine and budipine) was examined. Twenty male wistar rats were trained to discriminate HM (0.2 mg/kg s.c.) in a two lever drug discrimination paradigm. Hydrocodone at doses of 0.1, 0.3, 1, and 2 mg/kg s.c. showed 0%, 31%, 95%, and 100% generalization from HM respectively. Administration of the CYP2D1 inhibitors, quinine (40 mg/kg i.p.) one hour prior to HC (1 mg/kg s.c.) and budipine (10 mg/kg i.p.) 0.5 hours prior to HC (2 mg/kg s.c.) reduced peak HM plasma levels by 88% and 85% respectively. Plasma HC levels were unchanged. Neither quinine (20 or 40 mg/kg i.p.) nor budipine (5, 10, or 15 mg/kg i.p.) one hour prior to HC affected HC generalization from HM. Manipulation of route (s.c. vs. i.p.), pretreatment time (30 vs. 60 minutes), or chronic exposure to quinine (20 mg/kg s.c. over 10 days) had no effect on the results. Similarly, an independent replication of this study was unable to show any effect of quinine on HC discrimination in morphine-trained Sprague-Dawley rats.

The alteration in hydromorphone kinetics without a corresponding effect on drug discrimination suggests that hydromorphone may not be important in the discriminative stimulus effects of hydrocodone using this behavioral model. Alternatively, the CYP2D1 inhibitors, quinine and budipine. may not have affected the central conversion of hydrocodone to hydromorphone which may be responsible for the stimulus properties of this drug.

REFERENCES:

Available upon request of senior author.

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OPIOID DISCRIMINATION IN HUMANS: HYDROMORPHONE DOSE-RESPONSE CURVES PRE- AND POST-TRAINING AT PROGRESSIVELY LOWER DOSES

K. L. Preston, R. Fromme, and G. E. Bigelow

The purpose of this study was to examine the effect of discrimination training at progressively lower doses on the dose-response to hydromorphone on subjective and discriminative stimulus measures. Participants were eight adult male opioid abusers not currently physically dependent. With daily sessions in a residential laboratory and financial reinforcement for correct responses, subjects were trained to discriminate the mu-receptor agonist hydromorphone (20 mg, p.o.) from placebo; a hydromorphone dose-response curve was determined (PRE). The hydromorphone training dose was then progressively reduced from 20, to 14, 10, 7, 5, and, finally, 3.5 mg while the discrimination reinforcement contingencies remained in effect. The hydromorphone dose-response curve was then repeated (POST). Measures of subjective and physiological effects were concurrently collected during each discrimination session. As training dose was decreased, discriminative performance was generally well-maintained, although the percent of drug-appropriate responses to hydromorphone declined from 95% to 77%. In preliminary data analyses, there were few statistically significant differences between the PRE- and POST-training hydromorphone dose-response curves, though the sensitivity of discrimination performance tended to improve with training (POST > PRE). Responses on subjective effect measures also tended to increase in magnitude - ***i.e.,*** the dose-response function tended to shift to the left. These data suggest that training at progressively lower discrimination doses increases sensitivity to both discriminative and subjective effects of drugs.

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HYDROCODONE (HC) EFFECTS IN CYTOCHROME P450 2D6 (CYP2D6) DEFICIENT INDIVIDUALS

G. J. Baylon, H. L. Kaplan, U. Busto, S. W. Cheung, S. V. Otton, G. Somer, and E. M. Sellers

Hydrocodone (HC) is converted by genetically polymorphic Cytochrome P450 2D6 (CYP2D6) to the metabolite hydromorphone (HM) which is believed to be responsible for its opiate effects. After an oral dose of 10 mg hydrocodone plasma HM C_{max} (mean ± SD) is significantly lower ($p < 0.001$) among (PMs) poor metabolizers (0.96 ± 0.29 ng/ml) than in (EMs) extensive metabolizers (5.22 ± 1.77 ng/ml) while HC plasma levels were no different.

In a double blind study, seven EMs, eight PMs, and ten intermediate metabolizers (IMs) who could reliably report opiate effects after HM (10 or 20 μg/kg S.C.) were tested with oral HC. The HM screening revealed no phenotypic differences. After oral HC, significantly greater ($p < 0.04$) miosis (pupil diameter decrease) was observed among PMs than EMs or IMs. Quinidine (100 mg p.o. 12 hours prior to H.C.) inhibited CYP2D6 activity in EMs demonstrated by a 3-9 fold increase in urinary HC/HM ratios but had no effect on subjective HC drug response. No significant difference in drug response was found between the three groups on subjective sedation, abuse potential, drug effect, feeling in mind and drug satisfaction scales.

These results demonstrate a CYP2D6 status effect on hydrocodone kinetics. In spite of the observed kinetic differences we were unable to demonstrate significant physiologic or psychologic drug response differences between EMs and PMs. Study data suggest that pupillary changes and subjective drug effects after oral HC are not explained by the usual HM-dose-effect relationship. This is possibly due to greater HC sensitivity among PMs.

REFERENCE:

Otton *et. al.,* Clin Pharmacol Ther, 54:463-472, 1993.

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COMPARING THE SUBJECTIVE, PSYCHOMOTOR, AND PHYSIOLOGICAL EFFECTS OF INTRAVENOUS BUTORPHANOL AND MORPHINE IN HEALTHY VOLUNTEERS

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Butorphanol (Stadol) is a mixed agonist-antagonist opiate that is used in pain relief in medical settings. The purposes of this study were to characterize the subjective, psychomotor, and physiological effects of intravenous butorphanol in healthy volunteers, up to clinically-relevant doses, and to compare and contrast the effects of butorphanol to that of morphine. Subjects (seven males, five females) without histories of opiate dependence were injected in a forearm vein with 0, 0.5, 1.0 or 2.0 mg/70 kg butorphanol, or 10 mg/70 kg morphine, using a randomized, double-blind, crossover design. Subjective effects of butorphanol included dose-related increased scores on the PCAG and LSD scales of the ARCI, increased VAS ratings of "sedated," "coasting or spaced out" and "difficulty concentrating," increased adjective checklist ratings of "sweating," "skin itchy," and "sleepy," and increased "feel drug effect" and drug liking ratings. Morphine had some subjective effects of similar magnitude to that of an equianalgesic dose of butorphanol (2 mg) [*e.g.,* "feel drug effect," "sedated," "heavy or sluggish feeling," "high]. Other effects of morphine, however, were lesser in magnitude than that of butorphanol (e.g., "coasting or spaced out," "drunken," "lightheaded"). Morphine also did not affect a number of ratings that were affected by butorphanol (e.g., "confused," "dreamy," "difficulty concentrating," "floating," "sweating"). Psychomotor impairing effects of butorphanol (as measured by performance on the DSST, Maddox Wing test, and an eye-hand coordination test) were dose-related - in contrast, morphine had little effect on psychomotor functioning. Both butorphanol and morphine induced miosis. The results of the present study demonstrate that a clinically-relevant dose of butorphanol produces a somewhat different profile of subjective effects, and greater psychomotor impairment, than that of an equianalgesic dose of morphine.

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ACUTE OPIOID PHYSICAL DEPENDENCE IN HUMANS: PHARMACOLOGICAL SPECIFICITY

M. K. Greenwald and M. L. Stitzer

Previous animal studies have found that mu and *kappa* opioid agonists can produce different profiles of physical dependence, suggesting that opioid physical dependence development is pharmacologically specific. This study determined whether acute opioid physical dependence is pharmacologically specific in humans. We predicted that naloxone-precipitated opioid withdrawal symptoms would be greater after single pretreatment doses of the *mu*-preferring agonist morphine than the *kappa*-preferring agonist butorphanol (within drug class specificity), lorazepam (between drug class specificity) or saline.

Six male, nondependent, regular heroin users were each exposed to six conditions in a within-subject, Latin square design, with double-blind procedures. An acute dependence protocol was used. In each session, pretreatment with either a single morphine (15 or 30 mg/70 kg), butorphanol (3 or 6 mg/70 kg), lorazepam (4 mg/70 kg) or saline i.m. injection was followed six hours later by naloxone (10 mg/70 kg i.m.). A broad range of subjective, behavioral and physiological measures was recorded before and periodically after each drug administration.

Morphine and butorphanol produced dose-related opioid agonist effects, relative to lorazepam and placebo. The doses of morphine and butorphanol selected were well matched on subjective potency and pupil constriction. Morphine produced pleasant subjective effects without sedation, whereas butorphanol and lorazepam produced mild-to-moderate dysphoria and sedation.

As predicted, naloxone precipitated significant dose-related increases in withdrawal symptoms after morphine. After 30 mg morphine, symptoms persisted throughout the 90 minute post-naloxone assessment period. In contrast, withdrawal symptoms after butorphanol were mild and transient (lasting only about 15-30 minutes post-naloxone). No withdrawal was observed after lorazepam or saline pretreatments.

This study showed that the mu-preferring agonist morphine produced greater opioid physical dependence than the *kappa*-preferring agonist butorphanol at equipotent doses. These results are consistent with previous animal data showing different dependence profiles of *mu* and *kappa* agonists. The data suggest that acute physical dependence is pharmacologically specific in humans, both within the opioid drug class (morphine > butorphanol) and between drug class (morphine > lorazepam). The acute physical dependence model appears useful for testing the dependence liability of opioid drugs with different receptor activity profiles.

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A SURVEY OF SLEEP PROBLEMS IN A SUBSTANCE ABUSE POPULATION

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Sleep problems are frequently noted among the substance abusing population, occurring in various stages of treatment and across a variety of treatment modalities. This study surveyed the prevalence of reported sleep problems in clients enrolled in a methadone maintenance program, an alcohol treatment program and a naltrexone treatment program. Methods: A cross sectional survey by an anonymous self-report questionnaire of adult out-patients on a voluntary basis (n=86). Results: 50.1% of patients reported sleep problems. 32.2% of the population as a whole reported depressive symptoms; a very high co-prevalence of sleep difficulties and depression was noted ($p<.01$). 16.3% of the population used sedative hypnotics and demonstrated a significant degree of co-prevalence of sleep difficulties. 67.9% of the population reported regular use of coffee; the consumption of more than four cups of regular coffee per day was statistically significant for the co-prevalence of sleep problems. The presence of anxiety, alcohol or cocaine use was not significant for co-prevalence of sleep difficulties. 85.7% of patients reported a current history of the use of cigarettes, however this was not statistically associated with reported sleep problems. There was no statistical difference in the prevalence of sleep problems among the three patient populations surveyed. Conclusions: The data demonstrate a high prevalence of reported sleep problems in this sample population of substance abusing individuals. Modifiable cofactors appear to be the presence of depression, the use of sedative hypnotics and the consumption of more than four cups of coffee per day. The ongoing abuse of alcohol and/or cocaine did not correlate significantly with the prevalence of anxiety, depression, or sleep problems. Individuals with depression, sedative hypnotic use and high coffee consumption may represent a sub-set of the substancing abusing population amenable to more specific diagnoses and treatment.

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GAMMA-HYDROXYBUTYRATE: A PUTATIVE NEUROTRANSMITTER THAT IS ABUSED AND CAUSES PHYSICAL DEPENDENCE

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Gamma-hydroxybutyrate (GHB) is a compound found in mammalian brain which meets many criteria of a neurotransmitter. GHB has a specific enzyme for its biosynthesis, specific, high affinity binding sites, and a high-affinity uptake system. It is located primarily in the synaptosomal compartment and is released from brain tissue by membrane depolarizing concentrations of K^+ in a Ca^{2+}-dependent process. A GHB antagonist has been characterized but nerve pathways for GHB have yet to be demonstrated.

GHB has also been investigated as a tool for inducing absence seizures, for use as an anesthetic, and for treatment of narcolepsy and alcoholism. It is currently approved for use in the treatment of narcolepsy in the United Kingdom. Therapeutic doses of 40-60 mg/kg induce a rousable sleep of approximately 3h in which stages three and four, and particularly slow wave sleep are increased at the expense of stage one sleep.

Since 1990, GHB has been abused in the United States for euphoric, sedative, and anabolic effects. Coma and seizures have been reported following abuse of GHB, but no instances of physical dependence have yet been reported. We describe a case series of persons using GHB which includes aspects of GHB use in humans not previously reported. These involve cases of prolonged abuse (up to 3.5 years), generally with increasing dosage over time and tolerance to sedative and euphoric effects. Reports of combining GHB with other drugs suggest increased risk of seizure when combined with methamphetamine and potentiation of the effects of alcohol including nausea/vomiting and respiratory depression. There is also evidence of a withdrawal syndrome including insomnia, anxiety, tremor, sweating (or a subset of such symptoms); withdrawal symptoms appear to resolve in 3-12 days.

GHB has the potential to cause a significant incidence of abuse and adverse effects. Prolonged use of high doses may lead to a withdrawal syndrome, which resolves without sequelae. Educational efforts designed to reduce use of, and harm from, this agent should address the narrow therapeutic index, possible physical dependence, and dangers of combining it with other drugs of abuse.

REFERENCES:

Furnished at request of first author.

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THE EFFECT OF GAMMA HYDROXYBUTYRIC ACID (GHB) ON NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

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INTRODUCTION: GHB, a GABA metabolite, has been shown to attenuate spontaneous opiate withdrawal in a published clinical study. We studied the effect of GHB pre-treatment on naloxone (NLX)-precipitated opiate withdrawal.

METHOD: Opiate-dependent subjects were hospitalized and stabilized on the opioid levorphanol 6mg po tid. After at least five days, an acclimatization challenge was done with placebo GHB pre-treatment followed one hour later by i.v. NLX at 0.2mg/70 kg. Three double-blind challenges were then done on consecutive days with balanced, randomized pre-treatment with either placebo, GHB 15mg/kg, or 30mg/kg, followed an hour later by i.v. NLX at a dose of 0.4mg/70kg.

DATA ANALYSIS: Outcome measures included subject-rated GHB effects, vital signs, pupillary size, subject and observer ratings of opiate withdrawal. Summary measures of mean pre-GHB; mean post-GHB and pre-NLX; and AUC and peak values post-NLX were calculated.

RESULTS: One-factor (GHB dose) repeated measures ANOVA revealed no significant ($p<.05$) main effects of GHB on withdrawal. GHB alone decreased "friendly" ratings, with trends toward more sleepiness and stomach upset.

CONCLUSIONS: Preliminary results suggest minimal effects of GHB on NLX-precipitated opiate withdrawal. Possible explanations for the difference from findings in spontaneous withdrawal include: 1) GHB administration prior to withdrawal in our study (given post-withdrawal in a prior study); 2) Direct blockade of GHB's anti-withdrawal effects by NLX; 3) Behavioral or neurochemical differences between NLX-precipitated and spontaneous opiate withdrawal.

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ATTENUATION OF OPIOID WITHDRAWAL: PHARMACOLOGICAL PROFILES OF NITRIC OXIDE SYNTHASE INHIBITORS

D. B. Vaupel, A. S. Kimes, and E. D. London

Initial studies demonstrating that two nonselective inhibitors of nitric oxide synthase (NOS), L-N^G-nitroarginine (L-NNA) and L-N^G-nitroarginine methyl ester (L-NAME), reduced some signs of naloxone-precipitated morphine withdrawal in rats (Kimes *et. al.,* 1993) were extended to include other NOS inhibitors. Rats received one 75 mg morphine pellet on day one of the experiment and naloxone-precipitated withdrawal was on day four. Effects of NOS inhibitors specific for cerebral NOS (7-nitroindazole; 7-NI) or endothelial NOS (N(5)-(1-iminoethyl)-L-omithine; L-NIO) were tested. NOS inhibitors or vehicle were administered IP one hour before the naloxone (0.5 mg/kg SC) challenge. Signs of opioid withdrawal were scored over a 15 minute period begining one minute after naloxone administration. Like L-NAME and L-NNA, 7-NI (1-100 mg/kg) and L-NIO (1-300 mg/kg) produced dose-related decreases in weight loss, diarrhea, wet dog shakes and grooming. In addition, 7-NI reduced chewing movements, salivation and genital effects (penis licis plus ejaculations). In contrast, L-NNA, L-NAME, and L-NIO tended to increase genital effects. Seven-NI and L-NIO also increased escape jumps, thereby differing in their pharmacologic profile from L-NAME and L-NNA, which lacked these effects. Both 7-NI and L-NIO did not produce overt toxicity. Clonidine (0.01-0.1 mg/kg), an $alpha_2$ adrenoceptor agonist used clinically lo treat opioid withdrawal, produced effects similar to 7-NI. Additional studies in unanesthetized rats prepared with left femoral arterial catheters, demonstrated that 7-NI did not produce an increase in blood pressure in morphine-naive or in morphine-dependent rats. In conclusion, the ability of 7-NI to affect more opiate withdrawal signs than L-NNA. L-NAME, and L-NIO without causing hypertension may reflect the selectivity of 7-NI for the cerebral enzyme (Moore *et. al.,* 1993).

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EFFECTS OF HIGH INTRAVENOUS DOSES OF DYNORPHIN A (1-13) ON TAIL FLICK LATENCY AND CENTRAL NERVOUS SYSTEM HISTOLOGY IN RATS

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BACKGROUND:

Dynorphin A 1-13 blocks opiate withdrawal in rats without producing dependence, and enhances analgesia in morphine tolerant animals. Its potential use in humans is therefore of interest. Dynorphin A (1-13) has little toxicity when administered at modest doses i.v. but has been reported to cause hind limb paralysis and necrosis of the spinal cord in rats, at the catheter tip, when administered intrathecally.

METHODS:

To further evaluate its potential neurotoxicity. we administered dynorphin A (1-13) to rats at very high doses i.v.. Rats (n = 6-10 per group) received dynorphin A (1-13) as bolus i.v. doses of 5 mg/kg, or as continuous i.v. infusion of 40 mg/kg/day for one day, with saline controls. Two additional groups received bolus injections of dynorphin A (1-13) 50 or 100 mg/kg i.v.

RESULTS:

The appearance and behavior of animals treated with the 5 mg/kg bolus or 40 mg/kg infusion was normal. Tail flick latencies remained unchanged ($P>0.5$). There were no histologic abnormalities of the spinal cord or brain examined by light microscopy. Animals receiving 50 mg/kg showed cutaneous flushing, labored respiration and decreased spontaneous movement which resolved within 10 minutes. Histology at one week was normal. All six animals receiving 100 mg/kg convulsed and died within minutes. Three animals that received dynorphin A (1-13) 40 mg/kg/day for seven days had normal behavior and histology.

CONCLUSIONS:

The previously observed neurotoxicity of intrathecally administered dynorphin A (1-13) is a local effect which does not occur when dynorphin A (1-13) is administered i.v., even at very high doses.

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PRECIPITATION OF MORPHINE WITHDRAWAL BY BUPRENORPHINE AND BUTORPHANOL IN MALE CYNOMOLGUS MONKEYS

H. Fukase, K. Fukuzaki, T. Koja, R. Nagata, and S. E. Lukas

This experiment was conducted to characterize buprenorphine's and butorphanol's agonist/antagonist profile in morphine-dependent cynomolgus monkeys (Macaca fascicularis).

Twelve male monkeys were maintained on morphine (7.5 mg/kg, b.i.d.) for at least six months. On test days, monkeys were scored for opiate withdrawal signs two hours after the last morphine dose. A dose of either buprenorphine (1 or 100 pg/kg, s.c.), butorphanol (0.1 or 1.0 mg/kg, s.c.) or saline was given and observation continued for an additional two hours. Observations were blind to the treatment.

Buprenorphine (100 μg/kg) precipitated withdrawal signs such as restlessness, rearing, chafing face, chewing and vocalization with or without intimidation (emotional signs), and wet dog shakes or backward gait (neurological signs) and retching or vomiting (autonomic signs); the 1 μg/kg dose of buprenorphine decreased the total withdrawal score in result of which autonomic signs were slightly increased and emotional signs and posture scores decreased. Butorphanol (0.1 mg/kg) decreased withdrawal severity within 30 minutes after injection. Although, the 1 mg/kg dose had no effect on the total score of withdrawal signs, it caused autonomic signs such as vomiting or salivation and decreased emotional signs and neurological signs. This data suggests that the high dose of buprenorphine only exhibit opioid antagonistic activity while agonistic effects appears after low dose. On the other hand, butorphanol shows only agonistic activity in 0.1 mg/kg. At 1 mg/kg, butorphanol produce agonistic effects on emotional factors in withdrawal signs while having antagonistic activity to autonomic factors of the signs. Buprenorphine and butorphanol especially were different from each other in effects on the emotional factor of withdrawal signs.

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INTESTINAL TOLERANCE TO MORPHINE AND PRECIPITATED WITHDRAWAL *IN VIVO*

T. F. Burks, G. C. Rosenfeld, and C. L. Williams

There has been no previous demonstration of opioid tolerance or dependence on the propulsive and contractile activities of the gut *in viva.* Morphine was administered continuously (1 mg/kg/hr s.c., 72 hr), and by bolus injection (10 mg/kg), and intestinal motility and transit were evaluated in rats. Morphine (1 mg/kg/hr) decreased the frequency of contractions in, and propulsion along the small bowel and colon, and produced mild antinociception. The frequency of duodenal and colonic contractions returned to normal within 8-22 hours, with the duodenum recovering before the colon. After 24 hours of morphine, the inhibitory effects of bolus doses of morphine on motility and transit were diminished and eventually lost (48 hr). In contrast, the antinociceptive effects of bolus doses of morphine were diminshed by 12-18 hours, and lost by 24 hours. Naloxone given to morphine tolerant animals resulted in an increase in the frequency and amplitude of contractions in the duodenum and colon, resulting in diarrhea. These results are the first direct demonstration of opioid tolerance and dependence on contractile activity in the rat intestine.

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TWO DIFFERENT ANTAGONISMS OF NOR-BNI AGAINST MORPHINE ON INTESTINAL TRANSIT IN MICE

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We have already reported that nor-BNI, a selective kappa antagonist, antagonized the mu agonists rather than kappa agonists in an early stage (30-60 min) after s.c. administration in the mouse analgesic test or body temperature test (Endoh *et al.,* 1992). In contrast to when given s.c., however, even 30 minutes after i.c.v. injection of nor-BNI the compound showed selective kappa antagonistic action, although weak mu antagonistic action was seen and apparent in the mouse analgesic test (Endoh *et al.,* 1994). In the present study, we investigated the mu antagonistic property of s.c. and i.c.v. administration of nor-BNI in the mouse intestinal transit test.

The inhibitory effect of morphine (10 mg/kg, s.c. or 4mcg/mouse, i.c.v.) was not antagonized by naloxonazine (mu1 antagonist; 10-40 mg/kg, s.c.) nor s.c. nor-BNI (20mg/kg, s.c.) at 24 hour-pretreatment. On the other hand, morphine-induced antitransit was antagonized by naloxone (mu1 and mu2 antagonist; 0.1-10 mg/kg, s.c.) and beta-FNA (mu2 dominant antagonist; 10-40 mg/kg, s.c.), and furthermore antagonistic action of beta-FNA against morphine-induced slowing of gastrointestinal transit(GIT) was more potent than that of naloxone. These findings indicate that GIT is not mediated by the mu1 or kappa receptor, but mainly by the mu2 receptor. Furthermore, the antagonism of i.c.v. naloxone was effective on i.c.v. morphine-induced slowing of GIT rather than s.c. morphine. Therefore, when administered s.c., morphine acts at peripheral sites more than central sites to inhibit transit. Gmerek *et. al.,* (1985) also reported that when administered s.c., morphine apparently acts solely at peripheral sites to inhibit, on the other hand when given i.c.v. it acts essentially at only central sites to inhibit GIT and that there are distinct central and peripheral receptors at which morphine acts to inhibit GIT. Thirty min pretreatment of s.c. nor-BNI (5-20 mg/kg) potently antagonized the antitransit effect of s.c. morphine. However, the antagonism of the same s.c. treatment of nor-BNI against i.c.v. morphine-induced antitransit was weaker than against s.c. morphine, and the antagonism against i.c.v. DAMGO was also weak and not dose-related. Furthermore, an early stage i.c.v. administration of nor-BNI only slightly antagonized i.c.v. morphine-induced transit and the antagonism was not dose-related. These results indicated that systemic administration of nor-BNI acts mainly at peripheral maybe mu2 sites to antagonize morphine-induced slowing of GIT, and that when given i.c.v., nor-BNI induced only weak mu antagonism against s.c. and i.c.v. morphine-induced antitransit as well as against mu agonists-induced analgesic action in mice.

REFERENCES: Available upon request of senior author.

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RESPIRATION FREQUENCY IS INCREASED IN RHESUS MONKEYS DURING MORPHINE WITHDRAWAL

C. A. Paronis and J. H. Woods

Opioid antagonist-induced increases in respiration, following exposure to morphine, have been reported in several species, including monkeys and humans. However, these effects have not been well characterized. The present study examimed the respiratory responses to naltrexone in monkeys that received 3.2 mg/kg/day morphine, in an effort to establish a model of opioid dependence in rhesus monkeys. At the same time, tolerance to the respiratory depressant and analgesic effects of morphine was also examined. Two rhesus monkeys were exposed to normal air and air mixed with 1%, 3%, or 5% CO_2; respiratory frequency (*f*,) tidal volume (V_T), and minute volume (V_E) were measured using a pressure-displacement plethysmograph technique. Prior to the daily dosing regimen, 0.032-10.0 mg/kg naltrexone had no effect on either air or 5% CO_2 breathing, however 32 mg/kg naltrexone increased breathing frequency in the presence of normal air from 26 to 36 breaths/minute. Following the onset of the daily morphine treatment, the potency of naltrexone increased dramatically. In monkeys maintained on 3.2 mg/kg/day morphine for at least five weeks, 0.001-0.01 mg/kg naltrexone dose-dependently increased the rate of respiration to up to 200% of baseline values. This increased breathing frequency was accompanied by a slightly decreased V_T, hence increases in V_E were lower than those observed in respiratory frequency. Though less pronounced, qualitatively similar changes in breathing pattern were apparent when the daily morphine dose was withheld for up to three days, a peak effect was seen 48 hours after the morphine injection. These results suggest that respiratory frequency can be used as a measure of opioid dependence.

Despite the increase in naltrexone potency, periodic determinations of cumulative morphine dose-effect curves demonstrated no shifts to the right. Moreover, the acute respiratory depressant effects of the 3.2 mg/kg morphine injection were unaltered over a 43 week period of daily morphine injections. Thus, tolerance did not develop to the respiratory depressant effects of morphine. However, a more than 2-fold shift was noted in the dose-response curve of the analgesic effects of morphine, as measured by a warm-water tail-withdrawal assay. This suggests that tolerance to the analgesic effects and the respiratory depressant effects of morphine develop differentially.

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MODIFICATION OF RESPIRATORY EFFECTS OF LEVORPHANOL BY NALBUPHINE, BUTORPHANOL, AND BUPRENORPHINE IN RHESUS MONKEYS

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Previous studies have shown that opioids with differing μ-efficacies may produce varying degrees of respiratory depression [measured by reduction in minute volume (V_E)] in rhesus monkeys. High-efficacy agonists may nearly fully depress the ventilatory stimulant effects of 5% CO_2 mixed in air [ventilatory ratio ($V_E BCO_2/V_E air$; *VR*) ≈ 1], whereas lower-efficacy agonists appear to have more modest effects. The present experiments continue studies of the respiratory effects of opioids differing in efficacy by determining how the ventilatory depressant effects of the μ agonist levorphanol are modified by prior administration of μ partial agonists. The effects of levorphanol (0.1-3.0 mg/kg) were measured in awake, seated rhesus monkeys breathing air or 5% CO_2 mixed in air and redetermined in the presence of levorphanol (LEV), nalbuphine (NALB), butorphanol (BUT), and buprenorphine (BUP).

LEV produced dose-related reductions in minute volume, reflected in monotonically decreasing values of *VR*. Prior administration of 0.3 mg/kg LEV or 0.1 mg/kg BUT (which reduced *VR* by approximately 50%) flattened the dose-effect curve for LEV. However, LEV, but not BUT, displaced the dose-effect curve downward. Thus, 1.0 mg/kg LEV had comparable effects alone and after 0.1 mg/kg BUT. In contrast, prior administration of BUP (1.0 and 3.0 mg/kg) or NALB (10 mg/kg), which decreased *VR* by approximately 50% or less, antagonized the effects of LEV. Antagonistic effects were most evident following BUP and doses of LEV up to 10 mg/kg had only modest effects on *VR*. In addition, the ventilatory depressant effects of BUP were noted to extend beyond the day's session; following the highest dose of BUP (10 mg/kg), *VR* values returned to control levels only over the course of two to four weeks. These results suggest that BUP and NALB have lower p-agonist efficacy than BUT or LEV at sites mediating the respiratory depressant effects of opioids. They also indicate that high doses of BUP can depress the ventilatory response to increased CO_2 in air for long periods. The clinical significance of such prolonged effects of BUP, administered alone or with other respiratory depressant drugs, remains to be determined.

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Available upon request to J. Bergman.

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SWIM STRESS IMMOBILITY AND PITUITARY ADRENAL CORTICAL ACTIVITY IN OPIOID WITHDRAWAL

K. Grasing and S. Bailey

Medications with clinical antidepressant activity diminish the immobility of rodents exposed to a forced warm water swim. The present study was designed to test the hypothesis that opioid withdrawal would be accompanied by alterations in the response to stress at behavioral and neurochemical levels. Our prediction was that tissue levels of dopamine in brain regions that receive mesolimbic dopaminergic projects would be diminished during stress in opioid dependent subjects, with increased immobility observed during swim testing.

Sprague Dawley rats received continuous infusion of morphine sulfate at 6.4 mg/kg/hour delivered by osmotic pump (n = 5) or sham operations with inert implants (n = 6). Two days after removal of osmotic pumps, immobility was scored by a blinded observer.

Subjects undergoing withdrawal had lower body weight (223 +/- 9 vs 285 +/- 16 for controls, $p < 0.001$). indicating that dependence was successfully achieved. Morphine treatment significantly decreased immobility at both immediately prior to removal of osmotic pumps and during withdrawal two days later.

Striatal dopamine was significantly lower in morphine treated animals under unstressed conditions, but did not differ in swim stressed subjects. A similar pattern was observed for striatal DOPAC, morphine treatment diminished resting levels but this difference is not observed in swim stressed animals. With morphine treatment, DOPAC levels after swim stress are significantly elevated relative to the unstressed condition. This effect was not observed in control subjects.

Striatal 5-HIAA was significantly lower in unstressed morphine treated animals, but did not differ in swim stressed morphine treated and control subjects. Plasma corticosterone elevations occurred both groups of morphine treated subjects and in untreated swim stressed subjects.

In conclusion, swim stress immobility is diminished after establishment of opioid dependence and during opioid withdrawal. Reductions in striatal dopamine and DOPAC levels are in agreement with other studies that have shown deficits in the function of dopaminergic mesolimbic projections during opioid withdrawal. In addition, our findings demonstrate that dependent subjects have an altered metabolism of dopamine during forced swim testing.

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ARE THERE TWO DELTA OPIOID RECEPTORS HAVING OPPOSING EFFECTS ON PLASMA CORTICOSTERONE?

R. M. Eisenberg

Initial experiments examined the effects of two delta (d)-opioid agonists on plasma corticosterone (CS). DPDPE (10-100µg i.c.v.) produced a dose-related effect whereas deltorphan II (1-10µg, i.c.v.) did not. This suggested a distinction between d1 and d2-receptor effects. Attempts to antagonize the effects of DPDPE were not successful. Pretreatment with naltrindole (NALT), ICI-174,864, DALCE. or ß-FNA i.c.v. did not block the CS response to DPDPE. NALT (1 or 10mg/kg bwt. i.v.) also did not antagonize this response. In control groups, it was observed that ICI- 174,864 or NALT i.v. elevated CS. Further, ICI-174,864 (5, 10, and 20µg i.c.v.) produced a dose-related elevation in CS. Experiments were conducted on conscious unrestrained male Sprague-Dawley rats with chronic i.v. catheters and i.c.v. cannula guides allowing for serial blood sampling and drug injection into the right lateral ventricle. During this process, animals remained isolated in sound-attenuated one-way vision boxes. In conclusion, the failure to block the effect of DPDPE on CS by various antagonists may be due to the operation of opposing forces: d1-receptors increase CS and d2 receptors act tonically to suppress it. Disinhibition of the d2 influence yields as great or greater CS response as d1 stimulation.

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LACK OF INVOLVEMENT OF OPIATE RECEPTORS IN THE DEXTRORPHAN-INDUCED INCREASE IN PLASMA ACTH IN THE RAT

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Opioids as well as some noncompetitive NMDA receptor antagonists can stimulate the hypothalamo-pituitary-adrenal axis in the rat (Pechnick *et al.,* 1989 and 1990; Pechnick 1993). Dextromethorphan is O-demethylated *in viva* to form dextrorphan, and both drugs are noncompetitive NMDA antagonists (Franklin and Murray 1992). Although dextromethorphan and dextrorphan have very low affinity for opioid receptors, levorphanol, the levorotatory isomer of dexuorphan, is a potent opioid analgesic. The purpose of the present study was to compare and contrast the effects of the acute administration of dextromethorphan, dextrorphan and levorphanol on plasma levels of ACTH, and to test the involvement of opiate receptors in the response. Male rats (7-10 per group) were injected s.c. with saline, dextromethorphan (3.0 - 30.0 mg/kg), dextrorphan (3.0 - 30.0 mg/kg) or levorphanol (1.0 - 10.0 mg/kg). Sixty minutes later trunk blood was collected and plasma levels of ACTH were measured by radioimmunoassay.

In a second study, rats were injected s.c. with saline or naloxone (2.0 mg/kg), immediately followed by a second injection of either saline, dextrorphan (30.0 mg/kg) or levorphanol (3.0 mg/kg). Blood samples were obtained 60 minutes later. The data were analyzed by one-way analysis of variance followed by Dunnett's or Scheffe's tests. Dextromethorphan had no effect within the dose range tested, but both dextrorphan and levorphanol increased plasma levels of ACTH. Whereas pretreatment with naloxone blocked the levorphanol-induced response, naloxone had no effect on the dextrorphan-induced increase in plasma levels of ACTH. These results demonstrate that the dextrorphan-induced stimulation of ACTH release is not mediated by opiate receptors, and support the hypothesis that drugs that have noncompetitive NMDA antagonist activity can activate the hypothalamo-pituitary-adrenal axis in the rat.

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INFLUENCE OF ADRENAL STEROID STATUS UPON THE BEHAVIORAL EFFECTS OF MORPHINE

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Alterations in plasma corticosterone (CORT) levels can markedly alter the behavioral effects of the psychostimulant, amphetamine (Cador *et. al.,* 1993). However, the role of adrenal steroids in mediating an individual's responsiveness to other drugs of abuse, *e.g.* opioids. is unclear. We therefore examined the influence of acute, repeated or chronic treatment with the synthetic corticosteroid dexamethasone (DEX) on the behavioral effects of morphine in rats.

Male Wistar rats received DEX (1.0 mg/kg; s.c.) or its vehicle either immediately or 60 minutes prior to saline or an acute morphine challenge (5 mg/kg; s.c.). Locomotor activity was then assessed for four hours. Other groups of animals received either daily injections of DEX (0.04-1.0 mg/kg; s.c.) or DEX (5 mg/l) in their drinking water over three days. Morphine and saline were then administered at various times after treatment cessation.

Although acute DEX treatment failed to modify the locomotor response to morphine, its repeated administration resulted in a dose-dependent potentiation of the stimulant effects of morphine. In contrast, chronic DEX administration resulted in an initial suppression of morphine-induced activity. However, following termination of chronic treatment, a potentiation of morphine-induced activity developed, with a maximal effect occuring after three days of DEX withdrawal.

In contrast to these results, chronic corticosterone treatment has been shown to result in sensitization to the locomotor stimulant effects of amphetamine (Cador *et. al.,* 1993) and morphine (Stoehr *et. al.,* unpublished). As CORT and DEX show different binding characteristics, we postulate an involvement of the mineralocorticoid receptor subtype. The strong feedback activity of DEX on CORT release probably suppressed basal and morphine induced CORT release during chronic DEX administration. But morphine's stimulating properties may, at least partly, depend on its corticosterone releasing effects. The cessation of chronic DEX treatment or its repeated administration may lead to a dysregulation of the HPA axis, resulting in hyper-responsiveness of the HPA system, which has been shown to predispose animals to drug seeking behavior (Piazza *et. al.,* 1991).

In summary we hypothesize, that manipulations of the HPA system, which alter basal and/or morphine-induced corticosterone release influence the locomotor activating actions of morphine, and maybe its reinforcing properties also.

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CORTICOTROPHIN-RELEASING HORMONE (CRH) mRNA DIURNAL RHYTHMS IN RAT HYPOTHALAMUS AND FRONTAL CORTEX AND INHIBITION BY DEXAMETHASONE

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We hypothesized that levels of mRNA for CRH might exhibit a diurnal rhythm and also be modulated by glucocorticoids in some, hut not all, brain regions. We measured CRH mRNA levels in several areas of rat brain at four time points across the light phase, using a solution hybridization assay for quantitation of mRNA. Male Fisher rats (250g) were housed in a stress-minimized facility under a 12-12 hrs light-dark cycle (lights on from 07:00h to 19:00h). After seven days of adjustment to the facility, rats were killed at 10:00, 13:00, 16:00 or 19:00h for the diurnal experiment. In the dexamethasone (DEX) experiment, animals received a daily i.p. injection of 400 ug DEX around 19:00h and were killed 24 hours after the final injection. Total cellular RNA was extracted and concentrations were measured by hybridization to a labeled antisense cRNA probe complementary to 18S rRNA. Rat brain RNA of known concentration was used as a standard. CRH mRNA levels were determined by hybridization of extracts to a labeled antisense cRNA (a specific activity of $7x10^7$dpm/ug from the pSP64 plasmid). The plasmid of the opposite polarity was copied to give the CRH sense transcript" for use as calibration standards. The assay is capable of measuring 0.9 pg of CRH mRNA. The intra-assay or inter-assay CV% is 3.5 and 7.2 respectively. At the time of decapitation, blood was collected in heparinised tubes for corticosterone measurement by RIA. All data are presented as mean ± SEM. Results were analyzed by one-way analysis of variance (ANOVA) or two-way ANOVA with repeated measures. Plasma corticosterone exhibited the well-characterized diurnal rhythm with very low levels at 10:00 h and very high levels at 19:00 h. CRH mRNA levels in hypothalamus (Hyp) at 19:00 h were significantly reduced compared to those at 10:00 h, 0.26±0.02 pg/µg (n=10) compared to 0.38±0.03 pg/µg (n=13); an orthogonal comparison following ANOVA gave an $F(1,33)=6.11$. $p<0.05$. Diurnal variation of CRH mRNA was also observed in the frontal cortex (FCx): there was a significant reduction from 0.19±0.02 pg/µg at 10:00 h (n=19) to 0.13±0.01 pg/µg at 19:00 h (n=10), with an orthogonal comparison after ANOVA yielding an $F(1,44)=5.21$, $p<0.05$, No diurnal changes were found in amygdala (Amy) and brainstem (Bstm). Diurnal variation of CRH mRNA in Hyp suggests that CRH mRNA follows the diurnal changes within the HPA axis, and similar diurnal variation in FCx suggests that some nonhypophysiotropic brain rhythmicity is regulated with the same mechanism. We therefore tested the effect of DEX, 400 µg/day for five days, on CRH mRNA in the brain regions mentioned above. ANOVA showed a significant Treatment X Brain Region interaction $F(3,30)=5.72$. $p<0.01$, with a 27% decrease in hypothalamic CRH mRNA 24 hrs after the final injection compared with saline control, and no effect on CRH mRNA levels in FCx, Amy and Bstm (n=6). Thus the changes in levels of CRH mRNA in FCx during the diurnal rhythm are probably not under glucocorticoid control.

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EFFECTS OF DRUG-INDUCED IMMUNOSUPPRESSION ON MORPHINE ANALGESIA IN RATS

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In the present study, we report preliminary results on the effects of immunomodulation on morphine-induced analgesia in male Sprague-Dawley rats. For immunosuppression, rats were treated chronically with dexamethasone (DXM; 22.5 mg/kg sc total dose, three injections of 7.5 mg/kg over one week) or cyclosporine (CsA; 70 mg/kg ip total dose, daily injections of 10 mg/kg for one week). For immunostimulation. rats were treated acutely with lipopolysaccharide (LPS; 10-100 μg icv, 90 min pretreatment). Analgesia was assessed using the cold water (-3°C) tail-flick test. A cumulative dosing procedure was used so that an entire morphine dose-effect curve was generated in each subject in a two to three hour test session. Body and spleen weights were also recorded after chronic treatments to roughly assess immune status. Morphine induced dose-related increases in tail-flick latency (ED50s=6.5 mg/kg in each vehicle-treated group). Chronic DXM reduced the analgesic potency of morphine by a factor of 2.3 (ED50=15 mg/kg). Chronic CsA, on the other hand, did not significantly affect the morphine dose-effect curve (ED50=6.4 mg/kg). Both DXM and CsA treatment reduced spleen size (in terms of % of body weight) which averaged 0.36% and 0.31% in the vehicle-treated groups, but was significantly reduced to 0.13% after DXM and 0.25% after CsA. Treatment with icv LPS enhanced the analgesic effect of low doses of morphine and attenuated the analgesic effect of high doses of morphine. Because the effects of LPS might not have been constant over the two to three hour cumulative dosing test, single doses of morphine were also tested to control for time-dependent factors. The same pattern of LPS effects occurred with single doses of morphine at 90, 180 and 270 minutes after LPS injection. To conclude, DXM has effects on the hypothalamic-pituitary-adrenal (HPA) axis in addition to the immune system, whereas CsA is a more selective immunosuppressive drug. This may explain the different effects of these treatments on morphine analgesia. LPS induced complex effects on morphine analgesia. We have shown that the cytokines interleukin-1 and interferon-alpha by themselves have no effect on morphine analgesia (Adams *et. al.,* Life Sci. 53: 1401-1409, 1993). LPS is known to induce a cascade of cytokine release; perhaps some combination of them is required to interact with morphine. More work is needed with different models of immunomodulation in conjunction with more detailed assessments of immune status to understand the role of the immune system in opioid-mediated effects.

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EVALUATION OF THE NOVEL KAPPA OPIOID AGONIST CI-977 (ENADOLINE) IN NEONATAL AND ADULT RATS

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The primary objective of the present study was to more fully characterize κ-opioid mediated antinociception in neonatal rat pups. To this end, the potency and efficacy of the new κ-agonist CI-977 (enadoline) were evaluated in the tail flick, hot plate and formalin nociceptive tests in neonatal and adult rats. The κ-opioid antagonist nor-binaltorphamine (nor-BNI) was used in an effort to assess the specificity of the observed antinociception. A second objective of the present study was to evaluate and pharmacologically characterize increases in activity observed in neonates after enadoline administration. The subjects were adult male Sprague-Dawley rats (250 g), and three day-old rat pups of both sexes bred in our colony. Enadoline was a potent antinociceptive agent against formalin-induced nociception in both neonates and adults. The AD50s generated from the dose-response curves confirm that the pups exhibited an increased sensitivity to enadoline when compared to adults (pup- AD50 = 10 μg/kg, 95% CL = 1 - 68 μg/kg; adult- AD50 = 60 μg/kg, 95% CL = 29 - 122 μg/kg). The potency ratio resulting from these data indicated that the pups were eight times more sensitive to enadoline-induced antinociception than the adults. Pretreatment with the k-antagonist nor-BNI (4.5 mg/kg) completely blocked enadoline-induced antinociception. In contrast, doses as high as 1000 μg/kg resulted in less than complete efficacy in both tail flick (< 50% MPE) and hot plate (< 60% MPE) tests in the neonates. The adults were similarly insensitive to the antinociceptive effects of enadoline in the tail flick test (< 20% MPE). Enadoline appeared to produce complete antinociception in the hot plate test in the adult animals, however significant decreases in activity in the open field test in the same dose range (100 - 1000 μg/kg) suggest that motor impairment may account for this finding; adult animals exhibited significant decreases in activity in the open-field test after enadoline administration. Conversely, enadoline significantly increased locomotor activity in the neonates, as assessed by the open-field test. U50,488 (U50), another κ–opioid agonist, also increased activity in the pups, although not to the same extent. Pretreatment with the k-antagonist *nor*-BNI (4.5 mg/kg) blocked the increase in behavior observed with both enadoline and U50. In conclusion, the κ–opioid agonist enadoline was found to be a very potent antinociceptive agent in both neonatal and adult rats in the formalin test, but not the tail flick or hot plate tests. Our results also indicated that r-agonists produce increases in activity which appear to be unique to neonates. Although the open field studies do not directly relate to κ-opioid induced antinociception, the behavioral activation observed in the pups merits additional study as it may have an impact on the future clinical Utility of κ-agonists in pediatric populations.

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INTERACTIONS BETWEEN CHOLECYSTOKININ (CCK) AND SELECTIVE μ AND κ OPIOID RECEPTOR AGONISTS IN THE PERIAQUEDUCTAL GRAY (PAG) OF THE RAT

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There is evidence to suggest that CCK is involved in the mediation of antinociceptive effects of opioids. Since the PAG is one of the important regions for antinociception, we investigated: a) the effects of different doses of sulphated CCK octapeptide administered into the PAG on analgesia; b) the effect of CCK on analgesia produced by a selective μ-opioid agonist PL017 and the blockade by selective CCK antagonists; c) the actions of selective opioid agonists on the release of CCK from the PAG of freely moving male S-D rats. All drugs were microinjected into the PAG. The rat cold water (-3 °C) tail flick test was used to assess antinociceptive actions. CCK, in a dose of 60 ng, induced analgesia, although 5 ng CCK did not. Pretreatment with 20-120 ng CCK enhanced the analgesic effect of PL017, while 0.5-5 ng CCK attenuated the PL017-induced analgesia. The CCK enhancement of opioid analgesia can be blocked by the CCK-B receptor antagonist L-365,260 and the CCK attenuation of the opioid analgesia can be blocked by the CCK-A receptor antagonist L-364,718. For release studies, artificial CSF was microdialyzed within the PAG for four hours. Samples were collected every 20 minutes and CCK-like immunoreactivity was measured by RIA. After a 60-minute baseline collection period, PL017 (1 μg), the k-opioid agonist dynorphin A 1-17 (Dyn, 5 μg), KCl (150 mM) or vehicle was micoinjected into the same region (PAG) where microdialysis probes were located. KCl or cold water stimulation increased CCK 50- and 16-fold over baseline concentration, respectively, while PL017 or Dyn induced 3- and 5-fold increases, respectively. PL017 or Dyn pretreatment reduced the 16-fold CCK release caused by cold water to 9- and 2-fold over baseline, respectively. These data indicate that a high level release of CCK in the PAG may be involved in mediating analgesia and a low level of CCK may act as an antagonist to opioids. In addition, the CCK-B receptor in the PAG is involved in the effects caused by a high dose of CCK, whereas the CCK-A receptor in the PAG is involved in the effect of a low dose of CCK.

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THE ROLE OF BRAIN μ, δ, AND κ OPIOID RECEPTORS IN ANALGESIA INDUCED BY ELECTROACUPUNCTURE STIMULATION OF DIFFERENT FREQUENCIES: THE RAT COLD WATER TAIL-FLICK TEST

X. H. Chen, E. B. Geller, and M. W. Adler

Previous studies have shown that electroacupuncture (EA) stimulation of different frequencies produces analgesic effects in the cold water tail-flick test (CWT), and the effects are blocked by s.c. injection of the opioid antagonist naloxone. The report that i.c.v. injection of naloxone can block EA analgesia suggests that the opioid system in the brain also participates in the analgesic effect induced by EA stimulation in peripheral sites. The present study was designed to analyze the opioid receptor mechanisms in the brain underlying 2 Hz-, 30 Hz- or 100 Hz-EA analgesia.

Highly selective receptor antagonists were injected icv: CTAP (μ) 0.5 and 1.0 nmol, naltrindole (NTI, δ) 1.0 and 2.0 nmol, or nor-BNI (κ) 6.25 and 12.5 nmol. One pair of stainless-steel needles of 0.25 mm diameter was inserted into the hind leg of male SD rats at the acupoints Zusanli and Sanyinjiao. Square waves of 0.3 ms duration were applied at frequencies of 2 Hz, 30 Hz or 100 Hz. The intensity (constant current) of stimulation was set at 1.5 mA for 15 minutes, then shifted to 3.0 mA for an additional 15 minutes. The latency to flick the tail in cold water was used as the analgesic index, according to a standard procedure in our laboratory. CTAP (1.0 nmol) can block 85.6% and 78.5% of the analgesic effect induced by 2 Hz- and 30 Hz-EA stimulation, respectively, but only 28.8% of that induced by 100 Hz-EA stimulation, suggesting that the mu opioid receptor in the brain is primarily involved in 2 Hz- and 30 Hz-EA analgesia, but only plays a small role in 100 Hz-EA analgesia. NTI (2.0 nmol) can block 80.1% and 73.6% of the analgesic effect induced by 2 Hz- and 30 Hz-EA stimulation, respectively, but only 31.3% of that induced by 100 Hz-EA stimulation. Similar to the mu opioid receptor, the delta opioid receptor in the brain is primarily involved in 2 Hz- and 30 Hz-EA analgesia, but only has a small role in 100 Hz-EA analgesia. Nor-BNI (12.5 nmol) almost completely blocked (93.1%) 100 Hz-EA analgesia and significantly antagonized (76.2%) 30 Hz-EA analgesia. However, it had no significant effect on 2 Hz-EA analgesia, suggesting that the kappa opioid receptor in the brain is involved in 30 Hz- or 100 Hz-EA analgesia, but not in 2 Hz-EA analgesia.

These results indicate that 2-Hz EA analgesia in the rat CWT is mediated by both μ and δ opioid receptors, 100-Hz EA analgesia is mediated by the κ receptor, and 30-Hz EA analgesia is simultaneously mediated by μ, δ and κ opioid receptors.

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MORPHINE AND KETOROLAC REVERSE BRADYKININ-INDUCED ALLODYNIA IN THE WARM-WATER TAIL WITHDRAWAL ASSAY IN RHESUS MONKEYS

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Bradykinin (BK) is an important mediator in pain and inflammation. It causes hyperalgesia and allodynia, sensitizes nociceptors, increases blood flow and extravasation, and causes release of prostaglandins in a number of species and assays. Here we report on the hyperalgesic and allodynic effects of BK and the reversal of these effects in a primate model of thermal hyperalgesia/ allodynia that was previously used to study the hyperalgesic effects of prostaglandin E_2 (PGE2).

Three rhesus monkeys served as subjects. The subjects sat in a restraint chair and the bottom 10 cm of their tails were shaved. Tail withdrawal latencies were tested in each of three water temperatures, 38°, 42° and 50°, immediately before injection, and 15, 30, 45, 60, 90, and 120 minutes after injection. The maximum latency was 20 sec. In some experiments, 46° was also tested. Injections of BK and PGE2 were given s.c. within 1 cm of the tip of the tail. Injections of morphine, quadazocine, or ketorolac were given s.c. in the back.

Tail injections of bradykinin caused dose-dependent thermal allodynia in 42° water, and hyperalgesia in 46° water in this assay, at doses similar to those which are effective in humans. Small morphine doses (0.32-1.0 mg/kg) reversed bradykinin induced allodynia, whereas slightly higher doses (1.0-3.2 mg/kg) were required to reverse PGE2-induced allodynia. A small dose of the opioid antagonist quadazocine (0.1 mg/kg) blocked the above effects which suggests they were mediated by mu-opioid receptors. The injectable NSAID, ketorolac, dose-dependently blocked BK-induced allodynia, but was ineffective against PGE2-induced allodynia. Quadazocine (1.0 mg/kg) failed to antagonize the effects of ketorolac (0.32-1.0 mg/kg) on BK-induced allodynia. Effective ketorolac doses (*e.g.,* 1 mg/kg) are similar to the range of clinically effective doses in humans.

Morphine, but not ketorolac, reverses the effects of BK-induced allodynia and hyperalgesia through mu-opioid receptors. The selectivity of ketorolac in contrast to morphine in this assay suggests that bradykinin-, but not PGE2-induced allodynia. is mediated by endogenous prostanoid synthesis and release.

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ANTINOCICEPTIVE PROFILE OF SNC 80, A HIGHLY SELECTIVE, NON-PEPTIDIC DELTA OPIOID AGONIST

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INTRODUCTION: The discovery of opioid analgesics which act via non-mu (μ) mechanisms has been a goal of opioid research for many years. Opioids acting via delta (δ) opioid receptors appear to have potential therapeutic advantages over μ opioid agonists including (a) limited (or no) abuse potential; (b) antinociceptive activity in most animal models; (c) decreased (or no) development of physical dependence; (d) lack of depression (and possible stimulation) of respiratory function and (e) little (or no) induction of constipation. These indications have been derived from studies with opioid peptides which have high selectivity for δ opioid receptors including [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and [D-Ala^2, Glu^4]deltorphin. Systemic administration of these peptides is generally not feasible due to limited blood brain barrier penetration. The development of systemically-active, non-peptidic opioid δ agonists is thus a desirable research objective. Recently, the pharmacology of BW 373U86 has been reported (JPET, November 1993). This non-peptidic opioid agonist has selectivity for δ opioid receptors. The present studies assess the pharmacology of SNC 80, an enantiomer of BW 373U86.

METHODS: Mouse vas deferens (MVD) and guinea pig ileum (GPI) bioassays: Dose-response curves for inhibition of electrically stimulated contractions in each tissue type were constructed for SNC 80, DPDPE and [D-Ala^2, Glu^4]deltorphin. **Antinociceptive testing:** Male ICR mice were tested in the warm water tail-flick test following administration of intracetebroventricular *(i.c.v.),* intrathecal *(i.th.)* or intraperitoneal *(i.p.)* injections of SNC 80.

RESULTS: IC_{50} values for SNC 80 in the MVD and GPI bioassays were 2.73±0.5 and 5457±2052 nM, respectively. The GPI/MVD ratio of IC_{50} values for SNC 80 was approximately 2000 compared to DPDPE (1800) or [D-Ala^2, Glu^4]deltorphin (17000) selectivity ratios. The I-selective antagonist ICI 174,864 (1 μM) and μ-selective antagonist CTAP (1 μM) produced 236- and 1.4-fold shifts in the IC_{50} values for SNC 80, respectively. SNC 80 produced dose- and time-related antinociception following *i.c.v., i.th.* and *i.p.* administration. The calculated A_{50} values (95% C.I.) were 104.9nmol (63.7-172.7), 69.0 nmol (51.8-92.1) and 57.0 mg/kg (44.5-73.1), respectively. SNC 80 antinociception *(i.c.v.)* was antagonized by *i.c.v.* pretreatment with naloxone (3 nmol, opioid antagonist), ICI 174,864 (4.4. nmol, δ_1 opioid antagonist), naltrindole (10 nmol, δ_1 opioid antagonist), [D-Ala^2, D-Leu^5, Cys^6]enkephalin (DALCE, 4.8 nmol, δ_1 opioid antagonist), [D-Ala^2, Cys^4]dehorphin (3 nmol, δ_2 opioid antagonist), but not by ß-FNA (18 nmol, μ opioid antagonist), suggesting that its antinociceptive actions are produced via activation of opioid δ_1 and δ_2 receptors.

CONCLUSION: Based on its profile in vivo and in vitro, SNC 80 is a highly selective, nonpetidic opioid δ_2 agonist. In mice, SNC 80 produces antinociception after *i.c.v., i.th.* and *i.p.* administration. Furthermore, SNC 80 does not produce convulsions at *i.p.* doses up to 300 mg/kg and at *i.c.v.* doses of 300 nmol/mouse. SNC 80 promises to be a useful compound for the exploration of opioid δ receptor pharmacology. Analogues of SNC 80 are also currently under study.

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KAPPA OPIOID RECEPTORS ON THREE RELATED THYMOMA CELL LINES ARE COUPLED TO ADENYLYL CYCLASE WITH DIFFERENT EFFICIENCY

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We have previously shown that the mouse thymoma R1.1 cell line expresses a high affinity kappa$_1$ opioid receptor (Bidlack *et. al.,* Eur J Pharmacol 227: 257-265, 1992) which, like brain opioid receptors, is negatively coupled to adenylyl cyclase (Lawrence and Bidlack, J Pharmacol Exp Ther 266: 1678-1683, 1993). Two out of three derivatives of the R1.1 cell line bound the kappa-selective ligand [^{3}H]U69,593 in a saturable manner, whereas none of the cell lines bound μ- or ∂-selective opioid radioligands. The R1.G1 cell line. a 6-thioguanine-resistant derivative of R1.1. bound [^{3}H]U69,593 with similar affinity compared to the parent line (K_d < 1 nM), but with a three-fold greater B_{max} value (193 ± 33 fmol/mg of protein). The R1E/TL8x.1 ("R1E") cell line, derived from R1.1 by immunoselection against the thymus leukemia antigen, showed no evidence of opioid receptor expression. However, the R1E/TL8x.1.G1.OUA^r.1 ("R1EGO") cell line, the 6-thioguanine- and ouabain-resistant derivative of R1E, bound [^{3}H]U69,593 with similar affinity compared to R1.1, but with a six-fold higher binding capacity (B_{max} = 372 ± 16 fmol/mg of protein). Bmax values obtained with the nonselective opioid (-)[^{3}H]bremazocine for each cell line were not significantly different than those obtained with [^{3}H]U69,593. Results from competition studies with dynorphin peptides and other opioids were consistent with expression of the same kappa$_1$ opioid receptor on all three cell lines. GTP and its nonhydrolyzable analog Gpp(NH)p inhibited [^{3}H]U69,593 binding to R1.1, R1.G1 and R1EG0 cell lines, suggesting that the kappa receptor expressed on these cell lines is coupled to a G protein. The kappa-selective agonist (-)U50,488 inhibited cyclic AMP production in membranes from all three cell lines with similar potency but different efficacy. Among these cell lines, maximal inhibition of adenylyl cyclase activity (R1.G1 > R1EGO > R1.1) did not correlate with the level of receptor expression (R1EGO > R1.G1 > R1.1) or with the potency of GTP inhibition of binding (R1EGO > R1.1 = R1.G1). Thus, there appear to be differences among the cell lines in the coupling of kappa opioid receptors to adenylyl cyclase. These thymoma cell lines provide an excellent model for studying the regulation of kappa opioid receptor-effector coupling.

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DOWN-REGULATION OF MU OPIOID BINDING SITES FOLLOWING CONTINUOUS ICV INFUSION OF NPFF AND MORPHINE: AN AUTORADIOGRAPHIC STUDY

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Several studies have demonstrated that neuropeptide FF (NPFF), a mammalian octapeptide, possesses the ability to modulate a variety of morphine-induced effects such as antinociception and the development of morphine tolerance and dependence. The purpose of this study was to determine the effect of chronic i.c.v. infusion of NPFF and morphine on mu opioid binding sites using the *in vitro* techniques of whole brain homogenate receptor binding and autoradiography. ALZET 2002 osmotic minipumps (0.5 µl/hr for 13 days) were filled with saline (control), NPFF (10 mg/ml) or morphine sulfate (40 mg/ml). The solutions were infused via i.c.v. cannula placed in the left lateral ventricle and attached to the osmotic minipumps. The rats were sacrificed on day #14 of the infusion, and prepared for one of the two binding techniques. To assess treatment effects of NPFF and morphine on mu opioid receptors, homogenate binding experiments were assayed using [^{3}H]DAMGO, while regional brain sections (20 µm in thickness) at the level of striatum, thalamus, and periaqueductal gray were labeled with [^{125}I]DAMGO. The homogenate binding data demonstrated that chronic administration of NPFF or morphine significantly ($p<0.05$) down-regulated mu receptors by 20% and 44% of control, respectively. Autoradiographic quantification of [^{125}I]DAMGO binding sites in specific brain nuclei for both NPFF- and morphine-treated animals verified the down-regulation seen in whole brain. Within the striatum and several nuclei of the thalamus, NPFF- and mor hine-treated rats showed a relatively consistent decrease in the density of [^{125}I]DAMGO binding sites ranging from 20-30% and 38-73% of control, respectively. These results suggest that NPFF may modulate opioid-mediated responses in part by regulating the density of mu opioid receptors.

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RESOLUTION OF SUBTYPES OF THE k_{2a} AND k_{2b} OPIOID RECEPTOR IN GUINEA PIG BRAIN USING [^{125}I]IOXY

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Previous studies demonstrated that, using membranes depleted of μ and d receptors by pretreatment with BIT and FIT, [^{125}I]IOXY. like [^{3}H]bremazocine, labels subtypes of the $\mathbf{k}_2$ receptor, termed $\mathbf{k}_{2a}$ and $\mathbf{k}_{2b}$. This study tested the hypothesis that there exist subtypes of $\mathbf{k}_{2a}$ and $\mathbf{k}_{2b}$ binding sites in guinea pig brain. [^{125}I]IOXY binding assays were conducted for four to six hours at 4° C in 50 mM TRIS-HCl 7.4, containing 10 mM NaCl. Binding surface analysis readily resolved $\mathbf{k}_{2a}$ and $\mathbf{k}_{2b}$ subtypes in the absence and presence of 100 μM GppNHp. The $\mathbf{k}_{2a}$ site and $\mathbf{k}_{2b}$ site were selectively assayed using blocking agents: 5 μM (-)-(1*S*,2*S*)-U50,488 for the $\mathbf{k}_{2a}$ site, and 5 μM [Leu^{5}]enkephalin for the $\mathbf{k}_{2b}$ site. Under these conditions, two subtypes of the $\mathbf{k}_{2a}$ and two subtypes of the $\mathbf{k}_{2b}$ site were resolved. These were termed the $\mathbf{k}_{2a\text{-}1}$, $\mathbf{k}_{2a\text{-}2}$, $\mathbf{k}_{2b\text{-}1}$ and $\mathbf{k}_{2b\text{-}2}$ sites, respectively. The ligand-selectivity profiles of these sites will be presented. Viewed collectively, these results provide further evidence for heterogeneity of the **k** opioid receptor.

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THE NON-PEPTIDE DELTA AGONIST, BW373U86, ITS ENANTIOMERS, AND RELATED COMPOUNDS: INTERACTIONS AT MULTIPLE δ_{ncx} BINDING SITES IN MOUSE BRAIN

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Previous studies resolved two subtypes of the δ_{ncx} binding site in rat and mouse brain. We also observed that the racemic non-peptide δ agonist, BW373U86, had high affinity at the δ_{ncx} site. Ligand-selective studies of BW373U86, its enantiomers, and related compounds showed that these drugs have higher affinities for δ sites than μ sites. In the present study, we determined the Ki values of one of these drugs (SNC86) for multiple δ_{ncx} binding sites in mouse brain. Mouse brain membranes were depleted of μ binding sites using the irreversible ligand, BIT. $\delta_{1\,ncx}$ binding sites were labeled with [^{3}H]DADL (4-6 hr at 25° C in 10 mM Tris-HCl, pH 7.4/100 mM NaCl/3 mM $MnCl_2$/2 μM GTP/5 mM 2-mercaptoethanol). Binding surface analysis readily resolved two δ_{ncx} binding sites. DPDPE was highly selective for the $\delta_{ncx\text{-}1}$ site. SNC86 had the same affinity for $\delta_{1ncx\text{-}1}$ and $\delta_{1ncx\text{-}2}$ binding sites. In contrast, the halogenated analog of DPDPE, [pCl]DPDPE. was 47-fold selective for the $\delta_{ncx\text{-}2}$ binding site. Detailed ligand-selectivity studies of the enantiomers of BW373U86 and related compounds are currently underway.

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THE NON-PEPTIDE DELTA AGONIST, BW373U86, ITS ENANTIOMERS, AND RELATED COMPOUNDS: INTERACTIONS AT MULTIPLE δ_{cx} BINDING SITES IN RAT BRAIN

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Previous studies delineated two classes of δ binding sites: a δ binding site not associated with the opioid receptor complex, termed the δ_{ncx} site, and a δ site associated with the opioid receptor complex, termed the δ_{cx} site. More recent studies resolved two δ_{cx} binding sites in rat brain termed δ_{cx-1} and δ_{cx-2}. Pretreatment of membranes with the δ-selective acylating agent (+)-trans-SUPERFIT depletes membranes of the δ_{ncx} binding site which permits selective labeling of the δ_{cx} binding sites with [^{3}H]DADLE. Ligand-selectivity studies of the non-peptide δ agonist, BW373U86, its enantiomers and related compounds showed that these drugs have higher affinities for δ sites than μ sites (Xu et al., this meeting). This study determined the selectivity of these compounds for the two δ_{cx} binding sites. The data indicated that SNC80 and deltorphin-II were highly selective for δ_{cx-2} binding site (1500-fold and 700-fold respectively). In contrast, DAMGO was selective for δ_{cx-1} binding site (440-fold). These results provide additional data supporting the striking δ-selectivity of the non-peptide systemically active analog of BW373U86, SNC80.

AFFILIATIONS:

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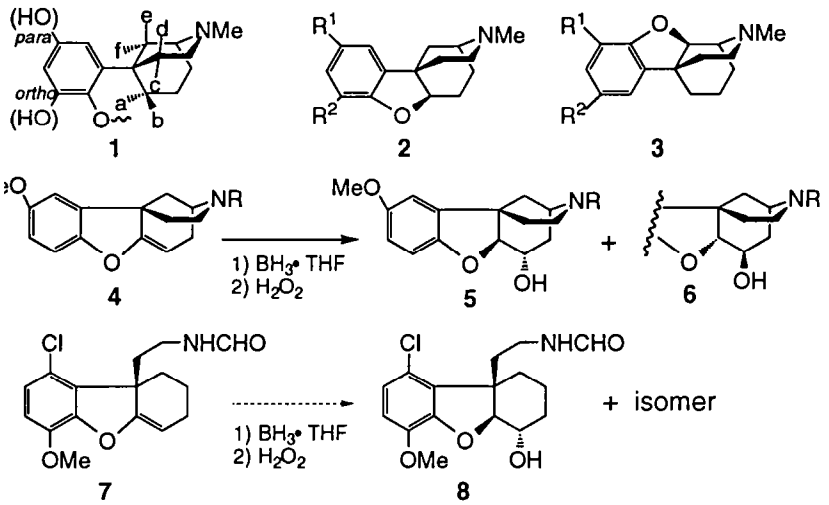
NEW SYNTHETIC APPROACHES TO OXIDE-BRIDGED 5-PHENYLMORPHANS AS PROBES FOR OPIOID RECEPTORS

E. Ohshima, S. Kodato, K. Yamada, R. B. Rothman, H. Xu, A. E. Jacobson, and K. C. Rice

We are continuing our efforts to complete the synthesis and biological study of the twelve isomeric racemates of the general structure **1.** The compounds in this series are being synthesized with the goal of identification of the receptor active conformation of the unbridged enantiomers. We now report a novel approach to **2** (B-type isomer) and **3** (E-type isomer). Electrophilic addition to the olefin **4** may be controlled by the steric hindrance which varies with conformation of the bicyclic ring system. We found hydroboration of **4** provided two possible isomers **5** and **6,** from which desired B-isomer (2) will be obtained. In this context, we are studying the synthesis of E-isomer (3) from the olefin **7.** The alcohol **8** is a key intermediate for the preparation of **3.** We are now intensively investigating the synthesis of B- and E-isomers by means of hydroboration of the olefin intermediates **4** and **7.**



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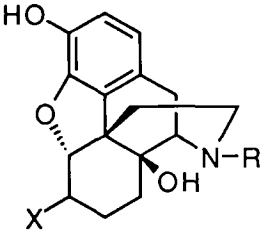
SYNTHESIS AND BIOLOGICAL EVALUATIONS OF 6ß- AND 6α-IODO-3,14-DIHYDROXY-17-METHYL-4,5 α-EPOXYMORPHINANS

H. Kayakiri, J. L. Flippen-Anderson, C. George, R. B. Rothman, H. Xu, J. S. Partilla, and K. C. Rice

We previously reported that the epimeric 6ß- and 6α-iodo-3,14-dihydroxy-17-(cyclopropylmethyl)-4,5α-epoxymorphinans IOXY(**4**) and EPIIOXY(**6**) were potent opioid receptor antagonists and that the 6ß.^{123}I derivative([^{123}I]-IOXY, **5**) would be suitable for SPECT studies (B. R. de Costa *et al,* 1992). The recent data which suggest that opioid agonists and antagonists bind to different domains on the same receptor protein prompted us to develop the agonist congener of IOXY. We have now synthesized (in five steps starting with oxymorphone in good overall yields) 6ß-iodo-17-methyl compound IOXY-AGO(**1**), its ^{125}I labeled derivative **2** and EPIIOXY-AGO(Q) as probes to gain insight into the binding of agonists *vs.* antagonists at the molecular level using cloned receptors, and for other studies. The X-ray crystallographic structure analysis showed that the iodo atoms of **1** and **2** are located very closely although the C-ring conformations of these compounds are quite different (chair form for **1** and twist-boat.form for **3**). The structure-activity relationships of these compounds suggested that the C-ring conformation does not greatly affect μ or δ binding affinities and that the 6-iodo substituent increases binding affinities relative to the hydroxy group. In contrast to the nonselective binding profile of the antagonist IOXY(**4**), IOXY-AGO(**1**) showed potent and selective binding affinity for the μ receptor (Rat Frotz-Frotz membranes, IC_{50} = 0.91, 32.5, 67.4 nM to ^{3}[H]DAMGO, ^{3}[H]DADLE, ^{3}[H]U69593, respectively) suggesting that [^{125}I]-IOXY(**2**) will be a useful ligand for studying opioid μ receptors.



1: R=Me, X=ß-I

2: R=Me, X=ß-^{125}I

3: R=Me, X=α-I

4: R=cyclopropylmethyl, X=ß-I

5: R=cyclopropylmethyl, X=ß-^{123}I

6: R=cyclopropylmethyl, X=α-I

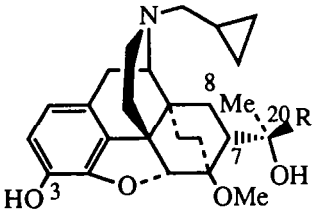
AFFILIATIONS:

LMC, NIDDK, NIH, Bethesda, MD 20892, Naval Research Laboratory, Washington, DC 20375, and LCP, NIDA Addiction Research Center, Baltimore, MD 21224

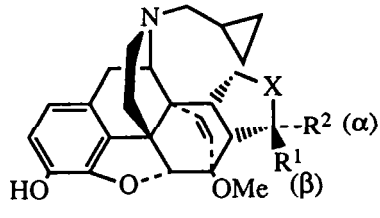
RING CONSTRAINED ANALOGS OF BUPRENORPHINE

A. Coop, J. W. Lewis, J. R. Traynor, and L. Guo

Buprenorphine is a potent opioid analgesic with a profile of μ (partial) agonism and κ antagonism (Lewis 1985). The κ antagonism is unusual as most close analogs, *e.g.* M6007, display κ agonism (Katz *et. al.,* 1982). One possible explanation for the κ intrinsic activity differences is that the orvinols adopt different conformations at C_{20} on interaction with opioid receptors. As part of a wider exploration of the effect of conformational constraint about C_{20} in the orvinols, we investigated the effect of incorporating the lipophilic group (R) as part of a ring joining C7α-C8α.



R = ^{t}Bu Buprenorphine
R = ^{n}Pr M6007



BU46 R^1 = OH, R^2 = H, X = CH_2
BU47 R^1 = H, R^2 = OH, X = CH_2
BU48 R^1 = H, R^2 = OH, X = $(CH_2)_2$

The adducts of N-cyclopropylmethylnorthebaine with cycloalkenones were prepared via $LiBF_4$-catalyzed Diels-Alder reactions (Barton *et. al.,* 1993). $LiA1H_4$ reduction and 3-O-demethylation yielded C_{20} secondary alcohol ring constrained analogs of buprenorphine (BU46, BU47, and BU48). All three analogs displayed high binding affinity for the three opioid receptor sites (μ, κ, δ), they displayed κ agonism in GPI and δ agonism in MVD. However, in mouse antinociceptive assays the ß-hydroxycyclopentanol (BU46) was a potent agonist (probably κ) whereas the α-hydroxy analogs (BU47, BU48) showed no antinociceptive activity, but showed potent morphine antagonism. All three showed morphine antagonist activity in dependent rhesus monkeys. The profile of activity of these orvinols (κ agonist; μ antagonist) Contrasts with that of buprenorphine and confirms the suggestion that there are lipophilic μ and κ agonist binding sites defined by the conformation of the orvinols agout C_{20}.

REFERENCES: Available upon request of senior author.

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DISPOSITION OF CODEINE IN HUMAN HAIR FOLLOWING SINGLE AND MULTIPLE DOSES

D. E. Rollins, D. G. Wilkins, G. G. Krueger, and R. L. Foltz

The measurement of drugs of abuse in hair provides an alternative to plasma and urine for monitoring drug use. To address the issues of drug incorporation into hair and the factors that control the drug hair concentrations, we have performed studies of the disposition of codeine and its metabolites into the hair of healthy human subjects following single (n=12) and multiple (n=7) doses. Caucasian male subjects with dark colored hair were administered either a single oral dose of codeine (120 mg) or multiple oral doses of codeine (30 mg three times a day for five days). Analysis of plasma, urine and hair were performed by positive ion chemical ionization GC/MS on an ITS-40® Magnum® mass spectrometer. This assay was sensitive to 10 pg of codeine/morphine on column. Hair was plucked from the scalp at various times for 28 days and cut from scalp, thereafter, for 10 weeks. Prior to analysis, plucked hair specimens were cut into two segments: (a) a proximal 1 cm segment containing the root (mean weight 2.51 mg) and (b) a distal segment containing all of the remaining hair (mean weight 20.10 mg). Following a single dose, codeine was detected in hair bulbs within 30 minutes with the mean peak concentration in the hair bulb of 4.4 ng/mg hair occuring at two hours after the dose. Three weeks after a single codeine dose, codeine could be detected in distal hair segments at a mean concentration of 30-50 picograms/mg hair. Following multiple codeine doses, codeine was initally detected in the hair bulb and was detected after three weeks in the distal hair segments at a mean concentration of 100 picograms/mg hair. Morphine was not detected in any hair specimen following the administration of codeine in these studies. These data demonstrate that drugs are rapidly distributed into the hair root; redistribution appears to occur out of the hair root. A fraction of the drug initially distributed into the hair root is incorporated in the hair shaft and can be detected for up to 10 weeks.

ACKNOWLEDGEMENT:

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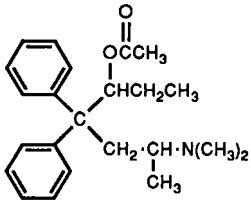
AFFILIATION:

Center for Human Toxicology, Department of Pharmacology and Toxicology, Department of Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, 84108

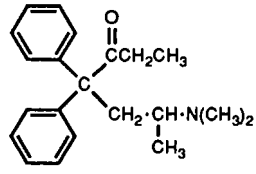
A GAS CHROMATOGRAPHIC/POSITIVE ION CHEMICAL IONIZATION MASS SPECTROMETRIC METHOD FOR DETERMINATION OF 1-α-ACETYLMETHADOL AND ITS TWO N-DEMETHYLATED METABOLITES IN PLASMA AND URINE

D. E. Moody, D. J. Crouch, C. 0. Sakashita, M. E. Alburges, K. Minear, J. E. Schulthies, and R. L. Foltz

l-α-Acetylmethadol (LAAM) is an analog of methadone, that has been approved as a methadone substitute for the treatment of opiate addiction.



l-alpha-Acetylmethadol (LAAM)



Methadone

Analytical methods are needed to quantitate LAAM and its two psychoactive metabolites. noracetylmethodol (NLAAM) and dinoracetylmethadol (DLAAM), to support pharmacokinetic and other studies.

We developed a gas chromatographic/mass spectrometric method for these analyses. The method uses 1.0 mL of urine or plasma, deuterated (d_3) analogs as internal standards (IS), methanol denaturation of protein (plasma only), and extraction of the buffered sample with n-butyl chloride. The NLAAM and DLAAM are derivatized with trifluoroacetic anhydride prior to analysis. Chromatographic separation of LAAM, NLAAM and DLAAM was achieved with a 5% phenyl methyl silicone capillary column. Positive ion chemical ionization detection using methane / ammonia as the reagent gas gave abundant protonated molecules (MH^+) for LAAM (m/z 354) and LAAM-d_3 (m/z 357) and ammonia adduct ions (MNH_4^+) for the trifluoroacetyl derivatives of NLAAM (m/z 453), NLAAM-d_3 (m/z 456). DLAAM (m/z 439) and DLAAM-d_3 (m/z 442). Calibration curves extended to 300 ng/mL in plasma with a limit of quantitation (LOQ) of 5 ng/mL, and to 1000 ng/mL in urine with an LOQ of 10 ng/mL. The method is precise with CVs < 15%. The method has also been validated for rat plasma, and is currently under evaluation for use with different tissues. (Supported by NIDA Contract N01DA-1-9205)

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THE PHARMACOKINETICS OF LAAM, NORLAAM AND DINORLAAM FOLLOWING ORAL DOSAGE OF LAAM

C. N. Chiang, C. Marschke, R. Hawks, D. Collins, and A. Forrest

LAAM (I-alpha-acetylmethadol) oral solution was approved for the treatment of drug abuse in July 1993. LAAM is extensively metabolized and subject to first pass metabolism. The oral bioavailability has been reported to be approximately 50%. The major metabolites are the N-demethylated metabolites -- norLAAM and dinorLAAM. LAAM, norLAAM and dinorLAAM are all pharmacologically active. In animals, norLAAM is about two to five times more potent than LAAM while dinorLAAM is about equipotent to LAAM.

The pharmacokinetics of LAAM was investigated in 25 addicts following an oral dosage regimen of three times a week for 15 days. The plasma and urine levels of LAAM and its metabolites were determined by a GC-MS method. There were large intersubject variabilities in plasma and urine levels for all three species. NorLAAM plasma levels peaked (3 hours) later than LAAM (2 hours) and dinorLAAM peaked latest (8 hours). Terminal phase plasma levels for LAAM and norLAAM declined slowly and parallel to each other. The terminal plasma half-life observed for both LAAM and norLAAM were similar -- approximately two to three days. This parallel decline of plasma levels for norLAAM and LAAM indicate that the slow decline of norLAAM is due to the slow formation of norLAAM from LAAM (norLAAM itself is eliminated at a faster rate -- half-life of 0.7 day). DinorLAAM concentrations in plasma declined at a much slower rate than those for LAAM and norLAAM, and the observed plasma half-life was much longer (greater than one week in some subjects). This very slow decline of dinorLAAM in plasma was primarily due to its slow elimination.

Since LAAM, norLAAM and dinorLAAM are all pharmacologically active with norLAAM being the most potent, the long duration of action of LAAM following oral administration is primarily due to the slow metabolism of LAAM to norLAAM and the slow elimination of dinorLAAM.

AFFILIATIONS:

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PLASMA CONCENTRATIONS OF LAAM, NLAAM AND DNLAAM IN FETAL AND MATERNAL RATS ORALLY ADMINISTERED ESCALATING DOSES OF LAAM FOR 11 WEEKS PRIOR TO MATING

M. E. Alburges, D. E. Moody, R. G. York, N. Chiang, H. Sorer and J. A. Nuite-Belleville

Plasma concentrations of LAAM and its two major metabolites, noracetylmethadol (NLAAM) and dinoracetylmethadol (DNLAAM), were measured in plasma samples from rat dams and their fetuses using gas chromatography/chemical ionization positive ion mass spectrometry. Rat dams (n = 5 per group) were treated via gavage with vehicle (Group 1) or LAAM at an initial dose of 2 mg/kg/day and either subsequently maintained (Group 2) or incrementally increased to 6 mg/kg/day (Group 3), 9 mg/kg/day (Group 4), 12 mg/kg/day (Group 5) or 15 mg/kg/day (Group 6) over a 12-week period. Following induction, females were mated with stock males and the desired treatment continued throughout pregnancy. On day 20 of gestation, dams were sacrificed using carbon dioxide, plasma samples of approximately 1 to 2 mL from each dam and approximately 0.5 to 1.0 mL pooled by litter for pups collected in heparinized tubes, labeled and frozen at -20 degrees C until analysis. There was a dose-dependent increase in the concentration of the parent compound and the two major metabolites in both dam and fetal plasma. For dams, the concentrations of the metabolites exceeded those of the parent, with DNLAAM concentration being consistently the highest of the three analytes. In contrast, LAAM concentrations in fetal plasma, although approximating the level observed in dam plasma, were consistently the highest and, except for the highest dose group, the concentration of NLAAM was higher than that of DNLAAM.

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BioDevelopment Corporation, McLean, VA

AFFILIATIONS:

University of Utah, Salt Lake City, UT; International Research Development Corporation, Mattawan, MI; NIDA/NIH, Rockville, MD and NB Associates, Rockville, MD

DEVELOPMENTAL OUTCOMES IN RABBITS ASSOCIATED WITH CHRONIC LAAM EXPOSURE

R. G. York, H. Sorer and J. A. Nuite-Belleville

The developmental effects of levo-alpha-acetylmethadol hydrochloride (LAAM) were examined in tolerant New Zealand White SPF female rabbits. Oral treatments included: vehicle controls (Group 1, N=40) and three groups of LAAM-treated animals (N=20 per group) begun at 2 mg/kg/day, and subsequently increased to either 4 mg/kg/day (Group 3) or 8 mg/kg/day (Group 4) over a 12-week period. Following induction, females were artificially inseminated and the desired treatment continued throughout pregnancy. Positive control groups (Groups 5 and 6; N=15 each) received either 1 or 3 mg/kg of 6-aminonicotinamide intraperitoneally on gestation day 9. On gestation day 29, surviving dams were sacrificed, Cesarean sections performed and fetuses examined. During induction, dose-related effects typically associated with morphine-type opiate agonists (e.g., constipation, CNS depression) were seen in all LAAM-treated groups. Upon dose escalation to 4 mg/kg/day, reductions in body weight gain achieved statistical significance. Even with dose stabilization during gestation, significant inhibition (approximately 40% of controls over days 0- 14 of gestation) of maternal body weight gain was observed at the highest dose, suggesting that the maximum tolerated dose had been achieved in dams. Necropsy findings, maternal deaths and abortions, pre- and post-implantation losses and average litter sizes were comparable across all groups. Although reductions in fetal body weight achieved statistical significance for the high-dose LAAM group, no drug-related visceral or skeletal abnormalities were found in kits exposed to LAAM. In contrast, kits exposed to 6-aminonicotinamide demonstrated structural abnormalities (*e.g.,* eye and skeletal) characteristic of this agent, documenting the sensitivity of this strain of rabbits to this known teratogen.

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BioDevelopment Corporation, McLean, VA

AFFILIATIONS:

International Research and Development Corporation, Mattawan, MI; NIDA/NIH, Rockville, MD and NB Associates, Inc., Rockville, MD

ACUTE 7-DAY AND 30-DAY TOXICITY OF LAAM AND NLAAM IN MALE AND FEMALE SPRAGUE-DAWLEY RATS

J. F. Borzelleca, J. L. Egle, Jr., L. S. Harris, D. N. Johnson, J. B. Terrill and J. A. Nuite-Belleville

A series of eight studies was conducted to evaluate the acute, short-term and longer-term toxicity of levo-alpha-acetylmethadol hydrochloride (LAAM) and its N-demethylated metabolite, noracetylmethadol (NLAAM). in rats. Both compounds produced qualitatively similar dose-related profiles of central nervous system (CNS) depression which differed primarily in their temporal pattern, with one exception: NLAAM produced muscle rigidity and cage biting, symptoms not reported for LAAM. Subcutaneous LD_{50} values were almost equal but lower than p.o. values for both compounds. Oral LD_{50} values were less for LAAM than NLAAM, with females showing an almost 2-fold lesser sensitivity than males to both compounds. Based on the outcome of 7-day dose-ranging studies, LAAM doses of 3, 10 and 17.8 mg/kg/day for males and 5.6, 18.3 and 33.5 mg/kg/day for females or NLAAM doses of 4.6, 14.7 and 25.9 mg/kg/day for males and 4.4, 13.2 and 21.4 mg/kg/day for females were administered for 30 days. Mortality was dose-dependent with most deaths occurring within the first week of treatment. Approximately 50% of males and females in the high-dose group and approximately 5% (males) and 40% (females) in the mid-dose group of LAAM-treated animals succumbed. Approximately 20% of males and 15% of females in the high-dose groups and 5% of females in the mid-dose group of NLAAM-treated animals succumbed. Hematuria concomitant with pronounced CNS depression and reduced food intake were observed with repeated administration of both compounds; these effects dissipated as tolerance developed. At termination of dosing (Day 30) treatment-related histopathological changes were observed in kidney and liver; these were not directly paralled by changes in serum chemistry and were generally reversible over a 2-week recovery period.

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NIDA Contract No. 271-89-8156
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AFFILIATIONS:

Virginia Commonwealth University, Medical College of Virginia, Richmond, VA
National Institute on Drug Abuse, National Institutes of Health, Rockville, MD
Nb Associates, Inc., Rockville, Maryland

CORRELATION OF LAAM PLASMA LEVELS WITH SUBJECT-REPORTED POSITIVE AND NEGATIVE EFFECTS, ADVERSE EXPERIENCES, AND CONCOMITANT MEDICATION USE

E. Yu, K. Kampman, and P. J. Fudala

LAAM (levo-alpha-acetylmethadol) is a synthetic mu-opioid agonist that has recently been approved by the FDA for the treatment of opioid dependence. It differs from classical morphine-like compounds primarily with respect to its duration of activity. It is sequentially N-demethylated in the liver to form two active metabolites, norLAAM and dinorLAAM. The kinetics of LAAM appear to be independent of dose. The half-life of LAAM is approximately 62 hours, for norLAAM 48 hours, and for dinorLAAM 96 hours (ORLAAM Product Labeling). This unique kinetic profile allows LAAM to be effectively administered on a three-times-weekly or alternate-day schedule.

The objective of the present study was to assess the potential correlation between plasma levels of LAAM and its metabolites with patient reported positive (opiate-like) and negative (withdrawal/overdosing) effects, and patient use of oxazepam, clonidine, ibuprofen, and chloral hydrate. This study was part of a larger (main) study which examined the pharmacokinetics of LAAM and its metabolites in adult male and female patients transferred from methadone maintenance to LAAM. The main study was conducted at three clinical sites and consisted of an 18-day inpatient phase during which individuals resided in a hospital or research clinic. Blood and urine samples were collected for pharmacokinetic and safety analyses. Following the inpatient phase, subjects could elect to remain on LAAM for the three-week outpatient/follow-up phase or return to methadone treatment. Eleven individuals who participated at the Philadelphia VA Medical Center contributed data to the present investigation.

A large amount of variation was observed through the course of the study with respect to plasma levels of LAAM and two active metabolites (norLAAM and dinorLAAM). Patients reported few positive or negative drug effects throughout the study. No serious adverse events related to LAAM administration were observed. Generally, small amounts of concomitant medications (*e.g.,* oxazepam for anxiety, clonidine for withdrawal discomfort) were requested by and administered to study patients. LAAM administration was well tolerated and no subjects discontinued their participation in the protocol.

AFFILIATION:

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TREATMENT SUCCESS AND FAILURE IN OPIATE-DEPENDENT TREATMENT-RESEARCH PATIENTS: PSYCHOPATHOLOGICAL AND OTHER CORRELATES

P. J. Fudala, I. D. Montoya, J. M. Hess, J. W. Cornish, J. H. Jaffe, and R. E. Johnson

Psychiatric symptomatology and morbidity, (*e.g.,* depression, anxiety, and personality disorders) are frequently observed in substance abusing patients and often influence treatment strategies and/or outcome. However, there is little published literature on factors that predict successful therapeutic outcome with respect to opiate-dependence treatment The purpose of the present study was to further identify pretreatment baseline characteristics that are associated with therapeutic success and failure. Patient completion of the maintenance phase of a treatment-research protocol assessing different pharmacotherapies for opiate dependence was used as an outcome measure. Discriminant analysis was used to assess variable potentially predictive of treatment outcome.

Data for the present investigation were obtained from 149 of the 162 individuals participating in an outpatient comparison study of buprenorphine and methadone for opiate-dependence treatment (Johnson *et. al.,* 1992). Discriminant function analyses were performed to assess which variables were useful as predictors of therapeutic outcome as assessed by retention in treatment. These variables included pharmacological treatment (buptenorphine or methadone), gender, race, and pretreatment scores from the Beck Depression Inventory, Symptom Checklist 90 - Revised, Clinical Institute Narcotic Assessment, and the WAIS IQ.

The percentages of cases classified correctly from the discriminant function were 94% for the group not completing treatment and 24% for the group completing treatment. The results indicated that the variables examined were good predictors of which individuals were likely not to complete treatment, but were not adequate to predict which individuals were likely to complete treatment. Future analyses will assess other potentially prognostic variables, and will attempt to reduce the data (*e.g.,* through the use of principal components analysis) to allow various patient characteristics to be expressed using fewer, pertinent variables.

REFERENCE:

Johnson, R. E.; Jaffe, J. H.; and Fudala, P. J. A controlled trial of buprenorphine treatment for opioid dependence. J. Amer. Med. Assoc., 267:2750-2755, 1992.

AFFILIATION:

University of Pennsylvania, Philadelphia, PA; NIDA Intramural Research Program, Baltimore, MD; Center for Substance Abuse Treatment/SAMHSA, Rockville; The Johns Hopkins University, Baltimore, MD

PSYCHOLOGICAL CHARACTERISTICS OF IVDU's IN AN ENHANCED METHADONE MAINTENANCE PROGRAM

S. E. Wugalter, C. E. Grella, and M. D. Anglin

This study reports the psychological characteristics of subjects participating in a NIDA-funded demonstration project designed to reduce the risk of HIV transmission among Intravenous Drug Users (IVDU's).

METHOD: The sample consists of 500 heroin addicts who met one of the following inclusion criteria: HIV-positive, Gay/Bisexual Males, Sex Workers, and Sex Partners of individuals from any of the previous high-risk groups. Members of these groups were compared to non-members on a battery of psychological tests: the Suicide Probability Scale, the Basic Personality Inventory and the Center for Epidemiological Studies Depression Scale. Four hundred and forty-eight subjects had completed the battery of psychological tests.

RESULTS: HIV-positive clients did not differ significantly from the HIV-negative clients. Gay/Bisexual males scored significantly higher on the SPS suicide ideation subscale and on the BPI anxiety and deviation subscales. Sex Workers scored significantly higher on the SPS suicide ideation, negative self-evaluation and hositility subscales. In addition, they also scored higher on the BPI alienation, anxiety, impulse expression and deviation subscales and on the CES-D total score. Clients who were Sex Partners did not differ significantly from clients who were not Sex Partners.

CONCLUSIONS: There were no differences found for either the HIV-positive or the Sex Partner groups. The Gay/Bisexual males showed a few more signs of affective problems when compared to their heterosexual counterparts. However, the Sex Workers showed marked disturbances which included anxiety, depression, suicidality and interpersonal problems. Treatment programs which include this latter group may need to address these psychological problems if treatment is to be successful. It is also recommended here that treatment outcome data needs to be examined in light of these psychological components.

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AFFILIATION:

UCLA Drug Abuse Research Center, University of California, Los Angeles, CA

MOOD EFFECTS OF METHADONE OR PLACEBO IN METHADONE MAINTENANCE PATIENTS

J. M. Peirce, S. J. Nixon, G. K. Borrell, and F. A. Holloway

Eighteen males from a methadone maintenance clinic participated in a double-blind, placebo-controlled study of mood response to dose administration designed to follow up a previous study. Subjects received either methadone or placebo at Dose one, and the other drug after the session. Eight subjects received placebo at Dose one (PLAC), and ten subjects received methadone at Dose one (METH). Subjects completed the ARCI (short form), POMS, and VAS immediately before and 90 minutes after receiving Dose one.

There was only a weak drug effect. Although subjects were not able to determine the drug received based on taste ($p>.12$). they were able to tell based on how they felt 90 minutes after dosing ($p<.03$). In addition, METH scores increased on the VAS HIGH scale, while PLAC scores decreased slightly ($p<.05$). In exploring the possibility that Study one subjects differed from Study two subjects, it was discovered that Study one POMS Anxiety and Confusion scale scores were higher before dosing than scores of Study two subjects ($p<.0001$). VAS "I feel anxious" scores for Study one subjects were also higher ($p<.03$). Study one subjects had also used non-methadone opiates more recently ($p<.001$), and had tested positive for illicit drugs more often in the last 6 months ($p<.0001$).

It is suggested that patients who continue to use drugs and exhibit mood difficulties may respond to methadone administration with greater mood improvement than patients who are more stable in treatment.

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AFFILIATIONS:

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DEPRESSION IN INJECTING DRUG USERS ENROLLED IN METHADONE MAINTENANCE TREATMENT

M. M. Lin, L. S. Brown, Jr., T. J. Meyer, and N. Siddiqui

A total of 766 injecting drug users (IDUs) voluntarily enrolled in an intake evaluation and treatment outcome study were interviewed. Measures included the Addiction Severity Index (ASI), Beck Depression Inventory (BDI), and Quick Diagnostic Interview Schedule III-R (DIS). The mean age was 37.1 years, 63.4% were male, 52% were African-American, 38% were Hispanic, and 6% nonhispanic white. At baseline 36% had BDI scores indicating depression of at least moderate severity. From the DIS, however, only 13.4% reported at least one lifetime occurrence of major depression. BDI scores had statistically significant positive correlations (rs .15-.41) with six of seven subscales of the ASI (all except employment). The BDI appears to be a sensitive measure of depressive symptoms in this population, and this depression should be addressed in treatment programs.

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EXPECTATIONS OF ABSTINENCE DURING METHADONE MAINTENANCE: PSYCHOLOGICAL CORRELATES AND RELATION TO HEROIN USE

D. A. Wasserman, S. M. Hall, and B. E. Havassy

Across substance-abuse treatment populations, abstinence goals and expectations at the end of treatment predict: later abstinence. We investigated these variables in relation to in-treatment abstinence in methadone-maintained heroin users. Ss were 120 patients at four clinics. Males were 62.5% of the sample and females 37.5%. Ss were 54.2% Caucasian, 25.8% African American, 10.8% Hispanic, and 9.2% other races and ethnicities. At study baseline (Week 1). Ss indicated both their "ideal" abstinence goal and their "realistic" expectations about their heroin use and completed other psychological measures. Urine toxicology screens were performed twice per week for the next seven weeks and at a single assessment six months after study intake. Urine screens were used to gauge relations between goals and expectations and subsequent heroin abstinence.

The "ideal goal" measure had poor variability and did not predict abstinence. One hundred and nine of the 120 Ss (90.8%) said they wished to attain permanent abstinence ("quit using heroin once and for all and never use again"). But, these Ss were not more likely than Ss with less stringent goals to be consistently abstinent during Weeks 02-08 or at the single six month assessment. Because so many Ss chose permanent abstinence as their ideal goal, further analyses were restricted to this more homogeneous subsample. Among these 109 Ss, the "realistic expectations" measure had acceptable variability and was predictive. Fifty-five Ss in this group (50.5%) expected to achieve permanent abstinence; the other 54 Ss did not. Ss who expected to become permanently abstinent were more likely to be abstinent during Weeks 02-08 (47.3% vs. 16.7%. $p < .001$), but not at month six (68.6% vs. 52.8%, $p < .173$). Six month data are still being collected, however. Significant correlates ($p < .05$) of expecting permanent abstinence were: dispositional optimism (+), positive moods (+), depressive symptoms (-), perceived stress (-), and antisocial personality disorder (-). That expectations correlated with several measures of psychological well-being, in addition to predicting abstinence, suggest that interventions that enhance positive moods and cognitions could have clinical value during methadone maintenance.

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AFFILIATION:

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IS THERE EVIDENCE OF INTERVIEWER-PATIENT MATCHES IN JUDGEMENTS MADE ABOUT THE SEVERITY OF SUBSTANCE ABUSE PROBLEMS?

A. R. Zaballero and L. S. Brown, Jr.

This study's primary objective is to examine whether the Addiction Severity Index's (ASI) interviewer seveiity rating (ISRs). a subjective rating, differs if the interviewer-patient are matched or unmatched racially/ethnically or by gender. "Matching effects" would provide indirect evidence or initial indication that "matching" may be important in substance abuse treatment. The subjects were 353 (62.4%) men and 213 (37.6%) women. Fifty-two percent (n = 292) were African American, 40% (n = 228) were Latino (38% Puerto Rican) and 8% were Caucasian and other. The trained interviewers were two African-American females, two white Latina females, one white Latino male, and one African-American male. For gender, there were no statistically significant differences between the matched interviewer patient group and the unmatched group in all seven ASI problem areas. However, there was borderline significance for the unmatched group's drug ISR (p. = .078) and for the unmatched group's legal ISR (p. = .062). For race/ethnicity. there were two significant differences for the matched group in the employment and family/social ISRs and for the unmatched group in the legal. In general we anticipated more differences in both categories because of our previous experience. One explanation may be that the patients' subjective ratings carried more weight than intended. Another reason may be that the anchoring of items along the interviewer severity scale have not been firmly established. These results suggest that future analyses should examine intragroup differences for gender and race/ethnicity. For example, compare the matched groups (male:male v. female:female) and the unmatched groups (African-American:Latino v. Latino:African-American).

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CHARACTERISTICS OF PATIENTS ENTERING COMMUNITY BASED METHADONE MAINTENANCE AND IMPLICATIONS FOR MATCHING PATIENTS TO INTERVENTIONS

A. F. Chu, L. S. Brown, Jr., B. Wallace, M. M. Lin, and A. Zaballero

A total of 766 IDUs were enrolled in an intake evaluation and treatment outcome study between May 1991 and June 1993. Findings show that African-American (52.3%) and Puerto Rican (38.3%) patients report some depression (57.7%) with 15.2% reporting severe depression. Also, 28.4% qualify as alcoholic and 35.6% as having a drinking problem. Patients have decade long histories of polydrug use and mean 7.7 years of cocaine use. Lifetime psychiatric diagnoses indicate antisocial personality disorder (45.2%), cocaine abuse and dependence (38.9%). generalized anxiety (15.4%), post-traumatic stress (14.4%), pathological gambling (13.7%). and major depressive episode (13.4%). Men present more antisocial personality disorder, pathological gambling and agoraphobia, while women present more generalized anxiety, post-traumatic stress, major depressive episode, simple phobia, somatization disorder, and bulimia. ASI composite scores indicate a high of .894 for employment. Women had significantly higher ASI composite scores for medical, employment, family/social and psychological domains. These findings suggest the need to match subsets of patients with severe depression, alcohol and polydrug use to special interventions.

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PREDICTORS OF METHADONE TREATMENT OUTCOME

A. J. Saxon, C. Fleming, T. R. Jackson, E. A. Wells, and D. A. Calsyn

Predictors of treatment outcome were examined at 18 months post-treatment entry for 353 admissions to methadone maintenance who received random assignment to one of three counseling conditions: (1) medication only (MOMT), (2) standard counseling (STAND), and (3) enhanced services (ENHAN); and one of two contingency conditions: (1) no contingencies (NC), and (2) contingency contracting (CC) in a six cell 3x2 design. All subjects completed the Addiction Severity Index (ASI) and provided weekly urine specimens. Subjects in CC conditions were placed on contingency contracts for positive UAs and ultimately discharged for unremitting drug use. Mean per cent of opiate positive UAs was 40.6 (sd=27.6). Percent of opiate positive specimens in a linear regression model was predicted by age (ß=-.16, p<.01). pre-treatment frequency of alcohol intoxication (ß=-.11, p<.05), ASI legal (ß=.22, p<.001) and employment (ß=-.21, p<.001) composite scores, and assignment to MOMT/NC condition (ß=.16, p<.05, R2=.18). Mean per cent of cocaine positive UAs was 40.9 (sd=32.2). Per cent of cocaine positives was predicted by age (ß=-.13, p<.01), black race (ß=.15, p<.01), ASI psychiatric composite score (ß=-.098, p<.05), pre-treatment frequency of IV cocaine (ß=.31, p<.001). smoked cocaine (ß=.25, p<.001), and marijuana use (ß=-.11, p<.05), methadone dose level (ß=-.15, p<.001). and assignment to ENHAN/CC condition (ß=-.16, p<.01, R2=.37). Treatment retention at 18 months (n=78. 22.2%) in a logistic regression model was predicted by age (odds ratio [OR]=1.09, 95% confidence interval [95%CI]=1.05-1.13, p<.001), non-black race (OR=2.24, 95%CI=1.16-4.33, p<.05), lower than median ASI legal composite score (OR=2.16, 95%CI=1.21-3.88, p<.01), methadone dose level (OR=1.04, 95%CI=1.01-1.07, p<.01) and assignment to NC conditions (OR=2.87, 95%CI=1.60-5.15, p<.001). While subject variables over which treatment providers have little control were, thus, related to outcome, type of treatment provided and methadone dose also influenced outcome. However, most of the variance related to drug use outcomes cannot be explained by the information obtained in this study. New approaches to understanding the forces driving drug use by methadone patients will be required to reduce drug use much further.

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AFFILIATIONS:

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REDUCING SUBJECT ATTRITION IN DRUG ABUSE STUDIES: IDENTIFYING ATTRITION RISK FACTORS AND TECHNIQUES TO IMPROVE FOLLOW-UP

D. DePhilippis and D. S. Metzger

INTRODUCTION:

Subject recruitment and assessment efforts at baseline may be made in vain if subjects are not followed up. This study examined variables that may be associated with subject attrition in longitudinal studies of methadone maintenance patients. Methodological factors -- how subjects were tracked -- and subject-related factors were tested for an association with loss to follow-up.

METHODS:

This study examines data collected from a sample of 409 volunteer opiate addicts enrolled in one of four methadone treatment programs located in the Philadelphia metropolitan area. At baseline, all subjects completed a questionnaire assessing addiction problems areas. Follow-up data was collected at six months, 12 months, and 18 months post-baseline. Subjects were grouped by whether they completed all, some, or none of the follow-up assessments. Subjects who died (N=11) during the course of the study were excluded from analyses. Follow-up was conducted from two sites (referred to here as A & B) in the Philadelphia metropolitan area. Because more resources were available to aid follow-up efforts at Site A, this study was allotted the opportunity to examine the differential effects of methodology and subject characteristics.

RESULTS:

Lower methadone dose, injection drug use, being employed, recent arrests, less time in treatment, recent hospitalizations, and not receiving welfare were associated with subject loss independent of methodology and whether or not the subject was in treatment at follow-up.

CONCLUSIONS:

In the absence of rigorous follow-up efforts, follow-up samples are likely to be unrepresentative of the population. Consequently, researchers could benefit by analyzing baseline data for the presence of the attrition risk factors.

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AFFILIATION:

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PROBLEM GAMBLING AMONG FORMER OPIATE ADDICTS: INVESTIGATING THE CORRELATES OF DUAL ADDICTION

W. Feigelman, P. H. Kleinman, H. R. Lesieur, R. B. Millman, and M. L. Lesser

This paper examines the correlates of problem gambling among a population of 220 former opiate addicts currently receiving treatment in a methadone program in the New York metropolitan area. Like most methadone maintenance patients, respondents were primarily adult males, ethnically mixed, of limited educational accomplishment and had long experiences with intravenous drug use. More than two-thirds of subjects had been convicted of one or more criminal offenses. Analysis of the data showed ten percent of respondents to be problem gamblers according to the SOGS--South Oaks Gambling Screen, indicating an elevated rate of gambling problems among this treatment population.

Consistent with past studies, analysis of the data showed problem gamblers more likely to be: men, with histories of alcohol abuse, and with childhood conduct disorders. The data also suggested that dual addicts were more likely to show greater evidence of social dysfunctionality compared to those who were exclusively substance abusers. Dually addicted respondents were more likely to report high levels of recent heroin use, unemployment, and hallucinations than respondents who did not have gambling problems. Problem gamblers who were substance abusers were also more likely to report being in conflict with their close friends than were others. A multiple regression analysis suggested this to be the closest linked correlate to being a problem gambler. Evidently, problem gamblers create antipathy towards themselves as their compulsion to gamble is expressed; this in turn, may drive them toward further gambling, as they respond to this perceived opposition. These last preliminary findings will require further confirmation in future research.

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AFFILIATION:

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WHY DO METHADONE CLIENTS VOLUNTEER FOR RESEARCH? REASONS FOR VOLUNTEERING AS CORRELATES OF SUCCESS IN A RESEARCH PROJECT AND IN METHADONE TREATMENT

S. D. Husband and J. J. Platt

Reasons why methadone clients volunteered to participate in a vocational problem-solving research project were examined as part of the research intake measures. Subjects were 55 outpatient opiate addicts (31 male, 24 female) receiving methadone treatment at an urban clinic in New Jersey. Each subject completed a form on which they identified 1) the reasons why they volunteered for the study and 2) the *single most important reason* why they volunteered. Twenty-four of the 55 subjects (44%) reported that they volunteered primarily to receive the monetary incentive. Subjects were followed for a minimum of three months and up to 14 months following entry into the research. Whether a subject ever worked following research intake, the number of vocational problem-solving group sessions attended (if assigned to a group condition), and whether a subject remained in treatment at the methadone clinic were monitored for all subjects who entered the protocol by completing the intake.

No differences were detected even at the $p < .1$ level for either the research goals (attending the group intervention sessions and finding work) or for retention in methadone treatment between those subjects who reported joining the research primarily for the financial incentives offered and subjects who reported joining primarily for other reasons (learning something, gaining work, having something to do, a friend joined the research, etc.).

These results suggest that those methadone clients who volunteered to participate in this treatment research project primarily to obtain the financial incentives offered by the investigators fared no better or worse than did subjects who volunteered for other reasons. It therefore may be that, at least for some clients, drug abuse treatment interventions might aim to involve drug users in treatment in whatever reasonable manner this can be accomplished. Even if clients at first participate for the "wrong" reasons, it appears that at least some can be engaged by a treatment intervention and its goals in spite of their original motivations.

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TEACHING PARENTING SKILLS TO DRUG ADDICTED PARENTS IN METHADONE TREATMENT

R. R. Gainey, K. P. Haggerty, R. F. Catalano, and M. J. Hoppe

Focus on Families (FOF) is a NIDA funded field experiment to test the effectiveness of an intervention designed to teach parenting skills and relapse avoidance skills to opiate addicts in methadone treatment. The objective was to decrease the risk of relapse among parents in methadone treatment and to decrease their children's risk of drug abuse. The intervention combined 33 group training sessions and six months of home-based case management services. Components of the parent training sessions included, "communicating with your child", "positive family management", and "teaching children skills".

The impact of the parenting skills training component of the intervention was assessed immediately following its completion. Parents reported what they perceived to be appropriate responses to six common problem parenting situations (*e.g.* dealing with a child who stays out late with negative peers, and dealing with a child not applying himself and who is doing poorly in school). Experimental and control subjects (n = 112) were interviewed by trained staff, blind to the experimental condition. Responses were recorded verbatim and later rated by trained staff. Inter-rater reliability was high (phi coefficients ranged from .71 to .81). A reliable scale was created standardizing the score for each situation and computing the mean across items (Cronbach's alpha = .67). The scale showed predictive validity by being positively correlated with general problem solving skills (r = .40) in role-play situations, the number of structured household rules (r = .30), and involvement of children in establishing household rules (r = .49).

Control subjects (n = 49) were compared with all randomly assigned experimental subjects (n = 63) as well as with experimental subjects who actually initiated treatment (n = 57) and experimental subjects who attended at least 16 sessions (over half the sessions offered). Experimental subjects scored significantly higher than all controls (mean = -.11 vs. .09, t = 1.74) and knowledge increased with levels of participation in the program (mean for initiators = .16 and high attendees = .25). The data provide empirical support for the efficacy of the FOF intervention to teach parenting skills to drug-addicted parents in methadone treatment.

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MAINTAINING THE STATUS QUO: STAGES OF CHANGE AMONG POLYDRUG USERS IN METHADONE TREATMENT

M. A. Belding, M. Y. Iguchi, and R. J. Lamb

This study employed a cross,-sectional design to assess the generalizability of Prochaska and Diclemente's stages-of-change model to a sample of patients in methadone maintenance treatment (MMT). Two hundred seventy-six Ss were recruited from four Philadelphia-area MMT clinics. Ss were divided into five stage categories based on their self reported drug use and their responses to a questionnaire asking about their intentions to discontinue unauthorized drug use in the future. Processes of change were assessed with a 60-item questionnaire which asked Ss how frequently they utilized a variety of activities to avoid drug use. EQS Confirmatory factor analytic procedures validated four change process scales derived from the twelve postulated by the model (Re-evaluation, Self-Liberation, Reinforcing Relationships, and Behavioral Processes).

Over 65% of Ss acknowledged unauthorized drug use in the 30 day pre-test period and were consequently classified into one of the first three stages of change. The data were analyzed to assess stage-related differences in reported use of change processes. Ss in different stages produced profiles of change process scores largely consistent with predictions, though these scores did not distinguish stages as clearly as has been reported in previous research.

Analysis of demographic data revealed that Ss in the Precontemplation stage reported significantly longer treatment tenures than Ss in any other stage besides Maintenance. Precontemplators reported spending an average of over six years at their current clinic - twice as long as subjects in the Contemplation, Preparation, or Action stages. Longer treatment tenure was also associated with a decreased likelihood of inclusion in the Preparation stage.

The study provides qualified support for the application of the stage model to the problem of polydrug use among MMT patients and also identifies a group of patients (Precontemplators) who pose a special challenge to treatment providers. Despite extended time in treatment, these patients report little change-related activity and no intention of quitting drugs in the near future. The results highlight the need for the development of aggressive strategies for treating long-term methadone maintenance patients and for preventing new patients from becoming long-term Precontemplators.

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ARE ALL PERSONS WITH ASP "TRUE" PSYCHOPATHS?

B. L. Kail, P. H. Kleinman, R. B. Millman, M. L. Lesser, and H. Robinson

This paper explores the hypothesis that some drug abusers diagnosed as ASP according to DSM-III-R criteria are not, in fact primary, or "true" psychopaths; and that the secondary ASP group would have more favorable treatment outcomes than the primary group. The study focuses on 90 drug abusers currently receiving methadone treatment in the New York metropolitan area who were diagnosed as ASP. The dynamic sub-scale of the Hare Psychopathy Checklist: Clinical Version was used to distinguish individuals into primary and secondary ASP groups.

It was found that at the 18 month follow-up, the secondary ASP group had significantly more current employment, and significantly less injected heroin use and criminal involvement, than the primary ASP group. Differences in four of the five other 18 month outcome measures of employment, drug use, and criminality, although not significantly different between the two groups, also showed more favorable outcomes for the secondary group. Multiple discriminant analysis showed that the variables which most strongly discriminated between the two groups were: working, heroin injection, and number of convictions in the post-treatment period.

These data provide support for the hypothesis, and suggest that treatment personnel would do well to be wary of tarring all drug abusers who have a diagnosis of ASP with the brush of "treatment resistant".

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AFFILIATION:

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TWO YEAR PREDICTIVE VALIDITY OF PSYCHOPATHY VERSUS ANTISOCIAL PERSONALITY DISORDER DIAGNOSES

A. I. Alterman, M. J. Rutherford, J. S. Cacciola, and J. R. McKay

The predictive validity of psychopathy and antisocial personality disorder (APD) categorizations were examined in 118 methadone maintained men for months 7-24 post-study entry.. Psychopathy was defined as having a score of 25 or more on the revised Psychopathy Checklist on any of three assessments- 0, 1, or 6 months. We applied the same rule to define the APD group, *i.e.,* the subject qualified for the APD group, if he met the APD criteria, using the Personality Disorder Examination and DSM-III-R criteria, at any of three assessments (0, 1, or 6 months). At month 24, we employed a modified time line follow-back technique to obtain monthly self-reported behavioral data for months 7-24 for 24 variables (*e.g.,* need for and form of controlled environment, employment pattern, sources of nonemployment income, crime, drug/alcohol use, and outpatient treatments).

The psychopathy (n=50) vs. nonpsychopathy (n=68) distinction revealed a number of group differences including a greater likelihood of criminal behavior, need for inpatient drug and alcohol treatment, more cocaine use, and less likelihood of continuation in outpatient methadone maintenance treatment. By contrast, the APD (n=57) vs. nonAPD (n=61) distinction was not generally predictive of more problem behaviors during the follow-up period. The findings provide some evidence for the hypothesis that psychopathy represents a more severe form of antisociality.

Future analyses will focus on more quantitative aspects of the data, a more detailed breakdown of the follow-up period, and will also incorporate a number of objective measures of outcome such as criminal records, hospitalization and DPA information, and urine toxicology data.

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PSYCHOPATHY, ANTISOCIAL PERSONALITY, AND OTHER PERSONALITY DISORDERS IN OPIOID ADDICTS: ASSESSMENT AND TREATMENT ISSUES

N. A. Piotrowski, D. J. Tusel, K. L. Sees, P. Banys, and S. M. Hall

This on-going study explored: (1) the concordance among three measures of antisocial behaviors and psychopathic traits' in a population of polysubstance abusing opioid addicts; and (2) the relationship between diagnoses of antisocial personality disorder (ASPD), psychopathy, and patient-treatment response to a four month methadone treatment. Measures included the Millon Clinical Multiaxial Inventory-II (MCMI-II). the Computerized Diagnostic Interview Schedule--Revised (CDISR), and the Hare Psychopathy Checklist--Revised (PCLR). On average, the first 71 subjects (50 males, 21 females) were 40.8 years of age; the modal subject was Caucasian, unemployed, educated at the high school level, and single. The MCMI-II diagnosed 23.3% as ASPD+ (Scale 6A above 85); the CDISR diagnosed 32.9% as ASPD+; the PCLR diagnosed 26.8% as POSITIVE for psychopathy (TOTAL score of 25 or more). CHI-SQUARE analyses demonstrated that men and women were diagnosed in similar proportions. Concordance was poor (KAPPAs -.18 to .24) with the exception of good agreement between the CDISR and the PCLR for men only (KAPPA=.5). The MCMI-II and CDISR related differently to PCLR scores by gender: the CDISR discriminated between psychopathic males, but not females; the MCMI-II discriminated between psychopathic females, but not males. ASPD or psychopathy status, alone or in combination with other personality disorder status, generally did not relate to treatment outcome or retention. For females, however, a CDISR ASPD+ diagnosis with another MCMI-II diagnosed personality disorder was associated with fewer days in treatment relative to females with no personality disorder or a personality disorder other than ASPD (28 vs. 111.3 vs. 117.8, $p<.0001$). Use of multiple measures and sensitivity to gender-based differences in the evaluation of these behaviors and traits in this population is recommended.

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AFFILIATION:

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HISTORY OF POST-TRAUMATIC STRESS DISORDER AND CURRENT TREATMENT GOALS FOR OPIOID ADDICTS IN METHADONE TREATMENT

P. S. Meek, N. A. Piotrowski, D. J. Tusel, and S. M. Hall

We report on the first 60 subjects in an on-going opioid addiction contingency contracting treatment study. Forty-one men and 19 women participated in a 180-day methadone program with intensive psychosocial treatment. Subjects received a stable dose of methadone for the first 120 days, then tapered for the last 60 days. Prior to beginning treatment, subjects were classified as PTSD-positive or PTSD-negative based on lifetime scores from the Computerized Diagnostic Interview Schedule - Revised. Based on self-report, subjects were also classified as having abstinence-oriented (AB) treatment goals, or nonabstinence-oriented (NA) goals. Of the 21 subjects with PTSD (none were military-related), 15 had abstinence goals (PTSD+/AB), and six had nonabstinence goals (PTSD+/NA). Of the 39 subjects without PTSD. 17 had abstinence goals (PTSD-/AB), and 22 had nonabstinence goals (PTSD-/NA). PTSD+ subjects were significantly more likely to set a goal of abstinence prior to treatment ($p<.039$). Both PTSD+ and PTSD- subjects expected equal difficulty in quitting, although PTSD+ subjects expected greater success ($p<.013$). Drug use was evaluated by examining the percentage of positive urines (missing tests were considered positive) and the longest string of consecutive drug-free urines occurring during the first 120 days. PTSD x GOAL ANOVAs revealed a main effect of PTSD, with PTSD- subjects showing a higher proportion of drug-free urines ($p<.036$) and longer strings of clean urines ($p<.027$) than PTSD+ subjects. A main effect of GOAL revealed that AB subjects had a significantly higher proportion of drug-free urines ($p<.011$) and a greater number of consecutive drug-free urines ($p<.027$) than NA subjects. Nonsignificant PTSD X GOAL interactions were observed for both dependent variables; however, informal inspection of the means showed that PTSD+/NA subjects had the greatest drug use, PTSD+/AB and PTSD-/NA were somewhat better, and PTSD-/AB showed dramatically less use. It is concluded that a lifetime diagnosis of PTSD is associated with treatment goals for opioid addicts entering methadone treatment, and that both PTSD diagnosis and abstinence goals influence progress in drug use reduction.

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BEHAVIORAL CONTINGENT PHARMACOTHERAPY IN THE TREATMENT OF OPIOID DEPENDENT PATIENTS

M. Kidorf, R. K. Brooner, and V. L. King

Although methadone treatment is effective in reducing illicit opioid use, most contemporary opioid abusers present with cocaine and other substance use disorders, and many have other psychiatric and psychosocial problems. Unfortunately, methadone has very limited efficacy in the treatment of these comorbid conditions. Intensified counseling service has proven effective in managing some of these problems, but opioid abusers are often noncompliant with even routine counseling interventions. Better integration of pharmacological treatment (*i.e.,* methadone) with nonpharmacological services (*i.e.,* counseling) may improve compliance with treatment and enhance overall treatment outcome. In this model, methadone substitution therapy is contingent on attending required psychosocial treatments. This model has been used effectively in our outpatient treatment program which incorporates methadone substitution therapy and increasing levels of outpatient counseling determined by rates of drug use and treatment compliance. In fact, at our highest level of treatment, patients are required to attend at least nine hours of counseling per week, including individual, group and family/significant other sessions, for six weeks. Patients referred to our highest level of treatment (N = 47) attended 82% of scheduled individual and group sessions, while 83% brought in a non-drug using significant other who was utilized to monitor community activity. A lifetime history of cocaine use disorder, major depression, and/or personality disorder were over-represented in these patients as compared to our entire clinic sample. Overall, 51% of the patients completed the program and achieved drug-free status. This model of treatment can be readily adapted to most outpatient methadone programs.

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CONTINGENT CONTRACT FAILURES IMPROVE UPON READMISSION WHEN THE SAME CONTINGENCIES ARE APPLIED

D. A. Calsyn, E. A. Wells, A. J. Saxon, R. Jackson, and V. Stanton

Our research group has previously reported on a contingency contracting (CC) system that discharged clients from methadone maintenance treatment for continuous drug use (Calsyn *et. al.,* 1994). Clients subjected to such a system provided fewer urines positive for illicit drugs than clients for whom there was no such contingency (NC). Although CC clients had been discharged at a faster rate than NC clients, they also had been readmitted at a faster rate. All clients readmitted were assigned to the same contingency condition as during their initial admission. Here we report on the treatment progress of clients who were readmitted to treatment.

Thirty-nine CC clients remained in treatment long enough (six months) during both the initial and a second treatment episode to be exposed to the discharge sanctions. Of these 34 (87.2%) were discharged due to contract failure in the initial treatment episode. Significantly fewer (n = 25 [64.1%], McNemar Binomial P = .02) were discharged for contract failure in the second treatment episode. Seventeen NC clients had two treatment episodes of six months or more. If the contingency contracting procedures had been applied to the NCs, 14 (82.4%) would have been discharged for contract failure initially, and 13 (76.5%) would have been discharged for contract failure during the second treatment episode (McNemar Binomial P = 1.0).

CC clients who succeeded during the second treatment episode after failing in the first were older and provided fewer opiate and benzodiazepine, but not cocaine, positive urines during the second episode compared to CC clients failing during both treatment episodes. During the initial treatment episode these two groups did not differ on the percentage of urines positive for opiates, cocaine or benzodiazepines.

For a subset of clients the full efficacy of our contingency contracting procedures may not be realized until reapplied during a subsequent treatment episode.

REFERENCES:

Available upon request of senior author.

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CONTINGENCY CONTRACTING FOR ILLICIT DRUG USE WITH OPIOID ADDICTS IN METHADONE TREATMENT

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This study examines the effect of positive contingencies in the treatment of heroin addiction. Data are presented on the first 71 subjects admitted into a six-month methadone treatment which provided for 80 mg methadone per day, an intensive psychosocial treatment schedule consisting of two therapy groups, one one-hour counseling session, and one education class per week. Urine samples were collected at random twice a week with at least 48 hours between specimens and were analyzed for opioids, cocaine, benzodiazepines, marijuana, amphetamines, and barbiturates. In addition, a breathometer test for alcohol was administered randomly one time per week. At treatment entry, subjects were randomly assigned to a contingency (N=36) or non-contingency (N=35) contract condition during the first four months of treatment. Subjects in the contingency condition were able to earn increasing cash credits (up to a maximum of $755) to be spent on items of their choice for submitting negative breathometer tests and urine samples demonstrating consistent avoidance of illicit drug use. During month one, combined avoidance of illicit opioid and cocaine use was the target behavior. During months two through four, all illicit drug use was targeted. On average, subjects were 40.8 years of age (range 23-56), primarily male (70.4%), single (47.9%), and unemployed (69%). Most were Caucasian (43.7%), abused at least one other drug in addition to heroin, and had 12 or less years of education. Demographically, there were no differences between the two groups. The unit of analysis targeted with the contingency contract was **continuous abstinence** from illicit drug use. By the end of month four, the subjects in the contingency contract group demonstrated significantly more consecutively clean urines (7.89) compared to the control group (2.89)--$p<.03$. There were no differences between the contingency and non-contingency contract groups in days in treatment, amount of psychosocial treatment received, or dose of methadone prescribed during the four month contract. We conclude from these interim results on 71 subjects (out of 102 enrolled) who have completed the study that contingency contracting has a significant effect in producing continuous abstinence from all illicit drug use.

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RESOURCE → PROCEDURE → PROCESS → OUTCOME ANALYSIS (RPPOA): PRELIMINARY FINDINGS OF COST-EFFECTIVENESS ANALYSIS OF A METHADONE MAINTENANCE PROGRAM

B. T. Yates, K. J. Besteman, J. Filipczak, L. Greenfield, and A. De Smet

Multiple regressions and analyses of variance were performed on data from a three year study of two methadone clinics. Only statistically significant findings are reported below.

RESOURCES → OUTCOMES
Patients who stayed longer in treatment participated in more group therapy sessions of shorter duration in the first month. The opposite relationship between duration of treatment and duration and frequency of sessions was found for individual counseling in the first month. Use of cocaine by the third month was lower for patients who received frequent but brief medical services initially. Also, participating in more groups but spending a lower total time in groups were related to less cocaine use during the third month. Opiate use during the third month of treatment was inversely related to the frequency of medical services during the second month.

PROCEDURES → OUTCOMES
The initial daily dose of methadone was inversely related to the total time spent in treatment, but daily methadone dose during the second month was directly related to treatment duration and lower cocaine use in the third month. Relative to the enhanced clinic, patients in the standard clinic had lower rates of cocaine and opiate use during the third month of treatment.

PROCESSES → OUTCOMES
Patients who initially reported greater anxiety stayed longer, as did patients who reported lower mental health initially. By the second month, patients whose self-reported mental and physical health and social functioning were higher than other patients' stayed longer. Similar relationships were found between health and social functioning and less cocaine use during the third month of treatment. Opiate use during the third month of treatment was lower for patients who initially were more depressed or disturbed.

PATIENT VARIABLES MODERATING OUTCOMES
Better retention was found for patients whose relatives had abused drugs, who reported a longer period of employment, who were older when they began their first methadone treatment, and who reported suicidal ideation. Shorter stays were found for patients who were older when they received their first substance abuse treatment, and for patients who had spent more time in prison. Patients with more convictions were more likely to use cocaine during the third month of treatment. More educated patients used cocaine less during the same period.

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THE SF-36 AS A MEASURE OF SUBSTANCE ABUSERS' HEALTH PERCEPTIONS

L. Greenfield, K. Besteman, C. Clark, J. Filipczak, and B. Yates

The utility for MMTP patients of the SF-36, a brief measure of perceived health status and functioning, was assessed in this two-part study. The 36 item instrument developed by Ware and Sherboume (1992), consists of eight scales: physical, role physical, role emotional, social, bodily pain, mental health, vitality, and general health. In part one, reliability and validity were assessed (N=528) upon admission to two NIDA funded outpatient clinics. Internal consistency (Alpha) was high (.71 to .95) for seven scales, as was test-retest reliability (r>.7, N=38) for six. Validity was supported. Patients who reported any of ten pre-admission health problems scored lower (worse functioning) on five scales (p<.05), and those diagnosed with a post-admission medical condition scored lower on seven scales, than those not. Patients were less consistent than the general population and perceived worse functioning.

In part two, the SF-36 was readministered over time to a followup sample (N=228) in one clinic. Patients were retained for varying durations including "short" (<4 months, N=99), "medium" (4-9.9, N=51), and "long" (10+, N=78). The periods assessed for all three groups were intake and months 1-2 (M1-2). Over time, mean health status scores increased for all but two scales (p<.05). Three scales had significant group by time interactions and two others approached significance (p<.10), indicating that over time better perceived health status was associated with longer stays. Finally, medium and long stays were compared at intake, M1-2 and M3-4. No further changes over time were evident.

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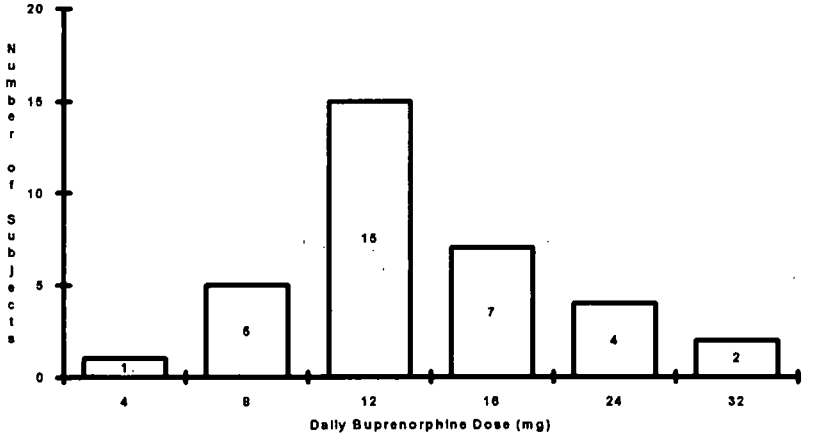
WHAT DOSE OF BUPRENORPHINE REDUCES OPIATE USE? A DOUBLE-BLIND DOSE-RANGING STUDY

P. Compton, W. Ling, C. Charuvastra, D. Wesson, and C. J. Klett

Recent evaluations of buprenorphine. the partial p-opiate agonist, have demonstrated its' effectiveness as an alternative to methadone maintenance pharmacotherapy. Eight mg of buprenorphine has been viewed as the optimal or modal daily dose to treat opiate addiction, although recent data from several methadone/buprenorphine comparison clinical trials provide evidence that this dose is only as effective as low to moderate doses of methadone in reducing opiate use. Using a dose-ranging paradigm to determine average stabilization buprenorphine maintenance dose, daily dose was increased incrementally (4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg) until the subject, for two consecutive weeks, consistently attended clinics and submitted five out of six opiate-free urines collected three times per week. Dose was increased either weekly or every other week, and administered in a double-blind manner. At 16 weeks, 34 of 100 consecutively admitted opiate addicts met stabilization criteria, while 19 were unable to do so. Retention was less than 16 weeks for the remaining 47 subjects. The doses at which stabilization was achieved tended to be higher than 8 mg (see Figure); in fact, 82% of the sample required 12 mg or more to meet these treatment stabilization criteria. The modal dose was 12 mg QD and the mean dose was 14.6 mg QD (S.D. = 6.52 mg). These data indicate that daily buprenorphine doses greater than 8 mg may be required to reduce opiate use. and, as with methadone, individual variation is evident for stabilization.



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NEGATIVE OPIATES IN URINE OF PATIENTS ON BUPRENORPHINE STUDY

R. I. H. Wang and L. D. Young

In the NIDA sponsored multicenter clinical investigation of buprenorphine in the treatment of opiate dependency urine samples were collected and analyzed by a central laboratory, but the investigators and the staff were blind to the results of urine tested. Some of our patients were referred to us by their probation or parole officers. As long as they were under treatment and were not abusing opiates, they remained free. We were surprised that some of the urine sent to commercial laboratories by their probation/parole officers were found to be negative for opiates while they were taking 16 to 32 mg daily of buprenorphine. indicating that they were not taking illicit narcotic drugs and that buprenorphine cannot be detected by the commercial labs.

To validate the above findings the urine samples from another group of patients taking 16 to 32 mg of buprenorphine daily, but not on parole/probation were tested by a commercial laboratory.

The Emit d.a.u. Opiate Assay (SYNA) was employed to detect a number of narcotic drugs from human urine.

A total of 23 urine specimens from 16 patients taking 8 to 32 mg of buprenorphine daily were tested. Eleven patients provided one urine sample each; three patients gave two specimens each; two patients gave three specimens. Four patients admitted using opiates besides buprenorphine medications, showed positive evidence of opiates in their urine (five specimens). Eighteen specimens were negative for opiates in their urine in spite of the fact that ten of the patients were taking 32 mg of buprenorphine daily.

It is concluded that urine drug surveillance in commercial laboratories using Emit method cannot detect buprenorphine in urine specimens that came from patients taking up to 32 mg of buprenorphine daily. Due to metabolic changes of buprenorphine other methods need to be devised.

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A PILOT STUDY OF PRIMARY CARE-BASED BUPRENORPHINE MAINTENANCE

P. G. O'Connor, A. Oliveto, J. M. Shi, K. M. Carroll, B. J. Rounsaville, and T. R. Kosten

INTRODUCTION: Methadone has been the standard pharmacologic agent for maintenance in the management of opioid addiction. More recently, buprenorphine has been demonstrated to effectively decrease drug use in individuals addicted to opioids. While both approaches may be effective, access to opioid maintenance currently restricted to individuals admitted to traditional drug treatment programs. The purpose of this six month pilot study is to evaluate the feasibility of buprenorphine maintenance performed in a primary care setting - The Central Medical Unit (CMU).

METHODS: The CMU is a licensed, free standing primary care clinic affiliated with the Yale Substance Abuse Treatment Unit. The clinic is staffed by primary care physicians and nurse practitioners. A three times per week protocol was developed in which buprenorphine was administered as 20mg sublingually on Monday and Wednesday, and 40mg on Friday. Patients meet weekly with their primary care provider. In addition, patients attend a once weekly group therapy session designed to support their efforts to be abstinent. Primary outcome measures include compliance with clinic visits and group therapy sessions, urine toxicology results, and retention in treatment. Those who-successfully completed six months of therapy are offered transfer to methadone maintenance or other drug treatment programs of their choice.

RESULTS: Seven opioid dependent individuals were entered into the pilot study: six were male, four were employed, their mean age was 27 years, they reported a mean duration of opioid dependence of 2.5 years and used a mean of 4.4 bags of heroin per day. To date, five patients are each in the sixth month of the study and two patients dropped out (one during month two and one during month three). Among the five patients remaining in treatment, there has been 100% (110/110) compliance with clinic visits and 97% (107/110) compliance with group therapy sessions. Urine toxicology results have improved during treatment. During the fifth month, the proportion of urines positive for opioids for each patient remaining in treatment was 0% (0/12), 0% (0/12). 17% (2/12), 33% (4/12) and 33% (4/12). No complications of therapy have been noted.

CONCLUSION: In conclusion, these preliminary results suggest that thrice weekly buprenorphine maintenance may be feasible in a primary care setting.

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TRIPLE BUPRENORPHINE MAINTENANCE DOSES MAINTAIN OPIOID-DEPENDENT OUTPATIENTS FOR 72 HOURS WITH MINIMAL WITHDRAWAL

W. K. Bickel, L. Amass, J. P. Crean, and S. T. Higgins

This study compared 24-, 48- and 72-hour buprenorphine (BUP) dosing schedules in opioid-dependent outpatients. To date, thirteen subjects receiving BUP (sublingual maintenance doses: N=6, 4 mg/70 kg; N=7, 8 mg/70 kg) completed this double-blind, placebo-controlled, triple crossover trial. Following a 10 day baseline of daily maintenance dosing, subjects received, in a mixed sequence, each of three, 21-day treatments: daily dosing (DD), alternate-day dosing (ADD) and triple dosing (TD). During DD, subjects received their maintenance dose every 24 hours. During ADD, subjects received twice their maintenance dose every 48 hours, with placebo on the interposed day. During TD, subjects received three times their maintenance dose every 72 hours, with placebo on the interposed days. Study participation was contingent on daily attendance and opioid abstinence. Measures of opioid agonist and withdrawal effects were assessed daily. Pupil diameter and agonist measures remained stable across dosing conditions, with no differences detected between active drug and placebo days during ADD or TD. Overall, observer- and subject-rated withdrawal differed minimally across treatments, and these ratings remained stable within ADD. Subject-ratings of withdrawal increased linearly over the 72-hour interval during TD, although magnitude of withdrawal was low and limited to mild somatic complaints. No adverse medical reactions occurred during any treatment. These results suggest that BUP can be administered safely and effectively every 72 hours by tripling the maintenance dose, although some subjects reported mild withdrawal during TD. Importantly, this TD schedule extends the advantages of ADD by permitting patients days off from the clinic for periods exceeding 24 hours without the use of take-home doses.

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DAILY VERSUS ALTERNATE-DAY DOSING OF BUPRENORPHINE IN THE OUTPATIENT TREATMENT OF OPIOID DEPENDENCE

R. E. Johnson, M. L. Stitzer, E. C. Strain, G. E. Bigelow, and I. A. Liebson

If buprenorphine can be dosed less often than daily, it will provide the same perceived advantages of LAAM without the disadvantages of slow onset of action and respiratory depression. Preliminary studies have suggested buprenorphine can be effective in the treatment of opioid abuse when used on an alternate-day basis. This clinical trial compared daily versus alternate-day buprenorphine dosing in opioid-dependent outpatients who had undergone a 14 day initial study comparing different doses of buprenorphine to placebo. After the initial study, participants were stabilized on 8 mg of daily sublingual buprenorphine, and then randomly assigned to double-blind daily (n=45) versus alternate-day (n=46) dosing for ten weeks. Alternate-day dosing consisted of 8 mg doses on active dose days, and placebo dosing on non-medication days; daily dosing consisted of continuation on 8 mg per day. Primary and secondary outcome measures were: 1) retention in treatment, and 2) percent urine specimens positive for opiates; and 1) clinic attendance, 2) self-reported opiate withdrawal symptoms, 3) self-reported dose adequacy, and 4) percent urine specimens positive for cocaine, respectively.

The two groups did not significantly differ on age, race, gender, marital, employment or legal status, but there was a significantly greater number of previous treatment episodes in the daily versus alternate-day groups (2.0 versus 1.2, respectively; $p<0.05$). Patients in the daily dosing group remained in treatment significantly ($p<0.03$) longer and attended clinic significantly more days than the alternate-day group (50.0 versus 39.5 of 70 possible days, $p<0.05$). There were no significant differences between groups on weekly reports of dose adequacy or opiate withdrawal symptoms and no differences between groups for percent of urine specimens positive for opiates or cocaine.

These preliminary results show that daily dosing is superior to alternate-day buptenorphine dosing. However, alternate-day dosing is equally tolerated and acceptable to a subgroup of patients. While daily dosing of buptenorphine 8 mg may be associated with better treatment retention and clinic attendance, alternate-day dosing of 8 mg is equally effective on rates of opioid and cocaine positive urine specimens. The lack of difference in self-reported withdrawal symptoms may be due to continued use of opiates. Although this study demonstrates that alternate-day dosing of buprenorphine 8 mg may only be appropriate for a subgroup of patients the clinical efficacy of an alternate-day schedule for buprenorphine may be improved by raising the maintenance dose.

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ALTERNATE-DAY BUPRENORPHNE DOSING IS AS EFFECTIVE AS, AND IS PREFERRED TO, DAILY DOSING IN OPIOID-DEPENDENT HUMANS

L. Amass, W. K. Bickel, J. P. Crean, and S. T. Higgins

This study examined an alternate-day buprenorphine dosing (ADD) procedure under blind and open dosing conditions and determined whether the ADD schedule was preferred to a daily dosing (DD) schedule. Eighteen opioid-dependent outpatients participated in this quadruple crossover trial. Following a ten day baseline of daily maintenance dosing, subjects experienced, in a mixed sequence, each of four, 14-day dosing conditions: blind daily (BD), open daily (OD), blind alternate-day (BAD) and open alternate-day (OAD). During open dosing, subjects were given explicit information about the dosing schedule; during blind dosing, no information was provided. During BD and OD, subjects received their maintenance dose every 24 hours. During BAD, subjects received twice their maintenance dose every 48 hours, with placebo on the interposed day. During OAD, subjects received twice their maintenance dose on Monday, Wednesday and Friday, and a maintenance dose on Sunday. Subjects completing all four dosing conditions were exposed to the four conditions a second time. After completing the second exposure, the subjects entered a one month choice phase during which they could choose either the OD or OAD schedule on a weekly basis. Study participation was contingent on daily attendance and opioid abstinence. Ten of the original 18 subjects completed one exposure (sublingual maintenance doses: n=2, 2 mg/70 kg; n=5, 4 mg/70 kg; n=3, 8 mg/70 kg); seven of these subjects completed the second exposure and choice phase. Observer- and subject-rated measures of opioid agonist and withdrawal effects obtained during ADD did not differ from DD across any of the dosing conditions. Six of seven subjects chose OAD exclusively during the choice phase. One subject chose OAD on three or four occasions. These results demonstrate similar efficacy of ADD relative to DD under blind and open dosing conditions. Preference for ADD also suggests utility as a positive reinforcer to enhance opioid treatment.

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A SURVEY OF POTENTIAL PROGRAM AND COMMUNITY-BASED REINFORCERS FOR USE IN OPIOID TREATMENT

J. P. Crean, L. Amass, W. K. Bickel, and S. T. Higgins

Utilizing positive reinforcers via contingency contracting to facilitate compliance with treatment goals may enhance outcomes for opioid-dependent patients. This study evaluated potential reinforcers for use in outpatient opioid dependence treatment. Fifty-three opioid-dependent patients enrolled in buprenorphine treatment for at least 30 days rank ordered 11 clinic privileges, 19 retail items and eight activities from most desirable to least desirable. Additional questions determined preference for counseling frequency and dosing level. A mean rank (MR) of "1" was the best possible rating. The top five clinic privileges were $50 cash for clean urines (MR 2.8). take-home doses of buprenorphine (MR 3.6), voucher points for clean urines (MR 4.7), change dose (MR 5.0) and retail items for clean urines (5.4). The top five retail items were restaurant gift certificates (MR 4.1), movie passes (MR 4.9), VCR & movie rentals (MR 6.8). bookstore gift certificate (MR 8.2) and YMCA passes (MR 8.6). The top five activities were movies (MR 2.4). barbecue (MR 3.8). hiking (MR 4.3). volleyball (MR 4.8) and softball (MR 4.8). There was no preference reported for counseling frequency. Seventy-four percent of subjects preferred to increase their buprenorphine dose. Subjects chose to increase their dose by an average of 60.84%. Consistent with previous findings from methadone treatment, cash payments for clean urines and take-home medication were the highest ranked program-related reinforcers. These results also suggest that community-based variables may be useful for reinforcing positive treatment outcomes during outpatient treatment.

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BUPRENORPHINE-NALOXONE COMBINATION DRUG FOR THE TREATMENT OF DRUG ADDICTION

R. Hawks and C. N. Chiang

Buprenorphine, an opiate partial agonist, is currently under development for the treatment of opioid addiction. Additionally, a combination of buprenorphine and naloxone is being developed as a "take home" medication. Naloxone, a narcotic antagonist with low sublingual bioavailability, has been included in the formulation to reduce the abuse potential (through diversion) of this product. NIDA's ongoing development program for this combination product includes clinical pharmacology studies of buprenorphine and naloxone in methadone maintained patients, in subchronic buprenorphine patients, in heroin addicts and in morphine-dependent subjects. Current data indicate that the combination of buprenorphine and naloxone at a dose ratio of 1:1 is as efficacious as buprenorphine alone in buprenorphine subchronic patients when it is given in a sublingual alcohol solution. This combination dose is aversive to either methadone-maintained or moderately dependent heroin addicts when given intravenously.

Due to the concerns about the cost of naloxone and about the limited availability of safety data for the chronic use of naloxone, future development is aimed at a combination which contains a minimal yet effective amount of naloxone for deterring the intravenous use by moderately dependent addicts. A dose ratio of 4:1 is currently being targeted. Clinical pharmacology studies are planned for the investigation of the abuse potential of dose ratios ranging from 2:1 to 8:1 in subjects at a quantifiable dependency level -- maintenance on 60 mg morphine daily. Also planned are bioequivalence studies to assess the clinical equivalency between the combination tablets and the buprenorphine mono tablets and clinical studies to collect usage and safety data for the combination product.

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IMPROVING THE HEDONIC AND GUSTATORY QUALITIES OF SUBLINGUAL NALOXONE WITH VARIOUS FLAVORING AGENTS

J. Mendelson and R. T. Jones

Buprenorphine and naloxone in combination show promise in the treatment of opiate dependence. Buprenorphine has a mildly bitter taste while naloxone has an intensely bitter taste. Although taste is not a limiting factor in the acceptance of sublingual buprenorphine and naloxone combinations, a markedly unpalatable dose form could limit clinical acceptance. Therefore, a strategy to improve the palatability of sublingual buprenorphine and naloxone and develop an adequate placebo for naloxone could be important. Bitrex (denatonium benzoate) was assessed as a placebo for naloxone. Nine female and three male healthy, nonopiate-dependent subjects were tested on three separate occasions. Naloxone or Bitrex were combined with cherry, chocolate, mint, orange and vanilla flavoring agents and flavor preferences were rank-ordered. The hedonic and gustatory qualities of the flavor preferences were assessed by visual analog and semantic adjective differential scales and data was analyzed by analysis of variance. Results show unflavored naloxone to be significantly more bitter, less likable, less palatable, and to have a significantly unpleasant aftertaste when compared with all flavored naloxone combinations. Naloxone combined with mint was the preferred flavoring agent followed by orange. The flavor qualities of Bitrex and naloxone were indistinguishable, making Bitrex an acceptable placebo for naloxone. These results suggest the palatability of unflavored naloxone can be improved by the addition of flavoring agents.

RANK ORDER OF FLAVORS

	Preferred Flavors					Least Preferred
Flavor	**#1**	**#2**	**#3**	**#4**	**#5**	**Flavor**
Mint	7	2	3	0	0	0
Orange	2	5	1	1	2	1
Vanilla	2	3	1	3	2	1
Cherry	1	1	4	4	2	0
Chocolate	0	1	3	4	4	
Naloxone	0	0	0	0	2	10

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INPATIENT MEDICALLY SUPERVISED OPIOID WITHDRAWAL WITH BUPRENORPHINE ALONE OR IN COMBINATION WITH NALTREXONE

D. J. Mann, I. D. Montoya, C. Contoreggi, P. A. Ellison, W. R. Lange, and K. L. Preston

The safety and effectiveness of buprenorphine alone or in combination with naltrexone was evaluated in an eight day inpatient medically supervised withdrawal single-blind study. Nnltrexone 12.5, 25 or 50 mg was administered on days three and four, three to eight, five to eight, or not at all; placebo was given on all days when active naltrexone was not given. All subjects received one sublingual buprenorphine dose daily in the following order: 4 mg (day one), 6 mg (day two), 4 mg (day three), 2 mg (day four), and 0 mg (day five to eight).

Forty-five subjects who met DSM-IIIR criteria for opioid dependence consented to be studied. All subjects who started receiving naltrexone on day five (n = 4) had severe opiate withdrawal and recruitment of subjects for this group was stopped. The group on buprenorphine alone (n = 33) had equal or less withdrawal from day two through four compared to the group that started naltrexone on day two (n = 8). However, from day five through day seven the naltrexone-treated group had less withdrawal than the group with buprenorphine alone.

These results suggest that administration of naltrexone on day two may increase opiate withdrawal at the beginning of treatment but lead to decrcased withdrawal thereafter compared to placebo. This result may bear on the hypothesis that the partial resetting of the opiate receptor by the partial antagonist effect of buprenorphine may be enhanced by the early administration of naltrexone, resulting in less withdrawal after day four of treatment. This data also supports the development of cost-effective short-term inpatient opiate detoxification and early transition to opiate-free treatment using naltrexone.

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WITHDRAWAL FROM CHRONIC BUPRENORPHINE ADMINISTRATION: PRELIMINARY FINDINGS

A. M. Washburn, L. Brooks, S. L. Batki, D. Tusel, N. Nanda, and K. White

This pilot study is examining the withdrawal syndrome associated with a gradual taper from long-term buprenorphine administration for the treatment of opioid dependence. The results of earlier trials suggest that the abstinence syndrome may be mild, but little is known about how to optimize a withdrawal regimen.

Subjects (N=23) who had completed a 16-week, Phase III trial of buprenorphine and were enrolled in an extension protocol for up to one year were tapered from the medication over six weeks. Prior to the first dose drop, subjects completed the Detoxification Fear Survey Schedule. During the taper and for a four-week follow-up period, they were monitored for withdrawal signs and symptoms and drug use. Clonodine was prescribed as needed. The study will compare responses across stabilization dose levels when the blind is broken.

All subjects completed the six-week taper; 22 of 23 returned for a mean of 5.2 follow-up visits. During the taper, 68% showed an increase in withdrawal symptom level, whereas for the post-taper phase 70% reported a decrease in symptoms over time. Overall symptom level for 41% of subjects was slight; for the remaining, symptoms were, at most, moderate. Scores on the Detoxification Fear measure were positively correlated with mean symptom scores for both phases of the study. Regardless of the severity of symptoms reported, observed signs of withdrawal were few with the median for all weeks zero. A majority tested positive for opiates throughout the study, although self-reports of use were low with means of 2.0 and 3.7 times/week for the taper and post-taper phases respectively.

Withdrawal from buprenorphine appears to be physiologically mild to moderate. Further research is needed, however, to determine how to optimize a withdrawal regimen to prevent a relapse to illicit opiate use.

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RITANSERIN (RIT) BLOCKS THE VASOCONSTRICTION CAUSED BY INJECTION OF COCAINE (COC) INTO CHICKEN EGGS WITH 15 DAY-OLD EMBRYOS

S. B. Sparber, A. Wasserman, and G. Bollweg

Of the multiple mechanisms through which drugs may be toxic, especially to developing organisms, vasoconstriction leading to hypoxia or vasoconstriction followed by reperfusion, leading to reactive oxygen (free radical) species must be considered. The relatively potent but short lived vasoconstriction caused by COC is probably mediated, in part, by indirect stimulation of 5-HT2 receptors in embryonic and/or extra-embryonic vascular beds. We used the chick embryo to test this possibility. Within 20 minutes after injection of COC (11.25-67.5 mg/kg egg) beneath the shell on E-15, there was a significant reduction of spontaneous embryonic motility. The highest dose reduces hatchability when injected on E-18, which is blocked by RIT pretreatment (1). This dose of COC is not lethal when injected on E-15, suggesting that the older embryo with more mature 5-HT pathways (2) is more sensitive to COC's toxic effects. Injection of RIT (0.4 mg/kg egg) on the P.M. of E-14 blocked the significant decrease in apparent diameter of blood vessels in the membrane just beneath the shell after COC (67.5 mg/kg egg) was injected on E-15. RIT itself was inactive in this regard. The 20±% reduction ($F_{3,18}=3.965;p=0.025$) in vessel diameter caused by COC can translate into an increase in resistance of up to 250%. based upon the relationship of $Res=l/r^4$, in the absence of other factors, such as eddy currents, etc. Thus, RIT-like drugs may be efficacious in treating or preventing the consequences of severe vasoconstriction/hypertension related to 5-HT2 receptor stimulation, as is probably the case with COC exposure.

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RITANSERIN (RIT) INJECTED INTO EGGS WITH CHICKEN EMBRYOS ON E-14 DOES NOT AFFECT DETOUR LEARNING 1-2 WEEKS AFTER HATCHING

G. Bollweg and S.B. Sparber

Drugs that affect serotonin (5-hydroxytryptamine, 5HT) have received increasing attention as potential therapeutic agents for pathologic conditions that include depression, sleep disorders, hypertension, cardiovascular disease and withdrawal from substances of abuse. Motivation for the present experiment arose during testing of the 5HT2 antagonist ritanserin (RIT) for its ability to block certain effects of cocaine exposure during embryonic development. We addressed the potential toxicity of RIT itself under such conditions. Despite the emphasis placed on cocaine's action at dopaminergic and noradrenergic transporter sites, its capacity to block 5HT reuptake is as great or greater than for the catecholamines. Thus, characterization of cocaine's pharmacologic and toxicologic actions requires consideration of 5HT. Since 5HT2 antagonists are effective in attenuating the expression of opiate withdrawal, many manifestations of which are similar to those of cocaine's action, 5HT2 antagonists may likewise be effective against certain of cocaine's effects, including its potential developmental toxicity. Because of its ability to transiently decrease vascular perfusion, Fantel *et al.,* (1) proposed that prenatal cocaine exposure may result in hypoxia and ischemia/reperfusion injury mediated by reactive oxygen species (free radicals). Since cocaine-induced vasoconstriction is probably due largely to indirect stimulation of 5HT2 receptors, blocking them may decrease vasoconstriction and potential free radical generation, an hypothesis we are testing in chick embryos. Gustafsson *et al.* (2) recently found that RIT blocked decreased blood flow and oxygenation in rabbit skeletal muscle induced by hypoxia, supporting the plausibility of the hypothesis.

Our preliminary work indicates that embryonic day 14 (E-14) administration of 0.4 mg RIT/kg egg blocks cocaine-induced vasoconstriction on E-15 (Sparber *et al.,* 1994 CPDD abstract 192) and that E-18 cocaine exposure increases hydroxyl radical generation, using salicylate hydroxylation (2.3- and 2,5-dihydroxybenzoic acid formation) measured with HPLC-ED (Kubak and Sparber 1994 CPDD abstract 195). To address the issue of potential RIT "side effects" under such conditions, we exposed E-14 chick embryos (n=12/group) to 0, 0.1, 0.3, 0.9, and 2.7 mg RIT/kg egg. Hatching was unaffected by any RIT dose. At one to two weeks posthatching, detour learning, a task sensitive to developmental exposure to cocaine (Kim and Sparber, in preparation) and other xenobiotics, was tested. RIT did not affect detour learning at any tested dose (no difference in mean detours nor mean latencies over 12 trials). A later experiment measured serum corticosterone concentration in the same subjects under basal and stress conditions. While basal concentrations were unaffected at any RIT dose, the 2.7 dose (six to seven times the dose that blocked vasoconstriction) sensitized 19-day old chicks to mild stress, manifest as elevated corticosterone concentration (Wei and Sparber 1994 CPDD abstract 194). The results indicate that neither acquisition of a simple learned response nor concentrations of one stress hormone are affected by "protective" RIT doses in the chick embryo.

REFERENCES:

Available upon request of senior author.

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MILD STRESS RAISES SERUM CORTICOSTERONE (CORT) LEVELS IN TWO WEEK-OLD CHICKS HATCHED FROM EGGS INJECTED ON E-14 WITH A HIGH DOSE OF RITANSERIN (RIT) MORE THAN IN CONTROLS

Y. X. Wei and S. B. Sparber

The importance of 5-HT in the hypothalamo-pituitary-adrenal axis response to stress has been known for some tune. There is now extensive evidence showing that both direct-acting and indirect-acting serotonin agonists increase serum corticosterone levels in rats. The 5-HT receptor subtype regulating the number of hippocampal glucocorticoid receptors during development appears to be of the 5-HT2 type (1). Drugs of abuse can induce a stress response by virtue of their novel stimulus effect, by sympathomimetic effects (*e.g.* cocaine, amphetamine), and/or because of withdrawal-induced stress. As part of our program attempting to characterize the consequences of exposure of developing organisms to drugs of abuse, we have included studies with domestic chicken embryos and chickens, so as to study the direct effects of drugs or withdrawal, instead of their potential indirect effects via actions on pregnant subjects. RIT may protect against some of the developmentally toxic actions of opiate withdrawal or cocaine. It is therefore important to determine if doses of RIT which are efficacious in this regard may also be potentially toxic.

Eggs (N=3/group) were injected on the 14th day of incubation (E14) with tartrate or 0.1 - 2.7 mg RIT/kg of egg. The highest dose (2.7 mg/kg) is three to *seven* times greater than necessary to block effects of the 5-HT2 agonist DOI or cocaine in chick embryos. At two weeks posthatch, blood from nonstressed or mildly stressed chicks was drawn and serum was separated. Serum corticosterone was determined by direct radioimmunoassay (RIA). None of the doses affected hatchability or basal (*i.e.* nonstressed) serum CORT concentration (overall mean=0.66 µg%). Exposure to 15 minutes of mild stress increased levels to 1.11 µg%, on average ($F_{1,20}$=23.248; $p \leq 0.0001$). Injection of 2.7 mg RIT/kg egg on E14 sensitized two week old chicks to mild stress or desensitized the feedback suppression associated with elevated serum/CNS concentrations of the glucocorticoid. An overall effect of prenatal RIT treatment emerged only in the stressed groups ($F_{4,10}$=4.073; $p<0.01$). Serum corticosterone in the highest dose of RIT group was significantly elevated above controls (1.77 µg% vs 0.79 µg%), as well as the other groups. These results of a high dose prenatal RIT-enhanced response to mild stress in two week old chicks may be related to an earlier observation that inhibition of brain 5-HT synthesis enhanced a stress response, and that increasing brain serotonin concentrations by administration of its Precursor reduced a stress response significantly (2). Thus it appears that efficacious doses of RIT in this species are devoid of acute developmental toxicity (*e.g.* hatchability) and do not alter postnatal neuroendocrine function (*e.g.* basal CORT and response to stress).

REFERENCES:

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EVIDENCE OF ·OH FREE RADICALS IN HEARTS AND BRAINS OF CHICK EMBRYOS AFTER COCAINE (COC) INJECTION

M. A. Kubak and S. B. Sparber

Salicylate + ·OH yields 2,3-; 2,5-dihydroxybenzoic acid (DHBA), which can be quantified (1). It has been suggested, not demonstrated *in vivo,* that ischernia-reperfusion, leading to reactive ·OH; may be responsible for COC's developmental toxicity (2). To determine if ·OH can be detected in hearts and/or brains of developing chick embryos and whether COC exposure can elevate ·OH, eggs at E-18 were injected with avian saline or NaSalicylate (Nasal), 200 mg/kg egg (egg wt=50 g; N=5/group), two hours prior to injection of COCHCl (67.5 mg/kg egg), or water (water only after Nasal). Embryonic hearts and brains were taken for analyses five hours later. The dose of Nasal was determined to be free of toxicity (*i.e.,* no reduced hatchability or apparent teratogenicity upon visual inspection of hatchlings). There were no detectable levels of 2,3-DHBA and barely detectable levels of 2,5-DHBA (*e.g.,* 0.04 ng/mg tissue) in hearts and brains of embryos exposed only to COC, in the absence of Nasal. NaSal+COC yielded significant increases of 2,5-DHBA in hearts and brains, compared with Nasal alone (3.92 vs 2.60 ng/mg, hearts; 1.56 vs 1.03 ng/mg, brains, respectively). While significant concentrations of 2,3-DHBA could be detected in hearts after NaSal+COC injections, it was undetectable in brains, under the conditions of the experiment. These preliminary findings support the notion that ischemia, followed by reperfusion injury, rather than ischemia-hypoxia, or in addition to hypoxia, may be responsible for some of COC's acute and/or long-lasting developmental toxicity. Additional experiments are underway to more fully characterize the phenomenon and to determine if treatment with free radical scavengers or drugs which prevent cocaine-associated vasoconstriction can block these effects and any associated functional teratogenic effects of COC.

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SHORT TERM SUBCUTANEOUS COCAINE ADMINISTRATION DURING PREGNANCY DOES NOT ALTER STRESS HORMONE LEVELS IN POSTPARTUM DAMS

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We have previously reported marked and long-term functional alterations in 5-HT systems in progeny following prenatal exposure to cocaine (15 mg/kg, b.i.d.) administered by the subcutaneous (s.c.) route (Synapse, 15:158-168, 1993; Brain Res. Bull, 34:93-97, 1994). However, some concerns have been raised regarding the utility of this route of cocaine administration since it has been postulated to result in tissue necrosis which may act as a long-term "stressor" in the dams and thereby confound interpretation of data obtained in progeny. To our knowledge, no studies have evaluated the dose-dependency of tissue pathology associated with the s.c. administration of cocaine and whether such changes produce consequent long-lasting increases in plasma ACTH or corticosterone, two indices of stress in an animal. The present study investigates basal and stimulated stress hormone levels in postpartum dams following s.c. administration of cocaine. Pregnant Sprague-Dawley rats (N = 6-8/group) received 0.9% saline (1 ml/kg) or 15 mg/kg (-)cocaine (b.i.d.) from gestational day 13-20 by s.c. injection at various sites along the dorsal surface adjacent to the midline. For comparative purposes, an additional group of dams received s.c. fluoxetine (10 mg/kg) daily. On postpartum day four, dams from each of the treatment groups received either saline or the 5-HT releaser, p-chloronmphetamine (5mg/kg s.c.) and were sacrificed 60 minutes post-injection. Trunk blood was collected for RIA of plasma hormones. No differences were observed in maternal weight gain among the groups. Histopathologic evaluation of the most severely affected tissue sections indicated marked deep chronic inflammation and mild to moderate epidermal/superficial dermal changes which were comparable in cocaine and fluoxetine-treated dams. Despite these changes, there were **no** differences in basal plasma levels of ACTH or corticosterone among treatment groups nor was the 5-HT mediated stimulation of plasma ACTH or corticosterone altered in cocaine-exposed dams. These data indicate that cocaine (15 mg/kg s.c. b.i.d.), while producing some tissue pathology, does not produce long-lasting increases in the hormonal markers of stress in the cocaine-treated dams. These data refute the contention that pathologic tissue changes associated with s.c. cocaine injections necessarily act as long term "stressors" in rats.

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MATERNAL COCAINE DURING PREGNANCY, VIA INTRAVENOUS ACCESS PORT, ALTERS FETAL NEUROBEHAVIORAL DEVELOPMENT

C. F. Mactutus and R. M. Booze

The intravenous route of administration, accessed via a SC implanted port, was employed in pregnant rats as a model for studying the developmental effects of maternal cocaine abuse. Prior to mating, catheterization of young adult female Sprague-Dawley rats was performed under anesthesia (Ketamine/Rompun) using aseptic techniques. A sterile Intracath iv catheter (22 ga., Becton/Dickinson) with a Luer-lock injection cap (Medex) was cut to -8 cm and implanted dorsally in a sc pouch. The distal end of the catheter was inserted into the jugular vein and threaded centrally. Patency of the catheter was maintained by daily flushing with 0.2 ml of heparinized saline. After a surgical recovery period of one week, the animals were bred. Cocaine at a dose of 3 mg/kg (GD8-14 1X/day, GD15-20 2X/day) did not significantly affect maternal weight gain during gestation, litter size, or birth weights. Growth of the offspring through the preweaning period was also unaffected by the prenatal cocaine exposure. However, locomotor activity at 30-32 days of age, as measured by infrared photocell interruptions in an open field. was significantly altered by prenatal cocaine. A gender-independent increase in locomotion within the center, but not periphery, of the open field was observed under dark (0.5 lux), but not dim (2.0 lux) conditions. The magnitude of the prenatal cocaine effect was comparable to that of the gender difference characteristic of this apparatus. In sum, although maternal cocaine exposure during pregnancy, administered iv, produced no general developmental toxicity, offspring neurobehavioral toxicity was detected. The specificity of both the response (centrally-directed activity) and environmental conditions (illumination levels) to which the alteration is offspring behavior was bound suggests the hypothesis of a noradrenergically-mediated alteration in neurobehavioral function.

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CNS DEVELOPMENT AND MOTHER-FATHER INTERACTIONS AMONG COCAINE EXPOSED INFANTS: A PRELIMINARY REPORT

P. E. Suess, M. A. Owrutsky, and R. I. Herning

Fourteen cocaine-exposed infants were compared to 16 non-exposed infants on measures of early postnatal CNS development. Cocaine mothers had a cocaine-positive urine at delivery or self-reported use during pregnancy. Control mothers were negative for all substances. At 40, 48, and 56 weeks conceptional age, sleep EEG and ECG were recorded. Videotaped interactions were collected at 48 and 56 weeks along with maternal urine samples. Assessments of substance abuse, SES, co-morbidity, and infant temperament were obtained. Cocaine-exposed infants weighed less at birth but did not differ in gestational age or head circumference. Control group mothers reported more prenatal care visits and were more often employed. Spectral and visual analyses of the EEG recordings revealed expected patterns of trace alternant at 40 weeks, sleep spindles at 48 and 56 weeks, and well developed sleep state organization in both groups. Sleep state heart rate and vagal tone did not differ between groups at any age. Mothers of cocaine exposed infants tended (p = .09) to rate their 56 week infants as more irritable and easily frustrated. During 48 week face-to-face interactions cocaine-exposed infants vocalized more than non-exposed. Mothers of cocaine-exposed infants used more infantized behaviors and responded more contingently to their infants than control mothers at 56 weeks. Overall interaction ratings at 56 weeks tended to be higher for the cocaine mothers (p = .09). These findings must be considered preliminary due to the small sample studied. The lack of differences in developmental EEG suggests the need for more long term follow-up. Additionally, the effects of cocaine exposure may be more evident when the infant is challenged and adaptability is measured. The slightly higher interaction scores for the cocaine group is possibly the result of a self-selection bias among the cocaine using women who volunteer for research.

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PRIMARY CARE INTERVENTIONS FOR COCAINE ABUSING PREGNANT WOMEN

R. S. Schottenfeld, B. Forsyth, S. Ball, J. Pakes, and C. Brady

Because cocaine abuse continues as a major public health problem for pregnant women, we are assessing the efficacy of primary care based drug abuse interventions in a prenatal clinic and the relationship of addiction severity, trimester enrolled for prenatal care, and pregnancy and drug abuse treatment outcomes. Drug abuse screening (interview, urine toxicology) of 1567 women between January 1, 1992 and May 31.1993 identified 233 current cocaine users (14.9%). of whom 174 self-reported cocaine use and 59 tested positive despite a negative self-report. Ninety-three of the 233 cocaine users enrolled in drug abuse treatment either during pregnancy (EP, n=45) or at the time of delivery (ED, n=38), and an additional 10 cocaine using women who received no prenatal care (NPC) enrolled at delivery. Younger cocaine using women (<25 years) and those entering prenatal care during the second and third trimesters were more likely to enroll in treatment than women >25 years (54.7% vs 44.7%) or those entering in the 1st trimester. Baseline ASI documented that NPC women had significantly greater use of alcohol and cocaine, fewer prior treatment episodes, and worse pregnancy outcomes (birth weight, gestational age, head circumference, length) compared to women enrolling for drug treatment during pregnancy, while ED women had intermediate pregnancy outcomes. These results suggest that prenatal drug abuse screening facilitates enrollment into drug treatment both during pregnancy and at the time of delivery, and that drug use severity and adverse pregnancy outcome are correlated with lack of prenatal care.

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CESSATION OF COCAINE USE DURING PREGNANCY: A PRELIMINARY COMPARISON

R. Elk, J. M. Schmitz, L. Manfredi, H. Rhoades, R. Andres, and J. Grabowski

Purpose: To characterize pregnant women who abstained from cocaine use with baseline treatment, by comparing their data with that of a similar group of cocaine-dependent women who, due to continued drug use. required more intensive treatment in the form of contingent reinforcements.

Methodology: Twenty-nine women with a primary diagnosis of cocaine dependence participated in a joint drug treatment and prenatal care program. Seven dropped out of the program early in treatment (< 4 weeks) and were therefore excluded from this evaluation. For the remaining 22 subjects, group membership was determined retrospectively, based on level of drug treatment intervention required. Intensive treatment group: Patients with > 50% cocaine-positive samples during first four weeks of treatment, therefore requiring additional treatment interventions (N = 9). Baseline treatment group: Patients with > 90% cocaine-positive samples throughout treatment, therefore not requiring additional treatment interventions (N = 13). Data from the two groups were compared using Chi-square tests, t-test and analysis of variance.

Results: The two groups did not differ in terms of any demographic variables. Two-thirds of the patients were African-American, 68% unmarried and 68% were in their second to fourth pregnancy, with no differences between the groups. Significantly more patients in the baseline treatment group were cocaine-free at intake ($X^2 = 3.955$, $p = 0.046$) and had a higher rate of compliance with clinic attendance ($t = 2.02$, $p = 0.058$).

Conclusions: Drug-free status at intake may be an indicator of high degree of motivation to be drug-free and of a decision to cease cocaine use prior to entering treatment. Cessation of cocaine use may be in response to factor(s) associated with pregnancy. Despite the small sample size, the findings demonstrate that there are a significant proportion of drug-dependent minority women of lower socio-economic status who cease cocaine use and remain cocaine-free during pregnancy. These preliminary findings establish the need for prospective, long-term outcome studies on the treatment of coaine dependence during pregnancy. Treatment studies comparing the relative efficacy of various treatment interventions are being conducted at our clinic.

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TYPES OF ABUSE AND COCAINE USE IN PREGNANT WOMEN

K. Jantzen, S. Ball, and R. Schottenfeld

Previous findings indicated a relationship between childhood abuse and adult abuse and cocaine use. The current study follows-up these findings in a larger sample of (N=1189) pregnant women and analyzes the effects of specific types of abuse and onset of abuse. These 1189 subjects are also part of a larger cross-sectional study being conducted in a hospital based prenatal clinic caring for a predominantly inner-city, poor, and minority population. Pregnant women who experienced any childhood abuse reported significantly greater rates of cocaine use during lifetime (41% vs. 17%. $p < .001$) and pregnancy (14% vs. 6%, $p < .001$) than women who were not abused in childhood. Pregnant women who experienced any childhood abuse also reported significantly more abuse in adulthood (29% vs. 13%, $p < .001$) and during the current pregnancy (13% vs. 5%. $p < .001$) than pregnant women not abused in childhood. Women abused only in adulthood reported greater rates of cocaine use during lifetime (49% vs. 17%, $p < .001$) and pregnancy (20% vs. 5%, $p < .001$) than females reporting no adult abuse. However, there were no differences in cocaine use for childhood vs. adulthood onset abuse. Lifetime cocaine use was associated more strongly with childhood sexual abuse alone (53%) or in combination with physical abuse (55%) than with physical abuse alone (26%), [$X2 = 15.32$. $p < .001$]. Severe forms of abuse were more associated with lifetime cocaine use than less severe forms of abuse (47% vs. 30%, $p < .05$). Women abused in childhood [$t(1046)=7.32$, $p < .0001$] and adulthood [$t(1012)=8.00$, $p < .0001$], reported use of a larger number of drugs than women not abused. Women abused as adults reported heavier recent use of cocaine [$t(56)=2.10$, $p < .01$] and more often reported use of alcohol during pregnancy than non-abused women, [$X2 = 24.61$, $p < .001$]. The findings suggest that childhood physical and sexual abuse appear to be risk factors for substance use and subsequent abuse in adulthood and pregnancy.

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ENHANCED PROGRAM RETENTION OF PERINATAL SUBSTANCE ABUSERS FOLLOWING PATIENT INCENTIVE PROGRAM

J. H. Lee and D. Svikis

Several studies have shown behavioral incentive programs to be an effective strategy for promoting drug abstinence in outpatient programs. but little research has addressed the issues of program retention. The present study examined the effectiveness of an incentive program targeting program attendance. Forty-eight substance abusing pregnant women were given the opportunity to earn two tickets to the Baltimore National Aquarium (worth $21.00) by completing seven consecutive days of full programming following transfer from inpatient to outpatient programming. The number of patients attending full programming was calculated for the first seven days following transfer and then again for 30 days post transfer. A control sample of 47 patients, not offered the incentive program, consisted of all admissions for the two months prior to start-up of the incentive program. Twenty-five percent of patients offered the ticket incentive attended full programming for seven consecudve days post-transfer as compared to only 9% of patients not offered the ticket incentive. More importantly, 100% of those patients who earned aquarium tickets were still in treatment 30 days following transfer as compared to only 33% of controls. The results of this report demonstrate the effectiveness of behavioral incentives in the treatment of pregnant drug abusing women in improving program retention.

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PEDIATRIC OUTCOMES IN INFANTS OF PREGNANT DRUG ABUSING WOMEN

L. Jansson, D. Svikis, P. Paluzzi, and F. Hackerman

The Center for Addiction and Pregnancy (CAP) is a multidisciplinary "one stop shopping" program treating pregnant drug abusing women and their families in Baltimore, Maryland. CAP components include Obstetrics, Pediatrics, Family Planning, Nursing, and Mental Health. The center currently provides care to over 200 women and 116 children per year. Pediatric care, developmental assessment, and child care are provided for all infants born within the program as well as their siblings. Children with special needs receive some services (physical, occupational and speech therapy) within the program or are referred for special services. The Developmental Play Program at CAP provides child care as well as insight into patenting abilities and developmental strengths and weaknesses.

During the first year of operation, there were 100 CAP births. The mean gestational age by Ballard exam was 39.3 weeks. Mean birth weights, lengths, and head circumferences were at the 40-50th% tiles for term infants. Eighty-eight percent of infants were average for gestational age. The Neonatal Intensive Care Unit admission rate was 10%, with a mean length of stay of 6.3 days, which is lower than previously reported means for drug exposed infants. Twenty-seven percent of infants had a urine positive for illicit substances at birth. It is of note that birth length and weight for all infants is significantly positively correlated with full day attendance in drug treatment.

Routine developmental testing consists of a battery of examinations administered from birth to 30 months of age (see table 1). Included in these examinations is the Bayley scales of Infant Development, which are performed at 6, 12 and 24 months. At six months, 26 infants were tested, with a mean mental developmental index of 104, and mean psychomotor Developmental index of 110. Nineteen 12 month examinations were performed, yielding a mean MDI of 107 and mean PDI of 107. Only two 24 month tests were administered, with a mean MDI of 98 and a mean PDI of 119. Keeping in mind the small numbers and possible skewing of the population tested, cognitive testing results for this population of drug exposed infants was generally within normal limits. Of note was that the interviewer severity ratings for family violence of the Addiction Severity Index were significantly negatively correlated with Bayley Mental Developmental Index at six months of age.

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IMPACT OF AN ENHANCED MODEL OF PRENATAL CARE FOR SUBSTANCE ABUSERS IN A COMPREHENSIVE TREATMENT PROGRAM

P. A. Paluzzi, J. Emerling, J. Leiva, P. Gazaway, and G. Huggins

Substance abuse and drug dependence are increasingly associated with perinatal morbidity and mortality. Adverse outcomes may be attenuated by enhanced prenatal care. Unfortunately drug using women are often afraid to seek treatment or find few options available. The Center for Addiction and Pregnancy (CAP) is a multidisciplinary treatment program for drug affected women and their children. Services include on-site OB/GYN and family planning care, substance abuse/mental health services, pediatric care and developmental day care for preschool aged children. There is a 16 bed domiciliary unit with 24 hour nursing coverage and 80 ambulatory treatment slots. The OB/GYN and family planning services are provided by a team of Certified Nurse Midwives and OB/GYN physicians. The midwives are the primary providers including antepartum coverage for delivery. The prenatal care follows an enhanced model of more frequent visits and intensified screening With an estimated gestational age at first visit at CAP of 26.5 weeks, the average number of visits provided at CAP is 8.4 per pregnancy. The greatest risks for drug affected infants without prenatal care are prematurity (<37 weeks) and small size (<2500 gms.) with high rates of admission to the Neonatal Intensive Care Unit (NICU) (national range of 20-40%) and long lengths of stay (22 days, FSKMC, 1989). The infants born to women active in the CAP program in the first year and one-half (n=100) have a mean birth weight of 2946 gms., with a mean delivery EGA of 38 weeks, and have a mean NICU admission rate of 10% with an average length of stay of six days. Positive maternal toxicology screens at delivery were 21%. These outcomes seem to indicate that the intervention of prenatal care and the reduction of drug use may vastly improve the neonatal outcomes for the drug exposed infant and mother.

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AN EXAMINATION OF PERCEIVED RISKS AND BEHAVIOR AMONG ADOLESCENTS IN THERAPEUTIC COMMUNITIES

G. Bhattacharya, N. Jainchill, J. Yagelka, K. J. Hindmand, and S. Holland

Treatment providers as well as researchers are always interested to see if the provision of treatment services leads to any changes (or for that reason, no changes) in the perception and consequently, to the behavior pattern of the clients. This study examines the changes in clients' perceptions of the risks and possible consequences of behavior -- during treatment in residential therapeutic community (TC). treatment programs for substance use/abuse problems.

Data has been collected at six TCs for adolescents (N = 416) located in the eastern U.S. and Canada. Both quantitative and qualitative data analytic techniques are used. The research subjects include all clients who completed interview batteries both at admission and at treatment midpoint. Findings reflecting clients' self-reported progress can provide feedback to program staff to improve the overall quality of the treatment program, and to some degree, optimize the treatment plan to meet the special needs of each client.

Results indicate that the clients do recognize changes in their perception of risks, that those changes are positive in nature, and indicate an intention to change their behavior patterns in the future. The findings have implications for expanding after-care programs for adolescents, especially, towards preventing relapse. Development of criteria for assessing progress in drug treatment programs may also be explored.

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PERSONALITY PROFILES OF DRUG DEPENDENT SUBJECTS

K. Boyle and M. Maglione

A sample of 193 illegal drug users (124 men and 49 women) was screened from patients at sexually transmitted disease clinics and from recent arrestees in jail, as part of the Treatment Utilization and Effectiveness Study (TUE). The Basic Personality Inventory (BPI) was administered and various measures of drug use were taken. A sub-sample of 75 subjects (48 men and 27 women) reported dependent use of illegal drugs. For this preliminary investigation, mean scores on the 12 BPI scales were calculated for males and females, for the sample as a whole and for the drug dependent sub-sample. These scores were plotted against the standardized normative scores for men and for women.

Elevations on four of the BPI scales were expected to be associated with abuse of drugs: Denial, Alienation, Interpersonal Problems, and Impulse Expression. Elevations on these scales have been shown to characterize those who tend to avoid problems and repress unpleasant emotions, who have been socialized in a deviant subculture, who are resentful of authority, and who are dangerously impulsive. These traits are often associated with substance abuse (Jackson 1989). The results from this sample did not meet all these expectations. The profiles showed that for the overall sample of drug users, men and women had similar profiles. The Denial score was in the normal range for both, contrary to expectations. The Deviation, Persecutory Ideas, and Alienation scales were elevated for both genders. For the women, but not the men, there was an elevation on the Thinking Disorder scale.

The profiles of the drug dependent sub-sample showed more divergence between the men and the women. Men were markedly more elevated on the Depression scale. While both genders were elevated on the Alienation and Persecutory Ideas scales, the elevation of the women on the Alienation scale was particularly high. The men were more elevated on the Social Introversion and Self Depreciation scales. Contrary to expectations, both men and women drug dependent subjects were below the mean scores on the Denial scale.

Further study will be conducted to attempt to assess with greater acuity personality differences between heavy and light drug users.

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SUBSTANCE USE AND PEOPLE SEEKING DISABILITY SERVICES

D. Moore and S. C. Acquilano

Although recent attention has been given to substance use and abuse among people with disabilities, there are numerous unresolved issues. Patterns of use across disability groups are still unclear due to methodological problems, and very little is known about the effects of disability-related factors on substance use. This pilot study included subjects from two samples, 916 people with disabilities accessing various disability service agencies and 227 adults with disabilities applying for vocational rehabilitation services. Alcohol abuse scores reported are based on the Alcohol Abuse Index, designed primarily from the Michigan Alcoholism Screening Test. Self-reports of substance use among the 916 subjects indicated that they used substances at least as much as the general population (for similar age and demographic background). People with quadriplegia reported the highest incidence of prescription medication use (85.7%), current alcohol use (74.6%), and current marijuana use (20.9%). Certain disability groups (quadriplegia, traumatic brain injury, and mental illness) had significantly higher alcohol abuse scores than other disability groups. Alcohol abuse scores were significantly higher for those with later onset (after age 19) versus early onset (before age 18) and congenital disabilities and alcohol abuse scores were significantly higher for those whose alcohol use onset predated the onset of their disability. Comparisons of lifetime use percentages among the 227 adult vocational rehabilitation candidates indicated that current use of cigarettes was almost twice that of the general population (51.1% vs. 27%), current use of alcohol was comparable (51.4% vs. 50.9%). lifetime use of cocaine was more than twice that of the general population (28.8% vs. 11.7%). and lifetime use of crack cocaine was over nine times higher than the general population (17.7% vs. 1.9%). Finally, there were significant correlations between favorable attitudes toward substance use among people with disabilities and both alcohol and drug use (.17, $p<.05$ and .26, $p<.001$, respectively). Substance use is certainly an important issue for many people with disabilities and specific disability groups appear to be at higher risk for substance abuse than others.

REFERENCES:

Available upon request from the authors.

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NURSES' DRUG USE: NEW NIDA FUNDED RESEARCH

A. Trinkoff and C. Storr

The drug use patterns of nurses, and women in general, are an understudied phenomenon, especially the relationship of drug use to the work environment. Nurses handle and administer most medications to hospitalized patients, giving them unique access to controlled substances. Nurses with drug use problems are important to identify, since they can maim or even kill patients if they practice undetected. This presentation is designed to introduce a four year study which will identify nurses at high-risk of substance USC, due to easy access to controlled substances in the workplace, and membership in high-risk nursing specialties. The study will implement a nationwide survey of 6,000 randomly sampled nurses, and collect data on drug use, worklife, and psychological well-being. Guiding this are results from pilot work, which indicated an increased risk of illicit use of prescription-type drugs by nurses with easy workplace access to these substances (O.R.=3.2) and an even higher risk of such drug use among those who had both easy workplace access and worked in critical care specialties (O.R.=6.2). From this, educational and preventive initiatives can be designed to address drug use among nurses, thereby increasing the safety of patients in their care.

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ADDICTION AMONG ANESTHESIOLOGY PERSONNEL - A 5-CASE REPORT

Y.-F. Sung

Anesthesiology personnel are particularly vulnerable to drug dependence due to stressful working environment and accessibility of drugs. The following are five case reports that I was involved in managing personally in the last 20 years.

Case 1 36 y/o/w/m, resident. On numerous agents for several years and tried to withdraw himself. He overdosed and died while attempting to treat his withdrawal syndrome.
Case 2 29 y/o/w/m, physician's assistant. He was caught taking fentanyl. After several hours of confrontation by colleagues, he finally agreed to admit himself to a rehabilitation hospital. Upon completion of treatment, he returned to practice and relapsed to fentanyl use. Subsequently, he left the medical field.
Case 3 28 y/o/w/m. resident. He was very elusive. His dependency was eventually detected after he moved to another institution.
Case 4 59 y/o/w/f, CRNA. Iatrogenic addiction after motor vehicle accident. She relapsed to drug use twice after the first time. Voluntarily admitted to hospital for treatment and retired.
Case 5 31 y/o/w/m, resident. Was caught using both long- and short-acting opioids. After long hours of confrontation by two attending physicians, he finally was admitted to rehabilitation center and decided to quit anesthesiology training.

CONCLUSIONS:

1) Even within a given medical specialty, patterns of drug dependencies can vary widely. 2) Only one of above five cases was iatrogenic. There was only one case who voluntarily went to rehabilitation. The remaining four cases were characterized by denial of the problem. 3) All medical personnel have to be alert to the problem of self-initiated addiction among their colleagues. One must be willing to take appropriate aggressive action to address the problem even though it is a painful process.

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DRUG USE AND OTHER RISK BEHAVIORS AMONG HOSPITAL EMERGENCY ROOM PATIENTS

J. Chen, Y.H. Hser, K. Boyle, M. Orlinsky, H. Fagelson, and R. Hutson

Patients in three hospital emergency rooms were interviewed confidentially in 1993 and 1994. Assessment was made of drug use history, risk factors for contracting HIV, and use of health services. A urine specimen was collected to verify recent drug use. The mean age of the sample was 36.7 and about two thirds of the respondents were men. The race/ethnic breakdown of the sample was as follows: 37 percent were African American, about 44 percent were Latino, about 15 percent white and about three percent Asian/Pacific Islander. Results of urinalysis showed that about 3 1 percent of the sample tested positive for an illegal drug. The street drug with the highest rate of current use was marijuana with about nine percent of the sample reporting use in the previous three days. However, the drug with the highest rate of current dependence was crack cocaine with 2.3 percent of the sample reporting dependence at the time of interview. Almost 20 percent of the sample had been in some form of drug treatment over the life span.

The mean number of sex partners in the past year was 4.3. About 20 percent had three or more partners in the previous year. Between 40 to 50 percent of those with three or more partners had used a condom for the last sex episode. About 33 percent had been treated for a sexually transmitted disease (STD) over the life span. The most commonly reported STD was gonorrhea with almost 23 percent reporting having been treated for this disease and another 6.2 percent having been treated for syphilis.

Medical services at private and public health clinics, hospitals, and other venues had been used an average of 7.79 times in the previous year, with 24.1 percent reporting having had unmet medical needs. About five percent of the sample reported having shared drug injection equipment in the past, and about one percent currently shared injection equipment. Less than one percent reported having stopped injecting due to concern with contracting HIV. Longitudinal interviews will be conducted with drug users screened from this sample in order to assess and monitor their drug use and use of health care and drug treatment services.

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AFFILIATION: UCLA Drug Abuse Research Center, Los Angeles County/University of Southern California Medical Center

DRUG USE AND OTHER RISK FACTORS AMONG STD PATIENTS

D. Longshore, Y. H. Hser, K. Boyle, D. Anglin, and G. Richwald

Patients (N=1520) in three sexually transmitted disease (STD) clinics in Los Angeles County were interviewed during 1992 through 1994. Assessment was made of patients' drug use, drug treatment participation, sexual behavior, condom use, arrest history, and medical services utilization.

The mean age of the subjects was 29.2. Two thirds of the sample were men. Race/ethnicity were as follows: about 52 percent African American, about 39 percent Latino. about seven percent white, and one percent Asian/Pacific Islander. The urinalysis results showed that about 25 percent of the sample tested positive for an illegal drug. The drug most used by this sample was marijuana -- about 17 percent had used in the previous three days and about three percent reported dependence. Cocaine, as crack or powder, was the next most used drug with 3.3 percent of the sample reporting use in the previous three days, although 9.4 percent tested positive for cocaine. Crack was the drug with the highest rate of previous dependence (8.1%) and highest rate of current dependence (1.3%).

The mean number of sex partners in the previous year was 8.5, with over 40 percent of the sample reporting three or more sex partners in the previous year. Of those with three or more sex partners that year the rate of condom use was over 40 percent. Respondents had an average of about two STD episodes over the life span. Gonorrhea was the STD most cited (38.7%) with the chlamydia rate at 16.6 percent and the syphilis rate at 12.8 percent. About .6 percent of the sample reported current sharing of drug injection equipment at the time of the interview. Fifteen percent stated that they had stopped injecting drugs due to fear of contracting HIV.

This sample will be monitored in yearly follow-up interviews to assess their future use of drugs, participation in the drug treatment system, and behaviors that are risky for contracting HIV.

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PERCEIVED NEED FOR DRUG TREATMENT AMONG PREGNANT ARRESTEE WOMEN AND ARRESTEE MOTHERS IN LOS ANGELES

D. M. Baldwin and M. D. Anglin

Previous research has pointed to the high rate of drug use by women arrestees in Los Angeles. Not only do women arrestees exhibit greater drug use than male arrestees, but women suffer the consequences of alcohol and other drug abuse more severely than men. This paper extends such findings by using four quarters of Drug Use Forecasting (DUF) data from 1993-1994 to examine whether or not a positive relationship exists between pregnancy and perceived need for substance abuse treatment. If pregnant and substance abusing arrestee women show an increased desire for drug treatment, it may provide a "window of opportunity" for intervention in areas such as drug treatment and prenatal care. We utilized a DUF sample of 519 arrestee women, 60 (11.6 percent) of whom believed they were pregnant. Of the 519 women, urinalysis tests determined that 419 (80.7 percent) were using or abusing substances at the time they were arrested. Of the 60 women who believed they were pregnant, 45 (75 percent) were using or abusing substances and 23 (38.3 percent) felt they needed drug treatment. Almost one half (48.9 percent) of these women who were using substances felt they did not need drug treatment.

In line with previous studies, we found that both pregnant and non-pregnant arrestee women are afflicted with high rates of substance abuse. Nevertheless, these high rates do not translate into equally high rates of perceived substance dependence and perceived need for drug treatment. One of the best predictors of recognized need for drug treatment was previous treatment history and a positive drug screen on the urinalysis test. Demographic factors that showed significant associations with perceived need for drug treatment were older age, ethnicity (white and latino). and employment status. In conclusion, our findings do not suggest that pregnancy among arrestee women provides a straightforward "window of opportunity" for intervention on their substance abuse careers.

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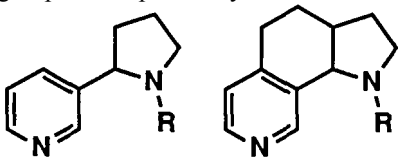
COMPARATIVE SAR STUDIES OF N-SUBSTITUTED NORNICOTINES AND N-SUBSTITUTED NORBRIDGED NICOTINES

W. Glassco, E. L. May, M. I. Damaj and B. R. Martin

We have found the rigid bridged nicotine analog (BN, **II**, R = CH_3) to posses nicotine-like activity in vivo, though not in vitro. Surprisingly, the more active (+)-BN failed to displace [^{3}H]-nicotine at 10 μM concentration. To explore the disparity between in vivo and in vitro potency a series of N-substituted nornicotine analogs (**I**) and a series of N-substituted norbridged nicotine analogs (**II**) were synthesized. In series **I** the affinity for sites in mouse brain labeled with [^{3}H]-nicotine decreased when nicotine's N-methyl group was replaced by either H or larger substituents. In series **II** compounds, very weak affinity was regained when the N-methyl group was replaced by H or by larger alkyl groups. Despite poor or nonexistent receptor affinity, many of the analogs in both series retained significant in vivo activity (see table). The general lack of correlation between in vivo and in vitro activity suggests that multiple nicotinergic mechanisms, and perhaps non-nicotinergic mechanisms, are involved.



I **II**

Compound, R	**K_i[a]**	**Inhibition of Spont. Activity[b]**	**Tail-flick[b]**
(-)-Nicotine	1.0	1.0	1.0[c]
I, H	18	7	12% at 68 μmol/kg
I, Cyclopropyl -methyl	>7000	2	7[d]
II, H	118	6	5.3
(+)-**II**, Methyl	>7000	1.3	1.7[d]
II, n-Propyl	4570	0.3	0.2[d]

[a]K_i of the compound divided by the K_i for nicotine (1.04 nM). [b]ED_{50} of the compound divided by the ED_{50} for nicotine (4.44 μmol/kg for inhibition of spontaneous activity and 4.81 μmol/kg for tail-flick). [c]Antagonized by mecamylamine (1 mg/kg s. c.). [d]Not antagonized by mecamylamine.

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LOBELINE ROBUSTLY INCREASES [^{3}H]DOPAMINE RELEASE FROM RAT STRIATAL SLICES

L. P. Dwoskin, L. H. Teng, S. T. Buxton, and P. A. Crooks

Lobeline (a-lobeline) is a lipophilic alkaloid in Indian tobacco *(Lobelia inflata).* No obvious structural similarities are apparent between lobeline and nicotine. These drugs produce similar pharmacological effects. Lobeline may be beneficial for smoking cessation (Wright and Littauer 1937; Kalyuzhnyy 1968). Lobeline is a nicotinic agonist which releases [^{3}H]dopamine ([^{3}H]DA) from striatal synaptosomal preparations (Grady *et al.,* 1992), displaces (Ki = 5 nM) [^{3}H]nicotine binding from brain membranes (Lippiello and Fernandes 1986), but does not substitute for nicotine in operant discrimination studies (Reavill *et al.,* 1990). In contrast to nicotine, chronic administration of lobeline does not result in brain nicotinic receptor upregulation (Bhat *et al.,* 1991).

The present study examined [^{3}H]DA release from rat striatal slices evoked by superfusion with lobeline (0.01-100 μM), compared to S(-)nicotine (0.05-100 μM). Both drugs increased [^{3}H]DA release in a concentration-dependent manner. At low concentrations (0.01-1.0 μM). the lobeline response was only 30-50% of the nicotine response. In contrast, response to lobeline (10-100 μM) was 10-32 fold greater than nicotine response. Lobeline (30 and 100 μM) depleted DA content (to 60% and 41% of control, respectively) and increased DOPAC content (2.9- and 4.2-fold, respectively). Continuous lobeline superfusion resulted in a diminished DA response (tachyphylaxis), even at concentrations (1 and 3 μM) which did not deplete DA content. To determine if lobeline administration in vivo depleted striatal DA content, rats were administered lobeline (1-30 mg/kg. s.c.) acutely or for 10 days. Surprisingly, lobeline did not deplete striatal DA content. Thus, concentrations of lobeline which robustly increase DA release *in vitro,* deplete DA tissue stores in vitro. However, lobeline does not appear to be toxic to DA neurons following in vivo acute or subchronic administration. These findings may be of significance with respect to lobeline inclusion in smoking cessation products.

References available from senior author.

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TIME COURSE OF DISSIPATION OF ACUTE TOLERANCE TO NICOTINE IN SMOKERS

K. A. Perkins, J. E. Grobe, and S. Mitchell

Knowledge of development and dissipation of acute tolerance to nicotine may help explain different temporal patterns of nicotine self-administration and differential magnitude of nicotine reinforcement in smokers. Many smokers report that the first cigarette of the day provides the biggest "boost", while succeeding cigarettes produce less effect, suggesting acute tolerance development. If nicotine effects are reduced following shorter latency since prior exposure, smokers may pace their smoking in such a way as to optimize the effects of each cigarette while minimizing withdrawal. The time course of dissipation of acute tolerance to nicotine per se was examined in 16 smokers (8M, 8F) participating in four sessions differing on pre-treatment dose or inter-dose interval prior to nicotine (20 ug/kg) challenge: placebo 30 minutes before, or nicotine (20 ug/kg) 30, 60, or 120 minutes before. These intervals were selected based on naturalistic studies showing that inter-cigarette interval in ad lib smoking generally ranges from 30-120 minutes. Nicotine and placebo were administered by measured-dose nasal spray. The measurement battery consisted of subjective (POMS, visual analog scales), cardiovascular (HR, BP, finger temperature), thermal pain detection, and behavioral performance measures (finger-tapping, handsteadiness, memory recognition).

Results demonstrated significant acute tolerance (*i.e.* smaller responses to nicotine challenge following nicotine vs. placebo pre-treatment) for most subjective measures and for HR. Acute tolerance dissipated with lengthening inter-dose interval for "dose strength" and arousal, but there was no significant tolerance dissipation for other measures. In contrast, nicotine pre-treatment resulted in acute sensitization of finger temperature response, which dissipated with lengthening interval. Nicotine generally increased performance and thermal latency responses, which were not significantly altered by inter-dose interval. These findings indicate that acute tolerance develops quickly to some subjective and cardiovascular effects of nicotine and that variability in inter-dose interval (*i.e.* interval between cigarettes) can produce variability in magnitude of some responses to nicotine. However, acute tolerance to most effects did not dissipate over two hours. This suggests that, following acute tolerance development from initial exposure (i.e. first few cigarettes of the day), most smokers generally obtain similar reduced magnitude of effects from each subsequent nicotine exposure (*i.e.* cigarettes smoked later in the day).

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THE ROLE OF NICOTINE DELIVERY RATE IN DEVELOPMENT OF SELECTIVELY TARGETED MEDICATIONS

J. E. Heningfield, A. J. Jenkins, K. Steinberg, R. M. Keenan, and E. J. Cone

Selective retention of clinically useful effects of nicotine with diminished toxic and addictive effects has been achieved by formulations which deliver nicotine transmucosally ("gum") and transdermally ("patch"). Our research has addressed the role of the delivery system as a determinant of the effects of potential nicotine replacement approaches. We summarize earlier research that demonstrated modulation of behavioral effects of nicotine by the delivery system, and new research that explored the role of nicotine delivery kinetics as a determinant of effects. Other relevant research findings were those by R. L. Balster and C. R. Schuster (1973). and H. DeWit, B. Bodker and J. Ambre (1992) which suggested that the reinforcing effects of cocaine and pentobarbital, respectively, were directly related to speed of drug administration. Recently, we administered 0, 0.75 and 1.5 mg nicotine intravenously to volunteers over 30, 60, 150, and 300 seconds. The volunteers were five male cigarette smokers who were approximately eight hour nicotine deprived at the time of testing. Each volunteer was tested with each dose of nicotine infused at the four rates. Placebo was administered to each subject at two rates. Measures of abuse liahility and samples of blood and saliva were collected prior to drug and over the following four hours. Preliminary analyses indicate that the magnitude of subjective and cardiovascular effects was directly related to the speed of drug delivery. Although preliminary, these data suggest that drug delivery rate is an important determinant of the nicotine's pharmacologic effects in humans. The findings have implications for the regulation of new forms of nicotine delivery that might be used to treat nicotine dependence and other medical disorders. Specifically, the findings are consistent with the concept that drug dosage forms which restrict the rate of nicotine delivery be labeled differently than those systems which readily provide rapid delivery of higher dosage levels. For example, a strong warning of the potential for abuse would be more appropriate for a rapid delivery system than for the presently marketed slow transdermal nicotine delivery systems.

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A NICOTINE PATCH REDUCES SUBJECTIVE AND OBJECTIVE MEASURES OF TOBACCO WITHDRAWAL

W. B. Pickworth, M. F. Butschky, and J. E. Henningfield

Although nicotine transdetmal delivery systems (patches) are claimed to promote smoking cessation through a reduction of the nicotine abstinence syndrome, nicotine patches have not been evaluated for efficacy on EEG and performance measures associated with tobacco withdrawal during the first days of abstinence. During four consecutive weeks, ten residential subjects smoked *ad libitum* on 4 d (Fri-Mon) and underwent monitored tobacco abstinence for 3 d (Tu-Th). On no smoking days, combinations of patches delivering 0, 10, 20 and 30 mg of nicotine were applied for 16 hours. Plasma nicotine levels averaged 18 ng/ml during *ad libitum* smoking and 26, 18, 10 and < 5 ng/ ml during the 30, 20, 10, and 0 patch conditions, respectively. Compared to *ad libitum* smoking, on days the subjects wore placebo patches (the abstinence condition) there were significant decreases in heart rate, increases in EEG theta power, decreases in EEG alpha frequency, and increased response times on cognitive performance tests, nicotine craving and other subjective measures of tobacco withdrawal. Physiologic signs of nicotine abstinence including EEG slowing and decreases in pulse rate were attenuated by the nicotine patches. The nicotine patches also decreased subjective ratings of withdrawal and nicotine craving and attenuated the slowing on the performance tests. The effects of the nicotine patches on EEG and performance measures were evident the first day of application (Tu), whereas their effect on subjective measures of withdrawal were most pronounced on Wednesday and Thursday. The 30 mg patch did not significantly differ from the 20 mg patch condition in reducing EEG and performance measures of nicotine withdrawal. These data, the first to explore the effects of the nicotine patch on short term enforced tobacco abstinence, tentatively support the effectiveness of nicotine replacement therapy for short term application.

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AFFILIATION:

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PILOT STUDY OF A NICOTINE VAPORIZER FOR SMOKING CESSATION

S. J. Leischow, F. Nilsson, M. Franzon, A. Hill, and P. Otte

A nicotine vaporizer - an oral puffing device that delivers nicotine - was found efficacious at increasing rates of smoking abstinence in one study but not in two others. Because abstinence rates increased as a function of nicotine vaporizer use, the present pilot study was designed to assess a method for increasing compliance and to assess factors related to abstinence.

METHOD: Thirty healthy smokers (54% female) participated in this open-label smoking cessation study. Prior to quit day subjects twice observed a videotape demonstrating proper vaporizer use, were asked to demonstrate vaporizer use, and were asked to use 4-20 vaporizers per day after cessation. Follow-up visits after quit day were at day two and weeks 1,2,3, and 6. Abstinence was determined by self-report and verified by breath carbon monoxide reading of <10 ppm.

RESULTS: The average number of vaporizers used per day was 5.4 at week one and 4.6 at week two. Fifty percent of the subjects were abstinent at week six (no slips after week 2). Abstinent subjects had average cotinine levels of 388 ng/ml at baseline, with an average cotinine replacement of 241 ng/ml (62%) at week three and 174 ng/ml (45%) at week six. Abstinent subjects (n=15) smoked fewer cigarettes per day at baseline (23.7 vs. 34.7, t=2.2, p=0.04) and had a lower baseline Fagerström Test of Nicotine Dependence score (4.6 vs. 6.2, t=2.3, p=0.03) than those who were unsuccessful (n=15). As Figures 1 and 2 show, any smoking within one week after quit day and any experience of adverse events during the study were related to treatment success.

Smoking at Week 6

Smoking During Week 1		yes	no
	yes	12	2
	no	3	13

$x^2 = 13.4$ ($p < 0.01$)

Figure 1. Week 1 Smoking & Success

Smoking at Week 6

Experienced Adverse Event		yes	no
	yes	12	5
	no	3	10

$x^2 = 6.65$ ($p < 0.01$)

Figure 2. Adverse Events & Success

The present pilot study suggests that a nicotine vaporizer can provide adequate nicotine when adequate training is provided, thus suggesting that such a method may have clinical utility and is worthy of continued Phase III evaluation.

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PSYCHOLOGICAL TREATMENT, NICOTINE GUM, AND DEPRESSION IN STUDY TREATMENT

S. M. Hall, R. Muñoz, V. Reus, K. Sees, G. Humfleet, C. Duncan

Earlier work (Hall *et. al.,* 1994) indicated that a cognitive-behavioral mood-management intervention might be differentially effective for smokers with a history of Major Depressive Disorder (MDD). The present study controlled for two variables not controlled for in earlier work: time in treatment and nicotine gum dose. Subjects (N = 198) were 53% female; 22% reported a history of MDD. Mean age = 39.7 years, SD = 9.5. All reported smoking at least ten cigarettes per day at study start (mean = 23.9, SD = 9.8). Subjects were randomly assigned to one of four experimental cells in a 2 X 2 factorial design: Cognitive-behavioral intervention vs. psychoeducational condition X 0 vs. 2 mg nicotine gum. There were five assessments: baseline, postreatment (Week 8), and 12, 26, and 52 weeks following treatment completion. Self-report and biochemical data on cigarette intake were collected. Measures of mood, pleasant events, and thinking patterns, conceptualized as process variables responsible for therapeutic effectiveness, were collected at these assessments. Gum use and gum dose identification conducted over an eight-week period. The cognitive-behavioral intervention focused on the development of skills to manage the affective distress associated with quitting smoking. The psychoeducational intervention provided health-related information and assisted individuals in developing personalized plans to quit smoking. Preliminary data analyses indicated (1) small and statistically nonsignificant differences in abstinence rates favoring the cognitive-behavioral condition. These data, combined with the earlier data and partial data from an ongoing study, suggest that although smokers with a depression history may be differentially aided in abstinence by intensive therapeutic support, optimal therapeutic content remains to be determined; (2) a significant gum dose X treatment condition effect at Week 8: differences between placebo and active gum were significant in the psychoeducational control but not in the cognitive-behavioral condition. Additional analyses will focus on process and compliance measures.

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AFFILIATION:

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TOBACCO SMOKING, TOBACCO DEPENDENCE AND SUSTAINED BOUTS OF DEPRESSED MOOD

E. O. Johnson and J. C. Anthony

We are studying a large epidemiologic sample of urban youth to shed light on processes and conditions linked to the occurrence of drug-related behavior, including a suspected causal linkage that leads from nicotine dependence to major depression. Annually, starting in 1989. we have measured initiation and level of tobacco use as part of a private interview with primary school students sampled for this study. In 1993, we added a new evaluation of major depression, and administered the Fagerstrom Test for Nicotine Dependence (FTND) to a sub-sample of 549 youths, then in grades seventh through eighth. Consistent with national school surveys, more than 30% reported that they had started to use tobacco. Nonetheless, all but five youths scored at the lowest level of the ten point FTND. Lifetime and recent smokers were more likely to have lifetime or currently active bouts of depressed mood that had lasted two weeks or longer ($p < 0.01$). These results set the stage for continuing longitudinal study of this epidemiologic sample during its high school years. Reciprocal relationships during early stages of nicotine dependence might well account for associations that have been observed between major depression and tobacco dependence in young adulthood. Analyzing longitudinal data collected annually through high school will enable us to test for these reciprocities, holding constant alternative explanatory variables we are measuring in this study.

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EFFICACY OF FREE TRANSDERMAL NICOTINE IN INDIGENT SMOKERS

T. S. Howard, J. R. Hughes, and D. Dameron

Smoking and smoking-related illnesses are more common in those of low socioeconomic status (SES). In addition, low SES smokers are less likely to stop smoking and are especially less likely to join intensive smoking cessation therapies. We studied the effectiveness of a free, brief intervention physician advice plus transdermal nicotine (TN) in this important, yet less-studied population of smokers. As part of a nationwide program, 1001 six week courses of a transdermal nicotine (TN) (Prostep) were donated free of charge to the VT Department of Health who distributed them to 40 physicians or physician groups. Physicians were instructed to prescribe the TN only to smokers of low income and under-insured. Upon receipt of TN, subjects (Ss) were asked to consent to a three-month telephone follow-up. We were able to contact 187 (67%) of the 281 Ss enrolled. One hundred and fifty-seven of these Ss (84%) used the patch. Our population was less educated, less likely to be employed and earned less annual income than the general Vermont population. At three months, 29% of Ss reported not smoking. Only 12% of Ss received cessation counseling. The average duration of patch use was three weeks. Our three-month quit rates are similar to those reported in 11 prior studies of TN in medical practice which used Ss of higher SES (x = 28%, range 14-45%). Thus, our results suggest providing free TN to indigent smokers is effective.

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RISK FACTORS FOR STARTING ILLICIT DRUG USE AMONG YOUTHS WITH NO CONDUCT DISORDER

C. G. Schütz and J. C. Anthony

There is a substantial body of research into childhood misbehavior and conduct disorder (CD) as explanations for illicit drug use, but less attention to the issue of whether risk factors for illicit drug use might vary by level of CD. We have started to investigate this issue by testing specifically for epidemiologic evidence that earning pay at a job or assuming other adult-like roles might signal an increased risk of starting illicit drug USC among youths with no CD or no more than minimal CD at the time they were assessed. These hypotheses were tested by conducting incident case-control analyses of self-report data gathered from 12-17 year olds sampled for the 1992 National Household Survey on Drug Abuse. Youths were excluded if they reported any positive responses to 11 questions on CD or if they reported starting illicit drug use before 1991 (*i.e.,* before current age minus one year). We used post-stratification to hold constant shared neighborhood characteristics, and multiple logistic regression models to estimate relative risk of starting illicit drug use in relation to the suspected risk factors. Out of 5123 youths at risk, we were able to match 162 incident cases who recently had started illicit drug use with 722 neighborhood controls. Adjusting for demographic factors and other factors such as enrollment in school and personal income, starting illicit drug use was independently associated with working for pay (RR:1.7, $p < 0.05$). There was some evidence implicating other adult-like roles, such as having children and being married, but these findings were based on relatively small numbers. Other significant associations involved age, being Hispanic, and stability of family residence. A parallel investigation of adolescents with at least one symptom of conduct disorder revealed the lack of association between starting illicit drug use and working for pay in this population. These findings are compatible with previous empirical research on the costs and benefits of adolescent work. This research indicated that there is a number of negative outcomes associated with adolescent work. Moving forward, we hope to examine similarities and differences in the profiles of risk factors for illicit drug use among youth with and without CD, and to broaden the profile of suspected risk factors to include potentially malleable influences that might be manipulated for prevention of illicit drug use, as well as other hypothesized vulnerability markers or indicators of increased risk.

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ASSOCIATION BETWEEN ILLICIT DRUG USE AND BEHAVIORAL REPERTOIRES IN MIDDLE SCHOOL STUDENTS

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Behavioral alternatives are among the determinants of drug use that have received attention in laboratory-based animal and human studies. The underlying notion is that availability of competing alternative reinforcers decreases drug-seeking behavior maintained by a drug reinforcer. This strategy is part of behavioral treatments that encourage patients to broaden their behavioral repertoire as a means of decreasing the reinforcing effects of drugs. To investigate this notion from a complementary perspective, we analyzed data from an epidemiologic sample of more than 1500 urban middle-school students, who had completed private interviews/questionnaires in Spring 1993 as part of a longitudinal field trial being conducted by the Johns Hopkins Prevention Research Center in collaboration with the Baltimore City Public Schools. The assessment included a questionnaire to assess current behavioral repertoire. Drawing upon a dichotomous variable factor analysis of the repertoire data, we constructed seven indicators to represent different behavioral domains and then used multiple logistic regression to estimate associations with illicit drug use, holding constant age and sex. Illicit drug use was associated independently with less involvement in religious activities and greater involvement in work and other adult-like roles ($p<0.05$). These results corroborate other evidence on the potential etiologic significance of behavioral repertoire in relation to the risk of illicit drug use. Since these results do not address issues of temporal sequencing or other limitations of cross-sectional data, the association will be reexamined in the continuing study of this epidemiologic sample. More specifically, it will be possible to determine the association of behavioral repertoires with initiation of drug use. In addition, a more complete analytic model may reveal interactions among the behavioral domains as well as the influence of other risk or protective factors.

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SERVICE NEEDS OF INJECTION DRUG USERS: GENDER DIFFERENCES

D. A. Mathis, H. Navaline, D. S. Metzger, and J. J. Platt

Female IDU's represent a large and increasing portion of the addicted population, and have particular treatment needs that differ from their male counterpartners. Data is presented from a recent study comparing the gender differences in characteristics and service utilization of subjects in methadone treatment. Subjects were 479 patients from five methadone maintenance clinics located in Philadelphia and Southern New Jersey. Subjects completed an extensive self-report questionnaire that measured basic demographics, education, sources of financial support, legal involvements, familial characteristics, substance abuse and treatment, and psychological symptomology. Psychological symptoms were also measured using the SCL-90 and Beck Depression Inventory. At six months post baseline, data were also collected using personal interviews with a randomly selected group of 165 participants. Important parameters that distinguish female addicts from their male counterpartners are presented, and the data clearly demonstrate that female addicts in methadone treatment have specific treatment needs. Females not only showed different addiction histories, more psychopathology, and more frequent dysfunctional family backgrounds than male addicts, but also had greater childcare responsibilities and fewer financial resources. Despite these pressing treatment needs, the females in this study showed significantly less treatment utilization than their male counterpartners. This lack of treatment utilization may result from: (a) methadone treatment services that do not meet the needs of female IDU's; (b) childcare responsibilities precluding participation in treatment programs; and (c) the difficulty of accessing a population that is rarely mandated into treatment.

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EVALUATING THE TREATMENT NEEDS OF OPIATE-ADDICTED WOMEN

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This study was designed to assess minority, inner-city opiate-addicted women along various dimensions of psycho-social functioning, and with respect to their response to participation in the Women in Treatment program, a component of the Substance Abuse Treatment Unit at Yale University. The program was designed in response to growing awareness that women's treatment needs have not been adequately met by traditional programs, which historically have catered to the needs of men. The difficulties women face when seeking substance abuse services are multifaceted, and include their lack of knowledge and inability to navigate a complex service system, the lack of adequate child care and transportation, as well as strong social sanctions against substance abuse during pregnancy.

Specifically, baseline and follow-up data were obtained from 69 women who enrolled in the program. Measures included the Addiction Severity Index, Beck Depression Inventory, Brief Symptom Index, Parental Bonding Instrument, the Dyadic Adjustment Scale, and the Perceived Social Support Scale. Preliminary findings indicate that, while subjects have extensive histories of opiate and cocaine abuse, the vast majority (over 75%) have received no formal treatment. Further, the data point to serious difficulties in subjects' childhood experiences, including paternal history of alcoholism among 40%. as well as perceptions among over a third of the women of their parents as having been emotionally rejecting during their development. Subjects also show elevated levels of several psychiatric disorders, most notably depression and anxiety, as well as poor dyadic adjustment and low social support from friends and family. Further, the majority are of childbearing ages and most have at least one child in their custody.

These problems constitute major therapeutic issues in designing treatment for women, and point to the need for sophisticated models of treatment which address high rates of comorbid psychopathology and interpersonal difficulties among them, as well as the importance of incorporating services which directly target children, who are a captive audience in a methadone maintenance program and clearly in need of such intervention.

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REDUCTION IN ADDICTION SEVERITY AMONG AFRICAN-AMERICAN AND HISPANIC PATIENTS RECEIVING STANDARD METHADONE MAINTENANCE: SIX MONTH TREATMENT OUTCOME

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Six month treatment outcome was investigated for 766 patients recruited for enrollment in methadone maintenance between May 1991 and April 1993. The mean age for the sample was 37.15 years with 486 (63.7) being male and 280 (36.3%) being female. In terms of race/ethnicity, 401 (52.3%) were African-American and 315 (41.1) were Hispanic. A majority (627, 81.9%) of patients successfully completed six months in treatment. Patients were given the Addiction Severity Index (ASI) at baseline and at six month follow-up, while the Treatment Services Review (TSR) was given for four consecutive weeks in the second month of treatment. Data analysis comparing baseline and six month ASI composite scores, examining TSR data, and comparing various ethnic/racial and gender groups was conducted using chi-square, t-tests, and analysis of variance. Results show significant reduction in ASI composite scores for patients (n = 507) who completed six months of treatment in the medical, drug, legal, and family/social areas ($p < .001$). Of note, patients who dropped out of treatment had a significantly higher alcohol composite score at baseline. Differences in utilization of services were found by gender with women utilizing more medical and family/social services and men utilizing more alcohol treatment services. A comparison of four ethnic/racial and gender groups showed significant differences by gender; men had higher employment and legal problem severity, while women had higher family/social and psychological problem severity. Findings suggest the need to match those with alcohol problems to interventions early in treatment to prevent drop-out -- just as the differential patterns of problem severity by gender suggest possible matching strategies.

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VIETNAM DRUG USERS TWO DECADES LATER. I. MORTALITY RESULTS

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In 1971. soldiers who fought in Vietnam were coming home to the United States by the thousands each month. A large number had been addicted to narcotics while in Vietnam. The White House Special Action Office for Drug Abuse Prevention initiated an epidemiologic study. Washington University conducted the first wave of face-to-face interviews with randomly-sampled returning veterans in 1972. The second wave followed in 1974. enriched by the inclusion of a matched nonveteran sample. The study found that the rate of opiate addiction dropped from 20% in Vietnam to 1% at one year after Vietnam, and that only 12% of those addicted in Vietnam had become readdicted to opiates at any time in the three years after returning from Vietnam. These findings indicated that narcotic addiction was more reversible than had been assumed.

A follow-up of this classic study is currently underway two decades after last contact (NIDA:DA07939). All study respondents are male and are reaching an average age of 44 years. A total of 1.229 veterans and nonveteran controls in the original study target sample was traced through multiple sources. We report preliminary results relating to mortality since veterans' departure from Vietnam, At present, 96 subjects have been identified as dead, yielding a cumulative death rate of 7.8% (96/1, 229) since 1971. Drug-use status ascertained through urinalysis at discharge appears to affect mortality. The death rate six years after discharge was 3.1% for drug-positive veterans, compared to 1.9% for drug-negative veterans, which is still higher than the six-year death rate (1.2%) for theater veterans discharged in 1964 in CDC's Vietnam Experience Study (1987). The mortality rate at 22 years after discharge is 13.5% among drug-positives, compared to 5.3% among drug-negative veterans (O.R. = 2.7, C.I. = 1.7-4.5). The rate for nonveterans is 1.4%, nine times less than the rate of drug-positive veterans. The median age at death is 36.3 among drug-positives, 33.5 among drug-negatives and 30.2 among nonveterans. Death rate differences among drug-positive and drug-negative veterans widens rapidly after veterans reach their med-30s. Of the 96 deceased, death certificates have been obtained for 55 veterans to date. Homicides, alcohol-related deaths, and drug-related deaths were reported only among drug-positive veterans (14%, 23%. 14% of 44). AIDS was cited for three cases, two were drug-positive and one drug-negative. The results will be updated as the remaining death certificates are received and new deaths discovered in the course of interviewing survivors.

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ATTITUDES, KNOWLEDGE, AND BEHAVIOR CONCERNING TB AMONG DRUG TREATMENT PROVIDERS IN TWO CALIFORNIA CITIES

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TB is especially prevalent in people with HIV disease or drug abuse problems. The CDC recommends that specific infection control policies and annual TB testing be implemented in drug treatment programs. The success or failure of these policies, however, may depend on the attitudes, knowledge and behavior of the drug treatment staff. Consequently, as a part of a larger survey of treatment providers, we administered nine questions concerning tuberculosis. We reviewed mailed survey data from public contract drug-treatment providers in San Francisco and San Jose, two California cities with populations over 700,000. A total of 889 surveys were mailed to 65 drug treatment programs, with a response rate of 55%. Treatment providers in San Francisco (SF) were more concerned about contracting TB at work than those in San Jose (SJ) (59.6% v. 34.9%, X^2=26.9, p<.0001)(N=488); San Francisco treatment providers were more likely to be TB tested than those in San Jose (85.4% v. 67.3%. X^2=22.2. p<.001)(N=491); more San Francisco treatment providers knew a person with TB (76.7% v. 63.9%. X^2=9.0, p<.003)(N=488). Treatment providers in both cities favored mandatory TB testing for patients (95% SF, 91% SJ) and for staff (93.7% SF, 92.6% SJ). The cities did not manifest differences in knowledge concerning TB. The annual case rate for TB in SF for 1992 was 47.7/100,000, while the rate in SJ was 19.2/100,000. The data from our study suggest that in areas with lower case rates of TB, an increased effort must be made to inform providers and patients about risk factors and prevention techniques about TB. An increased case rate of TB could result from inadequate surveillance and perceived lower risk of infection in substance abusing patients in lower prevalence rate communities.

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THE EFFECTS OF MORPHINE ON THE SELECTION OF SUCROSE AND ETHANOL

M. F. Stromberg, J. R. Volpicelli, B. L. Slifer, S. C. Meister, and R. R. Ulm

Endogenous opioid receptors appear to modulate the consumption of many palatable substances. Recently, particular attention has been focused on the role that endogenous opioids may play in promoting ethanol consumption. One specific approach used to examine the relationship between ethanol and opioids is the small dose morphine procedure. This procedure typically utilizes an injection of morphine, 1.0 to 1.5 mg/kg, s.c., shortly before a limited access to both an alcohol and water solution in a two-bottle preference test. Because nonselected rat strains find alcohol concentrations above 5 or 6% aversive, the ethanol solution is often adulterated with sucrose. A potential problem exists because the ingestion of sweet solutions, such as sucrose and saccharin, is also potentially modulated by endogenous opioid mechanisms. This experiment was designed to determine if the presence of sucrose in only the ethanol solution biased the choice of the rat in a two-bottle preference test with plain tap water as the alternative. Secondly, it sought to determine if the presence of sucrose was neutral with respect to the morphine-ethanol interaction or if morphine interacted with the sucrose-ethanol compound synergistically. The experiment used two groups. Group ES/W had access to a 6% ethanol, 5% sucrose solution in one bottle and plain tap water in a second bottle. Group ES/WS had access to a 6% ethanol, 5% sucrose solution in one bottle and a 5% sucrose solution in the second bottle. All rats were fluid deprived for 22 hours and given two hours access to the two bottles. Injections of either saline or morphine, 2.5 mg/kg, s.c., were administered 30 minutes before fluid access. The experiment contained the following treatments: baseline (21 days), saline injections (6 days), morphine injections (6 days), saline injections (3 days), and baseline three days.

During all experimental treatments rats in Group ES/W drank significantly more ethanol than tap water and significantly more ethanol than rats in Group ES/WS. Rats in Group ES/WS drank significantly more sweetened water than sweetened ethanol. Morphine injections produced a significant increase in ethanol consumption for Group ES/W, but not for Group ES/WS. A second experiment, with identical treatments, was conducted using a single group that had access to a 6% ethanol solution without sucrose and plain tap water. Morphine significantly increased the consumption of ethanol solution but the effect was not as robust as seen in the first experiment for Group ES/W. In summary, the results a small dose of morphine given shortly before the opportunity to drink can serve to prime the endogenous opioid system and occasion an increase in consumption of both ethanol and sucrose solutions. It is not entirely surprising that the endogenous opioid system serves to modulate the consumption of many palatable solutions. This does not necessarily lessen the importance of the relationship between opioids and ethanol consumption. However, the results do suggest that particular attention must be paid to insure that adequate controls are included in the design of experiments where compound stimuli are used.

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ETHANOL ATTENUATES THE SEVERITY OF NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

T. A. Kosten, S. Muly and W. J. Shoemaker

Recent research suggests that the glutamate/NMDA system is involved in long-term effects of chronic drug exposure. For example, morphine dependence, as assessed by the severity of naloxone-precipitated opiate withdrawal, is attenuated by co-treatment with the noncompetitive, excitatory amino acid (EAA) antagonist, MK-801 (Trujillo & Akil, Science 251:85-87, 1991). Because ethanol (EtOH) is a putative EAA antagonist, we tested whether co-treatment of EtOH with morphine would attenuate the development of morphine dependence similar to the effects of MK-801 co-treatment.

METHOD. Three groups of rats (n=10 ea) received morphine injections (10 mg/kg, s.c.) twice daily (9 am and 9 pm) for 9 days: 1) the EtOH group received EtOH infusions (0.5 g/kg, 10% solution) via oral gavage; 2) the MK-801 group received MK-801 injections (0.05 mg/kg. i.p.) and; 3) the control group received either water via oral gavage or i.p. saline injections 30 min prior to all morphine injections. On the 10th day, about 12-15 hr past the last morphine injection, spontaneous withdrawal signs were rated for 15 min. Then, nuloxone (4 mg/kg, s.c.) was given to precipitate withdrawal. Ratings (0-3) of 14 withdrawal signs were tabulated for 3 contiguous 15 min blocks by raters blind to treatment condition. Severity ratings for each withdrawal sign (e.g. ptosis, salivation, chewing, etc.) were summed across the 3 prccipituted withdrawal periods and all sign ratings were summed for each period.

RESULTS. Spontaneous withdrawal was low (≤ 1) and did not differ across groups. Total naloxone-precipitated withdrawal, summed across the 3 periods, was 16.0 ± 2.3 for controls which was significantly greater than the EtOH (7.0 ± 1.0) and MK-801 (9.1 ± 1.4) groups, $p<.03$. There were group differences in chewing and irritability, p's$<.05$, and trends for stretching and tremor, p's$<.10$, with greater severity in controls. Although withdrawal ratings did not differ by group during the first 15 min, they were significantly less in the EtOH and MK-801 groups during the last two 15 min periods, p's$<.05$.

DISCUSSION. The results of this study confirm those of Trujillo & Akil (1991) in that MK-801 attenuates the development of morphine dcpcndence. as assessed by the severity of naloxone-precipitated opiate withdrawal. We have extended these findings to show that EtOH also attenuates morphine dependence. This effect of EtOH may occur through its EAA antagonist action. Furthermore. these findings suggest that the co-abuse of alcohol among heroin addicts may be due to alcohol's ability to attenuate opiate withdrawal.

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A PRIMATE MODEL OF POLYDRUG ABUSE: IMPLICATIONS FOR EVALUATION OF NEW MEDICATIONS

N. K. Mello, S. S. Negus, S. E. Lukas, J. M. Drieze, and J. H. Mendelson

Concurrent opiate and cocaine abuse is an increasingly frequent form of polydrug abuse. Combinations of pharmacologically dissimilar drugs complicate the search for effective treatment medications. We now report the development of a primate model of simultaneous cocaine and heroin (*i.e., "speedball"*) self-administration that should be useful for preclinical evaluation of new medications for drug abuse treatment. Cocaine-experienced monkeys were given access to intravenous cocaine (0.001-0.1 mg/kg/inj) or heroin (0.0001-0.03 mg/kg/inj) alone, then the reinforcing effects of cocaine (0.001, 0.01 and 0.10 mg/kg) and heroin (0.0001 and 0.001 and 0.01 mg/kg/inj) combinations were examined. Drugs and food (1 gm banana pellets) were available in four daily sessions on a second-order FR4 (VR 16:S) schedule of reinforcement. Typical inverted U shaped dose effect curves were obtained for cocaine and for heroin alone. Simultaneous administration of cocaine (0.001 mg/kg/inj) and heroin (0.0001-0.01 mg/kg/inj) also resulted in an inverted U-shaped dose effect curve which was equivalent to the dose effect curve for heroin alone. When the cocaine dose was increased to 0.01 and 0.1 mg/kg/inj, the ascending limb of the speedball dose effect curve was elevated in comparison to heroin alone. Self-administration of the highest dose of heroin (0.01 mg/kg/inj) in combination with cocaine was similar to heroin alone. There was a cocaine and heroin dose-dependent decrease in food-maintained responding when each drug was studied alone. Speedball combinations also decreased food self-administration as much or more than heroin alone. The reinforcing effects of cocaine and heroin combinations were not addictive over the dose-range studied. Higher drug doses were not examined because pilot data indicated toxic effects. These data demonstrate the feasibility of maintaining polydrug self-administration in the primate model. This model should be useful for evaluating the effects of new medications for drug abuse treatment as well as for examining the relative reinforcing properties of cocaine and heroin combinations. Further studies to analyze cocaine and heroin interactions are now ongoing.

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NO EVIDENCE FOR VENTRICLOMEGALY IN POLYSUBSTANCE ABUSERS: A VOLUMETRIC MAGNETIC RESONANCE IMAGING STUDY

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In contrast to the growing documentation of quantitative structural abnormalities in the brain of alcoholics (Cala and Mastaglia 1981; Ron *et al.,* 1983), much less attention has been paid to cerebral structure in subjects with histories of drug abuse. Several studies yielded controversial results with regard to assessments of cerebral ventricles in subjects who abused illicit substances (Pascual-Leone *et al.,* 1991. Strang and Gurling 1989, Hill *et al.,* 1979, Co *et al.,* 1977). These studies were limited by confounding factors related to selection of subjects and experimental techniques. In the present study, magnetic resonance imaging (MRI) scans were performed on 10 polydrug abusers and 10 normal controls. Subjects were 21 - 39 years of age, and showed no illness other than substance abuse in a complete physical examination and standard diagnostic tests. MRI scans were acquired either on a 0.4 Tesla or a 1.5 Tesla scanner. An axial T1-weighted scan with 25 slices of 4-mm thickness, was obtained from each subject. The scan was interleaved, with no gaps between slices. The ventricles and brain tissue were segmented using a semi-automatic method. The lateral ventricles and a brain slab were reconstructed using the ANALYZE© program. Volumes of the reconstructed structures were then calculated. The brain slab contained ten MRI slices (including the first slice showing the lateral ventricles and the nine adjacent, inferior slices). Ventricle-to-brain ratio (VBR) was defined as the product of 100 and the quotient obtained by dividing the volume of the lateral ventricles by the difference between the volume of the brain slab and the volume of the lateral ventricles. Validity of using the brain slab to calculate VBR was tested by comparing VBRs calculated by using the volumes of the whole brain and the brain slab in each of four normal subjects who received a volumetric Spoiled Grass MRI scan that acquired data from the entire brain. Planimetric assessments were also conducted on the same set of data using the IMAGE® program. Areas of the lateral ventricles and the brain were measured on the slice depicting the lateral ventricles at their maximum area. No significant correlation was found between age or education and VBR. There was no significant difference in VBR between polydrug abusers and normal controls, nor was there any tendency toward ventriculomegaly in the substance abuse group. Therefore, the present findings provide no evidence that brain structure of relatively young and physically healthy polydrug abusers is abnormal, as assessed by volumetric MRI analysis of VBR. Comparison of planimetric and volumetric measures indicates that the shape of the lateral ventricles, slice selection, and partial volume effects could have substantial impact on planimetric measures.

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BUPRENORPHINE TREATMENT IMPROVES BRAIN PERFUSION ABNORMALITIES IN MEN WITH CONCURRENT COCAINE AND HEROIN DEPENDENCE: A SPECT BRAIN IMAGING ANALYSIS

J. H. Mendelson, B. L. Holman, S. K. Teoh, J. Levin, and N. K. Mello

Significant brain perfusion abnormalities have been detected in cocaine-dependent polydrug users (Holman *et. al.,* J. Nucl. 31:1456-1461, 1990) and improvement in regional cerebral blood flow occurs following protracted abstinence (Holman *et. al.,* J. Nucl. 34:723-727, 1993). The purpose of this study was to determine if buprenorphine pharmacotherapy reversed brain perfusion abnormalities. Fifteen men with concurrent cocaine and heroin dependence (DSM III-R) received ^{99m}Tc-HMPAO SPECT studies one day prior to and four days following administration of placebo or 6-12 mg of buprenorphine sublingually. SPECT analysis were carried out on a blind basis with respect to treatment regimen. Men who received placebo had no significant improvements in cerebral perfusion abnormalities. In contrast men who received either 6 or 12 mg of buprenorphine had significant reversal of cerebral perfusion abnormalities within four days following induction of buprenorphine pharmacotherapy. These findings will be discussed with respect to safety and effectiveness of buprenorphine treatment for polydrug dependence as well as advantages of buprenorphine as an analgesic for individuals at risk for cerebral perfusion disorders.

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DEPRESSION IN COCAINE ABUSING OPIOID ADDICTS TREATED WITH EITHER BUPRENORPHINE OR METHADONE

D. M. Ziedonis, C. Farren, and T. R. Kosten

PURPOSE AND METHODS: Depression and cocaine abuse are common problems and poor prognostic factors among opioid addicts. In this 24 week double blind randomized trial, the impact of depression on addiction treatment outcomes was compared in 111 cocaine abusing opioid addicts. Patients were randomized to either methadone (METH. 35 mg or 65 mg, n = 59) or buprenorphine (BUP, 2 mg or 6 mg, n = 52). Thirty-one patients (26%, BUP n = 13, METH n = 18) were diagnosed with current depression using DSM-III-R criteria and the LEAD procedure. Substance abuse was diagnosed with DSM criteria and urine toxicology.

RESULTS AND CONCLUSIONS: Overall, the METH group had better retention and urine toxicology outcomes than the BUP group. Depressed patients in both medication groups had better retention (61% completed the study versus 44%, $p < .05$) and less cocaine usage overall (44% cocaine positive urines versus 65%, $p < .05$) than the non-depressed patients. However, the depressed patients increased their cocaine usage during the trial (35% cocaine positive urines in the first month compared to 51% in the last month) while the non-depressed patients on BUP had the worst outcomes. For the depressed patients, there were no differences between METH or BUP in retention similar outcomes on either BUP or METH. More specific anti-depressant interventions should be considered for depressed patients receiving buprenorphine or methadone maintenance treatment.

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DIFFERENTIAL REINFORCEMENT OF SUSTAINED COCAINE ABSTINENCE IN INTRAVENOUS POLYDRUG ABUSERS

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Incentive therapies designed to reinforce drug abstinence have been effective in reducing drug use. Recent research suggests particular efficacy for a novel system in which patients earn vouchers exchangeable for goods and services for providing drug-free urines. This system used in combination with intensive behavioral treatment has produced impressive results in the treatment of cocaine dependence (Higgins *et al.,* 1993). One study showed that the voucher system improved treatment retention (Higgins *et al.,* in press); however, due to substantial dropout of control subjects, that study did not have the urinalysis data to assess fully the effects of the voucher system on cocaine use independent of treatment retention. The current study evaluated the efficacy of the voucher-based abstinence reinforcement system in reducing cocaine use. Thirty seven inner-city intravenous cocaine abusers receiving standard methadone maintenance treatment were randomly assigned to an abstinence reinforcement or a control group. For 12 weeks, abstinence reinforcement subjects received vouchers for providing cocaine-free urines. A unique and important aspect of the voucher program is that the monetary values of the vouchers increased as the number of consecutive drug-free urines increased. A continuously abstinent subject in this group could earn up to $1155 over 12 weeks. Control subjects received noncontingent vouchers. Over 80% of subjects in both groups completed the 12-week evaluation period. Abstinence reinforcement subjects achieved significantly longer durations of sustained cocaine abstinence than controls (P = 0.001). Nine abstinence reinforcement subjects (47%) achieved between 7 and 12 weeks of sustained cocaine abstinence. Only one control subject (6%) achieved more than two weeks of sustained abstinence. Furthermore, abstinence reinforcement subjects rated the overall treatment quality significantly higher than controls (P=.002). These results further suggest that voucher-based reinforcement for sustained abstinence is a promising approach for the treatment cocaine abuse.

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MARIJUANA USE IN COCAINE-DEPENDENT PATIENTS: ASSESSMENT AND TREATMENT

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The majority of cocaine-dependent persons seeking treatment also use marijuana. While such use is readily documented in this clinical population, there is a dearth of scientific information concerning differences between cocaine-dependent patients who do and do not use marijuana, or the influence of marijuana use on treatment outcome. This absence of information prevents clinicians from making empirically-based decisions regarding how to approach marijuana use in this clinical population. This study assessed marijuana use and associated factors in 199 persons seeking outpatient treatment for cocaine dependence. Those who used marijuana were compared to those who did not on sociodemographic and drug-use characteristics. Sixty-five percent of these patients reported marijuana use during the month prior to treatment and 21% were marijuana dependent. Marijuana users reported greater psychosocial impairment, depressive symptomatology, drug-use severity, and drug-related adverse consequences than nonusers. The relationship between continued marijuana use during treatment and treatment outcome was then examined in 75 patients who received a 24-week. outpatient behavioral treatment for cocaine dependence. Eighty percent of those who reported marijuana use prior to treatment continued use during treatment. Treatment retention did not differ between those who used marijuana and those who did not. Marijuana users achieved fewer weeks of continuous cocaine abstinence during treatment, but this difference was not statistically significant (*e.g.,* Weeks 1-12: 5.9 weeks ± 4.3 vs. 7.4 weeks ± 4.5, $p = 0.15$). Marijuana users also tended to show less improvement in other areas of psychosocial functioning as evidenced by higher post-treatment Addiction Severity Index subscale scores, but these differences were not statistically significant.

In summary, marijuana users presented for treatment with greater psychosocial impairment than nonusers. No robust relationship, however, was observed between continued marijuana use during treatment and treatment outcome. The generality of these findings are limited in that (1) this relationship was examined only in the context of one specific type of outpatient treatment, and (2) the retrospective design of the study did not allow the optimal controls or comparisons needed to clearly determine how marijuana use influences outcome of cocaine-dependence treatment. Prospective trials that experimentally manipulate marijuana use during treatment are needed to address this issue. Such trials will provide the information necessary to develop effective guidelines for addressing marijuana use in persons seeking treatment for cocaine-dependence.

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THE PREVALENCE OF NICOTINE AND CAFFEINE USE AND DEPENDENCE AMONG ALCOHOLICS AND NON-ALCOHOLICS

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As one of the DSM-IV field trial sites, we completed a random-digit-dial telephone survey of 196 residents, of greater Burlington, VT. Lifetime prevalence rates of alcohol dependence using DSM-III-R criteria were 5% for severe dependence (7-9 criteria), 9% for moderate dependence (5-6 criteria), 17% for mild dependence (3-4 criteria), and 69% for no alcohol dependence (0-2 criteria). Among these four groups, the prevalence of current smoking was 56% for those people meeting the severe alcohol dependence criteria, 39% for moderate, 21% for mild, and 18% for no dependence ($p<.01$). The one year prevalence rates of nicotine dependence were 44% for those with severe alcohol dependence, 39% for moderate, 20% for mild, and 12% for no alcohol dependence ($p<.01$). Among only current smokers ($N = 43$), the prevalence of nicotine dependence was 80% for severe, 100% for moderate, 86% for mild, and 67% for no alcohol dependence ($p=.10$-$.15$). No differences in the prevalence of caffeine use and mean mg of caffeine/day were found among these four groups; however, the one year prevalence rates of "caffeine dependence" using DSM-III-R generic substance dependence criteria were 56% for those people meeting the severe alcohol dependence criteria, 53% for moderate, 41% for mild, and 25% for no dependence ($p<.01$). These results suggest that persons with a lifetime history of alcohol dependence are more likely to meet criteria for caffeine and/or nicotine dependence than those without a history of alcohol dependence.

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DRUG TREATMENT HISTORIES OF INDIVIDUALS ABUSING A SINGLE DRUG COMPARED TO HISTORIES OF POLYDRUG ABUSERS

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Individuals who abuse different numbers of substances may develop different preferences for seeking admission to modalities of drug treatment. Medical records of 1,198 admissions to an inpatient hospital detoxification unit (detox) were analyzed in this study. Admissions were classified as current single or polydrug abusers. The most common primary addictions were to alcohol and to heroin. Numbers of past admissions to completed drug abuse treatment were categorized by type: detox, methadone, and all others. Admissions were totaled and ranked to determine the type of treatment entered most frequently.

Comparison within genders revealed a difference in treatment histories between single and polydrug abusers for males ages 26 to 30 only. Polydrug abusing males in this age group had a history of statistically significantly more previous admissions (x^2=7.81, $p \leq .05$, 2 d.f.) than single drug abusers in the same age group.

Comparisons between genders revealed no differences in treatment histories for single drug abusers. For polydrug abusers, there was a statistically significant difference for most age groups. In polydrug abusers ages 17 to 25, more women reported past admissions to detox and to methadone programs, while more men reported admissions to all other treatments (x^2=7.34). For ages 26 to 30, women reported more previous admissions to methadone programs; men reported more admissions to other treatment (x^2=11.76). In the 31 to 35 age group, men using multiple drugs reported more admissions than women (x^2=4.54, n.s.). Male polydrug abusers ages 36 to 40 reported more treatment of all types than women (x^2=7.93).

These results indicate that, for most age groups, treatment histories of single and polydrug abusers do not differ when data are compared within gender. The one exception is males as they approached age 30. At this time, histories of male polydrug abusers reflected increased admissions. Possible explanations are that men do not seek treatment before they develop medical complications of addiction or until external factors influence admission.

Before age 30, polydrug-abusing women reported more previous treatment than men. After age 30, the admissions of men surpassed those of women. This may be a reflection of treatment priority given to women during childbearing years and of a tendency of younger men not to enter treatment.

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DISCRIMINATIVE STIMULUS EFFECTS OF EPHEDRINE AND PHENYLPROPANOLAMINE

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After the 1970 Controlled Substances Act was instated, the supply of legally available amphetamines was eventually reduced by 80%. To fill the demand this produced, "look-alike" drugs have appeared containing legally available stimulants and stimulant combinations. The primary ingredient is usually a high dose of caffeine. In addition, most also contain one or more of the phenylethylamines, structural analogs of amphetamine. Ephedrine and phenylpropanolamine are the most commonly used. Little study has been done of the behavioral pharmacology of these over-the-counter stimulants, but there is suggestion that they may have abuse potential.

In this study, stimulant users learned a three-choice discrimination between d-amphetamine (30 mg), caffeine (400 mg) and placebo, identified to them by letter code only (A, B, and C). All drugs were administered orally. In addition, physiological, subjective, and performance measures were conducted before and after drug administration. Discrimination training involved administration of each training drug twice in randomized block order. Subjects were then exposed to each drug in randomized blocks until they reached a criterion of five of six correct discriminations during the acquisition testing phase. Generalization testing determined dose-response functions for ephedrine (0, 25, 50, and 100 mg), phenylpropanolamine (PPA; 0, 25, 50, 100 mg), and the combination of ephedrine and PPA in a 1:2 ratio (0, 6.25:12.5, 12.5:25, and 25:50 mg).

Subjects learned the discrimination in an average of 11 sessions (Range=5-17). Both drugs and their combination produced dose dependent decreases in placebo-appropriate responding. Ephedrine partially substituted for caffeine or d-amphetamine with increasing dose; PPA partially substituted for caffeine across the dose range; and the drug combination produced only modest caffeine and d-amphetamine responding. Ephedrine produced significant dose related increases on visual analog scales (VAS) of drug strength, drug liking, and good drug effects. In addition, ephedrine produced dose dependent increases on the BG and A scales of the ARCI, which are sensitive to stimulant effects and increases on the MBG scale, which is sensitive to euphoriant effects and may be indicative of abuse potential. Neither PPA nor the ephedrine:PPA combination produced differences from placebo on any of the VAS items or ARCI scales. In conclusion, ephedrine shares discriminative stimulus functions in common with caffeine and d-amphetamine, a CNS stimulant with known dependence potential. PPA and the ephedrine:PPA combination produced mainly placebo and caffeine appropriate responding. The three-choice procedure presented here may allow a more fine-grained discrimination of drug effects than traditional two-choice procedures.

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SUBJECTIVE EFFECTS OF INTRAVENOUS CAFFEINE IN DRUG ABUSERS

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This study characterized the effects of intravenously administered caffeine in subjects with histories of polydrug abuse, including cocaine, who resided on a residential behavioral pharmacology research unit. Subjects reported histories of moderate dietary caffeine consumption and were maintained on a caffeine-free diet throughout the study. Sessions were conducted in an isolated experimental room. After placement of the intravenous catheter, subjective effect ratings were obtained before and repeatedly for 60 minutes after a 4 ml intravenous injection over a 10 second period. A single-blind dose run-up to 300 mg/70kg was conducted to assure safely and tolerability. In the subsequent double-blind cross-over phase, five conditions (placebo, 37.5, 75, 150 and 300 mg/70 kg body weight) were assessed, generally twice each in counterbalanced order. At least 24 hours separated each condition. Results from 10 subjects generally showed orderly dose-related increases in ratings of "drug effect," "high," "good effects" and "liking." Maximal effects were observed two minutes after injection and typically progressively decreased across the 60 minute session. The highest dose of caffeine was almost always identified as "stimulant (like cocaine, amphetamine)" even though subjects were told that they could receive a wide range of sedative, antihistamine or stimulant compounds. Anecdotally, most subjects reported being reasonably certain that they had received cocaine. The robust effects observed with caffeine in the present study suggest that intravenous administration may be well suited for investigating certain behavioral pharmacological effects that have been elusive in previous caffeine studies involving oral administration. Moreover, the similarity between the subjective effects of intravenously administered caffeine and cocaine in subjects with histories of drug abuse suggest that intravenous caffeine may be a useful model for studying basic behavioral and pharmacological variables that contribute to the widespread use and abuse of stimulant drugs.

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METHYLPHENIDATE EFFECTS IN COCAINE DEPENDENT PATIENTS: LABORATORY ASSESSMENT AND TREATMENT OUTCOME

J. D. Roache, W. Thompson, J. Schmitz, and J. Grabowski

This is a preliminary report of an ongoing double-blind, placebo-controlled outpatient treatment study evaluating the efficacy of methylphenidate for the treatment of cocaine dependence. Due to safety concerns, patients received their initial doses of methylphenidate or placebo treatment in the human laboratory where vital signs, psychomotor/memory performance, and subjective mood, perceived drug effects, and cocaine craving were assessed at hourly intervals. For this report, 16 patients received methylphenidate and 13 received placebo.

Methylphenidate doses were 5 mg + 20 mg - SR (sustained release) at 0800 hours and 20 mg - SR at 1130 hours. Methylphenidate produced significant, but modest, stimulant effects as revealed by increases in heart rate and subjective ratings of feeling "shakey" and "anxious". Compared to placebo, methylphenidate did not increase significantly, measures predictive of abuse liability including drug liking and ARCI-MBG ratings. Similarly, methylphenidate did not significantly alter cocaine craving on four visual analog ratings of craving (crave, desire, would use, want to buy). Of the 27 patients who entered outpatient treatment following the laboratory evaluation, 16 completed treatment for a 59.3% retention rate; there were no differences between the groups in treatment retention. Also, there were no significant differences in the mean proportion of cocaine-free urines (approximately 40% for both groups).

These results do not support the concerns that methylphenidate would produce dangerous stimulant effects in cardiovascular parameters or abuse liability. Neither, have we detected any evidence for a therapeutic effect of methylphenidate in the treatment of cocaine dependence. These data are limited by the use of a single dose of the sustained release preparation, but suggest that further evaluations of "agonist-type" treatments for cocaine dependence can proceed safely.

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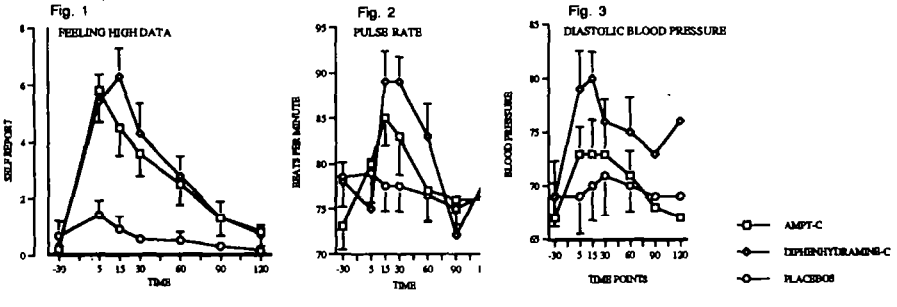
EFFECT OF AMPT ON RESPONSE TO COCAINE CHALLENGE

S. M. Stine, I. L. Petrakis, P. I. Jatlow, J. H. Krystal, T. R. Kosten, and D. S. Charney

Trearment with alpha-medlyl-para-tyrosine (AMPT), a tyrosine hydroxylase inhibitor, has been shown to diminish the euphoria after amphetamine (Jonsson *et. al.,* 1971). We have investigated the abilily of AMPT to diminish the effects of cocaine. AMPT may reduce cocaine induced euphoria after cocaine by decreasing dopnmine (DA) synthesis and release. This project. studied 10 active non-treatment-seeking cocaine abusers. All subjects had histories of intranasal cocaine use, and were current active abusers. Subjects were medically cleared, treated with AMPT (1 gm p.o. TID) or diphenhydramine (50 mg p.o. TID, an "active" placebo chosen for its sedative properties) then challenged with 2 mg/kg cocaine intranasally or placebo. Each subject received all four combinations of AMPT vs. diphenhydramine and cocaine vs. placebo in a blinded balanced for order design. Physiological assessments consist of blood pressure, EKG, heart-rate, and respiratory rate. Psychological assessments include repeated self-reported ratings of a variety of responses such as high, craving, rush, sedation and anxiety. Laboratory analyses consisted of repeated blood levels of cocaine to detect possible pharmacokinetic ineractions as well as prolactin and homovanillic acid to provide information concerning dopaminergic function.

Subjects reported a diminished cocaine "high" after AMPT treatment when compared with placcho (see Figure 1). Results were tested for significance using a three-way analysis of variance procedure. AMPT and Diphenhydramine conditions were significantly different (df = 9; F = 4.654; < .05) over time points +15, +30, and +60. No change was seen in "rush", "craving", "sleepiness", etc. However, AMPT pretreatment did lower physiological response (heart rate and blood pressure) to cocaine in this sample (see Figures 2-3). Three way analysis of variance revealed significant differences between AMPT and diphenhydramine across all seven time points for pulse rate (df = 10; F = 6.628; P < .02), systolic blood pressure (df = 10; F = 10.2; p < .009), and diastolic blood pressure (df = 10; F = 16.78; P < .002). The observed effects are not explained by differences in serum cocaine levels after AMPT vs. diphenhydramine. Prolactin levels were higher in AMPT treated subjects (mean of 17 ng/kg and SEM of 3 for AMPT and a mean of 7.3 ng/kg and SEM if .6) indicating expected decrease in dopaminergic activity. There was no observed effect of cocaine on prolactin levels. AMPT merits further investigation in studies of cocaine response as well as a possible agent in the treatment of cocaine abuse and dependence. Supported by V.A. Merit Award.



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LIMBIC ACTIVATION BY IV PROCAINE IN COCAINE ADDICTS

B. Adinoff, K. Brady, S. Sonne, S. Katz, and C. H. Kellner

The positive reinforcing effects of cocaine are generally considered to be a consequence of increased dopamine at the synapse. Subsequently, pharmacologic approaches in the treatment of cocaine addiction have generally focused upon the manipulation of the dopaminergic system. Cocaine also stimulates the limbic system, and previous investigators have suggested that a state of permanent limbic neuronal hyperexcitability may be present in cocaine addicts.[1] Procaine selectively activates limbic structures, presumably through its inhibition of neuronal conductance. In order to assess the state of limbic sensitivity in cocaine addicted patients, we administered procaine to patients with cocaine dependence.

METHODS: Nine hospitalized cocaine dependent patients were studied between two and three weeks of abstinence. Three infusions were administered iv: (1) placebo, (2) 0.46 mg/kg procaine, and (3) 1.84 mg/kg procaine. The following questionnaires were administered to assess the effects of each infusion: (1) similarity to cocaine, (2) cocaine craving,[2] (3) sensory-cognitive-mood disturbances, and (4) a checklist of psychiatric symptomatology (SCL90).

RESULTS: Six of the nine subjects identified the higher procaine dose as almost identical to a cocaine high. Repeated ANOVA showed significant differences across dose for similarity to cocaine experience ($p < 0.003$). cocaine craving ($p = 0.005$), and sensory-cognitive-mood disturbances ($p< 0.001$), as well as somatization ($p<0.02$), obsessive-compulsive symptoms ($p<0.02$), phobic anxiety ($p=0.05$), interpersonal sensitivity ($p=0.003$), anxiety ($p<0.007$), global severity ($p<0.005$), and positive symptoms ($p<0.005$) (from the SCL90). All of these ratings, except for somatization. were significantly higher ($p<0.05$) following infusion of 1.84 mg/kg procaine than following either placebo or 0.46 mg/kg procaine.

CONCLUSIONS: These findings are similar to those previously reported by Fischman *et al.*[3] Procaine has only 1% of cocaine's affinity for the dopamine reuptake receptor.[4] Our findings suggest that limbic activation in cocaine addicted patients may, without marked direct involvement of dopaminergic systems, induce a cocaine-like experience. Procaine may therefore offer a useful mechanism to investigate putative limbic neuronal sensitization in cocaine addiction. Further studies are required to determine if the cocaine-like effects of procaine are a consequence of its effects at the dopaminergic receptor or its effects upon the membrane conductance.

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EFFECTS OF ACUTE AND REPEATED INTRAVENOUS COCAINE IN HUMANS MAINTAINED ON METHADONE

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Cocaine use is a major problem in methadone-maintained opiate abusers. Sixteen adult methadone-maintained i.v. cocaine users, residing on a CRC, participated in eight laboratory sessions under each of two conditions: cocaine one hour after daily methadone and cocaine two hours before daily methadone. The conditions were separated by three to five weeks. During the first five sessions the cardiovascular and subjective effects of single i.v. doses (0, 8, 16, 32, 48 mg/70 kg) were determined and during the last three sessions the effects of four doses of 0, 8 or 32 mg/70 kg administered at 14 minute intervals were determined. Single cocaine doses produced dose-dependent increases in subjective effects similar to those reported for cocaine and morphine combinations: increased ratings of Alert, Anxious, High, On Edge, Good Drug Effect, Drug Liking, Drug Potency, Drug Quality, Stimulated, Opiate Symptom scores and Peak HR, DP, SP and RPP. When 8 mg cocaine was administered after methadone, significantly smaller subjective effects were reported than when it was administered before methadone. Increases in blood pressure following single cocaine doses were greater when cocaine was given after methadone. Subjects maintained on higher methadone doses (> 60 mg) reported larger cocaine effects on several measures including ratings of Good Drug Effect, Dose Liking, and Dose Quality, compared to subjects maintained on lower methadone doses. The timing of methadone administration had no effects on response to repeated doses of cocaine. Methadone patients who self-administer cocaine experience a profile of subjective effects similar to that observed following the administration of heroin-cocaine combinations, or "speedballs." There was no evidence that higher methadone doses attenuated the effects of cocaine. In contrast, there was evidence to suggest that a higher dose increased some of the effects of cocaine. While it has been suggested that maintenance on large methadone doses will decrease cocaine abuse, our data indicate that such an effect of high methadone doses is not related to a blocking of the subjective effects of cocaine.

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COCAETHYLENE: PHARMACOLOGY, PHYSIOLOGY, AND BEHAVIORAL EFFECTS IN HUMANS

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Simultaneous abuse of cocaine and alcohol is a common occurrence. We have recently shown that cocaethylene, the ethyl ester of benzoylecgonine, is formed in humans engaging in concurrent use of cocaine and ethanol. We obtained an IND for administration of cocaethylene fumarate (EC) by nasal insufflation. A study to evaluate the effect of EC in humans using cocaine as a comparator is ongoing at our institution. An interim analysis of the first six subjects to complete the study is reported.

Four drug administration sessions were conducted over an eight day using a double-blind, placebo-controlled, limited randomization design. The four test days included the following drug administration schedule: EC 0.5mg/kg; EC 1mg/kg; cocaine 1mg/kg, or placebo. Physiological and subjective (visual analog scales, "High" scale) measures and plasma cocaine or EC levels were assessed for 600 minutes after study drug administration. The area under the concentration versus time curve was greater for both EC 1.0 mg/kg and EC 0.5 mg/kg than for cocaine 1.0 mg/kg. Peak plasma concentration for the study drugs occurred at the 30 minute time point. Peak EC 1.0 mg/kg concentration was 210 ± 51 and for EC 0.5 mg/kg was 105 ± 23, while for cocaine 1.0 mg/kg the peak plasma concentration was 117 ± 19. The elimination half-life was approximately 144 minutes for EC and 89 minutes for cocaine ($p=0.03$). There was a trend ($p=0.065$) toward decreased diastolic blood pressure following cocaethylene administration relative to cocaine. The effect of cocaethylene 1.0 mg/kg on systolic blood pressure and heart rate was not significantly different that that for the equivalent dose of cocaine. Mean cocaine "high" was greater than that for the equivalent dose of cocaine, though the difference was not statistically significant. Subjects were able to correctly identify study drug received only 28% of the time when active drug was administered, indicating that cocaethylene and cocaine have similar psychological effects in experienced users.

This study shows that effects of EC in humans are similar to those of cocaine, but EC may have less effect on some cardiovascular indices than does an equivalent dose of cocaine. EC has a longer elimination half-life than cocaine, though the basis for this finding cannot be determined from the present study. A study of intravenous cocaethylene administration is planned. These findings have important implications for the pathogenesis of cocaine-alcohol abuse.

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COMPARISON OF PLASMA CONCENTRATIONS AND PHARMACOKINETICS OF COCAINE AND COCAETHYLENE IN HUMAN SUBJECTS GIVEN THE DRUGS INTRAVENOUSLY

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Cocaethylene has been shown to be formed enzymatically from cocaine and ethyl alcohol and reaches significant plasma concentrations in cocaine users who simultaneously consume alcohol. Since cocacthylene has similar but not identical neurochemical properties to those of cocaine, knowledge of its pharmacokinetic properties becomes of some importance. In the absence of direct administration of cocaethylene to human subjects, these have previously been inferred from the results of cocaine/ethanol administration. In this study, cocaine and cocaethylene were given in essentially equal doses (0.25 mg of the base/kg) as the hydrochloride and fumarate salts, respectively, by intravenous injection to human subjects in a single-blind crossover design. Plasma samples were analyzed for the two parent drugs (liquid-solid separation on C18 cartridge followed by acid-base partition and then capillary gas chromatography with a nitrogen-phosphorus detector and propyl benzoyl ecgonine as the internal standard). Urine was analyzed for parent drugs, benzoyl ecgonine, ecgonine methyl ester and ecgoninc ethyl ester (liquid-solid separation on Bond Elut Certify (cartridges followed by gas chromatography/mass spectrometry with single ion monitoring and deuterated compounds used as the standards.) Cardiovascular and subjective effects were also determined. Pharmacokinetic analysis of data from five subjects was carried out.

Plasma concentrations of the two drugs were similar shortly after administration. However cocaethylene had a significantly smaller ($p = 0.002$) elimination rate constant (0.421 SYMBOL 177 \f “Symbol” 0.075 hr-1) compared to cocaine (0.666 SYMBOL 177 \f “Symbol” 0.115 hr-1). These convert to half-lives of 99 and 62 minutes, respectively. Preliminary data from four subjects showed that both parent drugs were excreted in small amounts (renal clearance <5%). The amount of benzoylecgonine excreted in urine in 24th tended to be less after cocaethylene administration ($P < 0.1$) but amounts of ecgonine methyl ester after cocaine and ecgonine ethyl ester after cocaethylene were equivalent. Cocaethylene induced changes in heart rate and subjective high that were only 43% and 65% of those of cocaine (by comparison of AUC from 0 to 30 minutes) (Perez-Reyes *et al.,* Psychopharmacology, in press, 1994). Thus for the dose and parameters studied, cocaethylene had a longer half-life but was less potent than cocaine.

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A LABORATORY MODEL OF THE SELF-ADMINISTRATION OF SMOKED COCAINE

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The purpose of the present study is to develop a laboratory model of the self-administration of smoked cocaine. This model is used to examine: (1) the effect of various doses of smoked cocaine on subjective and physiological responses; (2) the effects of these doses on self-administration; and (3) the effects of varying the length of time between administration of a "priming" dose of cocaine and subsequent access to cocaine on self-administration.

Twelve male cocaine users participated in three experimental sessions. Each session consisted of a work period and a self-administration period. During the work period, subjects were allowed to earn up to five tokens, worth $5 each, by completing a simple computer task. During the self-administration period, subjects were allowed to exchange their tokens for individual doses of cocaine. Prior to the self-administration period, a single free "priming" dose was administered to subjects. The priming dose was equal in amount to the doses that could be purchased during the self-administration period. Dose size (5mg., 0.2mg./kg., 0.4mg./kg.) was varied between sessions. The time at which the priming dose was administered was varied between subjects. One group received the dose eight hours prior to the self-administration period. The other group received the dose immediately before the self-administration period. Dependent variables included: (1) self reported subjective state assessed before and after administration of the priming dose by an eighteen item visual analogue scale; (2) blood pressure and heart rate measured before and after the priming dose; and (3) the number of cocaine doses self-administered in each session. Results showed that subjective and physiological responses are dose related. A significant effect of dose size was found for self report ratings of "high", "desire for cocaine", "effect of dose", "stimulated", and "full of pep/lively". Significant dose effects were also found for diastolic blood pressure and heart rate. The two groups did not differ in their patterns of self-administration.

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ALCOHOL PREFERRING (HAD) RATS HAVE REDUCED DOPAMINE TRANSPORTER BUT NOT SEROTONIN TRANSPORTER DENSITIES

J.W. Boja and M.D. Schechter

Several studies have suggested that dopamine (DA) may play a major role in alcohol preference (Murphy *et al.*. 1987, Gongwer *et al.,* 1989, and Weiss *et al.,* 1993). In order to further elucidate the role of dopamine in alcohol preference we compared the number of dopamine (DAT) and serotonin (5-HTT) transporters in alcohol preferring (HAD) and genetically heterogenous Wistar (LAD) rats which were low alcohol drinking. The rats were first tested for alcohol preference, allowed 6 months of no alcohol intake, then sacrificed by decapitation. Striatal DAT was labeled *in vitro* using either [^{3}H]GBR 12935 or the selective DAT ligand [^{125}I]RTI-121. Cerebral cortical 5-HTT was labeled using [^{3}H]paroxetine. The affinity of [^{3}H]GBR 12935 for the striatal DAT was similar in both HAD (0.32 ± 0.03 nM) and LAD (0.28 ±0.03) rats. The density of labeled sites was however lower in the HAD rats than in LAD rats, 561 ± 85 pmols/g tissue and 419 ± 13 pmols/g tissue. The affinity of [^{125}I]RTI-121 for the high affinity site was also similar in both HAD and LAD rats (0.48 and 0.41). As observed with [^{3}H]GBR 12935, [^{125}I]RTI-121 labeled fewer DAT in the HAD rats (73 ± 24 pmols/g tissue) compared to LAD rats (160 ± 25) pmols/g tissue. In contrast to the findings with the DAT, the affinity (0.27 nM and 0.23 nM) and number of 5-HTT (297 and 264 fmols/mg tissue) sites labeled by [^{3}H]paroxetine was similar in both HAD and LAD rats.

Several studies have reported lower DA content in alcohol preferring (P) rats than in non-preferring (NP) rats (Murphy *et al.,* 1987 and Gongwer *et al.,* 1989). Additionally, Weiss *et al.* (1993) reported that DA efflux was lower in P rats than in NP rats. These results may suggest that there is a lower density of DA neurons in P rats than in NP rats. The results of this study is consistent with this interpretation. Further studies will be required to confirm this hypothesis.

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ANTAGONISM OF SEROTONIN TYPE 2 RECEPTORS BY SPIPERONE REVERSES ANXIETY-LIKE BEHAVIORS DURING ETHANOL WITHDRAWAL IN RATS

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It has been suggested that the "anxiety-like" symptoms measured during ethanol withdrawal (EW) may be partially due to a disturbance in serotonin (5HT) receptor activity (Lal *et. al.,* 1991). In the present studies, we investigated the efficacy of spiperone. a potent $5HT_2$ antagonist, to modify an EW symptom in two animal models of anxiety: the elevated plus-maze (EPM) and the dark/light box. Long-Evans hooded rats were given a nutritionally balanced liquid diet containing 4.5% ETOH for ten days (Lal *et. al.,* 1988). Twelve hours after removal of the ETOH diet, rats were tested in the EPM. We observed a significant reduction in the open-arm activity and the number of total arm entries indicative of EW. Spiperone (0.16 and 0.32 mg/kg) significantly increased the percent of entries made into the open arms and the time spent in the open arms (0.32 mg/kg) of the EPM. In addition, spiperone increased the total number of entries made to arms at moderate doses (0.08 and 0.16 mg/kg), but reduced total arm entries at the highest dose (0.32 mg/kg). On day four of ethanol abstinence, animals were tested for protracted ethanol withdrawal in the dark/light paradigm. Protracted ethanol withdrawal produced residual anxiety-like behavior as evidenced by reduced time spent in the light, reduced number of side changes, and reduced latency to enter the dark. Spiperone (0.16 and 0.64 mg/kg) dose-dependently increased the latency to enter the dark. Spiperone increased the time spent in the light only at the highest dose (0.64 mg/kg), which also dramatically reduced both horizontal and vertical locomotor activity. These data indicate that doses of spiperone adequate to reversing anxiety-like behavior in the EPM or dark/light paradigm are close to the doses required to inhibit general locomotor activity.

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THE EFFECTS OF CHRONIC ALCOHOL SELF-ADMINISTRATION ON THE MENSTRUAL CYCLE IN FEMALE RHESUS MONKEYS

J. M. Drieze, N. K. Mello, J. H. Mendelson, and N. Diaz-Migoyo

Alcohol abuse and alcoholism are associated with abnormal menstrual cycles in women but the relative contributions of alcohol, liver and pancreatic disease and other drug use is difficult to determine. One advantage of the primate model of alcohol self-administration is that alcohol's effects can be studied under controlled conditions where polydrug abuse and intercurrent illness cannot confound interpretation of data obtained. The effect of chronic alcohol self-administration on menstrual cycle regularity was evaluated in six female rhesus monkeys. Alcohol (0.12 g/kg/inj) was available on an FR2 (VR16:S) schedule of reinforcement in four daily sessions. Normal ovulatory menstrual cycles were observed during the pre-alcohol baseline adaptation period. These monkeys have self-administered an average of 2.27 to 3.53 g/kg/day of alcohol for 260 to 588 days and this study is still ongoing. Four amenorrheic cycles (62 to 166 days) were observed in three monkeys. Amenorrhea was defined as a menstrual cycle of 60 days or longer. Abnormally long or short cycles were those that differed from the pre-alcohol baseline cycle average by at least one standard deviation from the mean. According to these criteria, 14 long cycles (31 to 45 days) and nine short cycles were observed. Alcohol withdrawal was consistently associated with abnormally long cycles of 49 to 61 days duration. These data confirm and extend our previous observation that alcohol exposure and alcohol withdrawal disrupts the menstrual cycle in the female monkey model of alcoholism.

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IN VIVO PROTON MAGNETIC RESONANCE SPECTROSCOPY DETECTION OF ACUTE ALCOHOL TOLERANCE IN HUMANS

M. J. Kaufman, T.-M. Chiu, J. H. Mendelson, B. T. Woods, S. K. Teoh, M. Erös-Sarnyai, G. Mercer, and N. K. Mello

Magnetic Resonance Spectroscopy (MRS) detection of brain alcohol has been reported in humans and animals. MRS is not useful for quantitative determinations of brain alcohol levels because it does not detect all alcohol in brain. However, the fraction of brain alcohol detected by MRS is increased in humans and animals after chronic or repeated exposure, which suggests that MRS may be able to detect acquired alcohol tolerance. We conducted the present study in normal social drinking adult male subjects (n = 5) to determine whether repeated alcohol exposure resulted in increased MRS detection of brain alcohol.

MRS was conducted on a 1.5 T whole-body imager (General Electric, Milwaukee, WI) with a head coil using the STEAM pulse sequence. TE 270 msec spectra were acquired from a 27 cc voxel positioned over the left putamen. *N*-acetylaspartate (*N*-AA) was used as an internal standard. Subjects consumed two alcoholic drinks (0.6 g/kg vodka) each separated by a six hour interval. Following each drink, spectra and venous blood samples were collected at 12 minute intervals for analysis of brain and blood alcohol levels (BALs) by MRS and gas chromatography, respectively. Subjective ratings of alcohol's effects were quantified after each spectrum using a modified Subjective High Assessment Scale (SHAS). Between-drink differences in MRS detection of brain alcohol and subjective ratings of intoxication were calculated by comparing spectra/SHAS determinations acquired at near-peak BALs which closely reflect brain alcohol levels.

In spectra obtained on successive drinks matched for equivalent BALs (±5 mg/dl), brain alcohol resonance areas were increased by 60% ($p < 0.01$) following drink two, whereas internal standard N-AA resonance areas were statistically equivalent. SHAS ratings of euphoria and dysphoria were decreased and increased, respectively, following drink two, consistent with induction of acute alcohol tolerance. These changes in MRS brain alcohol detection and SHAS ratings of alcohol's effects were detected at statistically equivalent brain alcohol levels. Consequently, repeated alcohol exposure resulted in increased MRS brain alcohol detection which may be correlated with induction of acute alcohol tolerance.

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EFFECTS OF ETHANOL ON REGIONAL CEREBRAL METABOLIC RATE IN NORMAL VOLUNTEERS: TECHNOLOGICAL ADVANCES

H. de Wit, J. Metz, D. Dooley, J. Roemer, and M. Cooper

Positron emission tomography (PET) is potentially a powerful tool to study the effects of ethanol and other abused drugs on regional cerebral metabolic rate of glucose (rCMglu) in humans. However, studies to date have revealed few consistent regional changes after acute administration of drugs. This may be due in part to limitations of the technology and in part to inter-individual variability in responses to drugs. The present study utilized some recent technological advances which have improved the ability to detect effects in PET images, and also examined individual differences in responses to a drug. The study examined the effects of a moderate dose of ethanol on rCMglu in relation to the drug's effects on mood. PET data were analyzed using combined volumetric PET and MRI data and parametic comparison techniques. Twenty-two normal males underwent two PET scans during which they consumed beverages containing placebo or 0.5 g/kg ethanol (equivalent to about three standard drinks) under double-blind conditions. rCMglu was measured with a PETT VI scanner using FDG as the tracer. Mood changes were assessed using standardized self-report measures, administered while subjects were in the scanner. Each subject's PET and MRI images were co-registered in three-dimensional computer space (Pelizzari *et al.,* 1989) and transformed into standard anatomical space (Talairach and Tournoux 1988). The subjects were categorized into two groups based on their ratings of liking of the effects of ethanol (High Liking, HL, and Low Liking, LL). Ethanol and placebo data were compared for these two groups of subjects, using voxel-by-voxel t-tests. With the improved techniques of image analysis and anatomical localization, differences between the HL and LL groups were detected. Ethanol decreased rCMglu in the cerebellum in both groups, but the drug increased relative tCMglu in left temporal, and perhaps frontal, regions in the HL group only. Thus, the improved image analysis techniques revealed that ethanol may have specific regional effects on metabolic activity, which are related to preference for the drug.

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EFFECTS OF NALTREXONE ON ALCOHOL DRINKING: PRELIMINARY FINDINGS

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Several recent clinical studies have shown the opioid antagonist naltrexone to be effective in reducing relapse rates and craving in outpatient-treated alcoholics. However, at present there has been little systematic investigation of the mechanism by which naltrexone reduces alcohol drinking. We are currently conducting a double-blind placebo-controlled study of the subjective, behavioral, and physiological effects of naltrexone on alcohol drinking. Subjects are nonalcoholic individuals at high and low risk for future alcohol dependence (family history positive and negative, respectively). Each subject receives either an oral dose of naltrexone (50 mg) or identical placebo pill in the morning on two separate testing days. After a light lunch in the afternoon, the subject consumes .6 g/kg alcohol (beer) in three equal doses over a 30 minute period. The beverage matches the individuals' beverage of choice and is consumed in the afternoon to provide a naturalistic drinking experience.

Our preliminary data on the first 18 subjects indicated that naltrexone, compared to placebo, produced no significant adverse side effects alone or in combination with alcohol. High-risk subjects reported greater stimulation from. alcohol during the placebo pill. session compared to the low-risk group. These effects were most pronounced during rising BACs, *i.e.,* 30 minutes after the initiation of drinking. During the naltrexone session, reports of stimulation appeared attenuated in the high-risk group but not in the low-risk group. Groups were similar on subjective report of sedation, and naltrexone did not appear to affect sedation for either group. Finally, an exit interview showed a greater percentage of the high-risk (89%) compared to the low-risk group (44%) reported that the alcohol effect during the placebo pill session was more like drinking in everyday life. Although data are preliminary, the results suggest that naltrexone may reduce subjective stimulation of alcohol in subjects genetically at risk for alcoholism.

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EFFECTS OF NALTREXONE PRETREATMENT ON ACUTE RESPONSES TO ETHANOL IN SOCIAL DRINKERS

P. Doty and H. de Wit

Recent clinical studies suggest that the opioid antagonist, naltrexone (NTX), may be effective in the treatment of alcoholism (O'Malley *et al.,* 1992; Volpicelli et al., 1992). For example, alcoholics treated with NTX had higher abstention rates and reported lower levels of "craving" than placebo controls. In alcoholic patients who did lapse, NTX decreased the amount of alcohol consumed (drinks/day). The present study evaluated the effect of NTX on physiological, subjective and performance effects of an acute dose of ethanol (EtOH) in social drinkers. Thirteen males and females participated in a six-session double-blind, placebo-controlled, crossover design study. On each session, subjects ingested a capsule containing NTX (25 or 50 mg) or placebo and one hour later consumed a beverage containing EtOH (0.5 g/kg) or placebo. For three hours after the beverage was consumed, breath alcohol levels (BAL) were measured and subjects completed standardized self-report questionnaires rating their current mood state and the drugs' effects. Psychomotor and memory performance were also assessed.

EtOH alone produced its prototypic effects including increased ratings of "feel drug" and "like drug", increased ratings of euphoria, and impaired memory performance. In contrast, subjective responses to NTX (*e.g.,* ratings of "feel drug" and "like drug"), and performance effects of NTX. did not differ from placebo. NTX did not alter ethanol pharmacokinetics as evidenced by breath alcohol concentrations. NTX did not modify subjective responses to EtOH and did not alter the impairment of memory performance produced by EtOH. These data suggest that the opioid system does not modulate the acute effects of a moderate dose of ethanol in social drinkers. Whether similar results would be obtained following chronic administration of either EtOH or NTX is not known.

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COMBINED SEROTIN AND DOPAMINE INDIRECT AGONISTS CORRECT ALCOHOL ASSOCIATED NEUROSES

Pietr Hitzig

Contemporaneous serotonin (fenfluramine) and dopamine (phentermine) agonist administration (FEN/PHEN) dissipated alcohol and cocaine craving in the vast majority of patients (275) within hours, and, if administered daily, alcohol cravings, rarely recurred. Concomitant with FEN/PHEN treatment, marked improvement in all neurotic symptoms was noted. The **Symptom Check list 90 question (SCL)** is a widely accepted psychometric test that measures symptom severity of nine neurotic axes. To test further, 27 severely depressed alcoholics started FEN/PHEN after SCL self-administration. All 27 patients either lost their alcohol craving within two hours after the FEN/PHEN dose or did not experience craving when expected. Seven cocaine and one heroin co-addicted patients lost those cravings as well. EtOH and cocaine use markedly decreased. The 19 completing a second SCL more than one week after treatment were the study cohort. SCL normalcy was achieved in all 19. For example, the median **GSI** score went from greater than 3 to 0.2 standard deviations above norm (STDAN). The depressive sub-scale went from 3 to 1 STDAN. After six months, 16/19 remained in the program without significant addictive craving or neurotic problems. Patients consumed $\leq$ 10 alcohol at both two weeks and six months. The highly significant improvement in all SCL sub-scales continue. Rothman *et al.,* (this volume) report similar changes in a pilot study of cocaine addicted patients. Data derived from a large cohort of FEN/PHEN treated patients suggests patients with narcotic, PCP. or cannabis addiction experience a loss of craving. Patients with neurotic symptoms without, addiction respond to FEN/PHEN even if previously refractory to all other psych-pharmacologic approaches. FEN/PHEN appears to stop acutely all symptoms, including seizures, of the alcohol withdrawal syndrome. Double blind alcohol studies will begin shortly at the Addiction Research Center/NIDA.

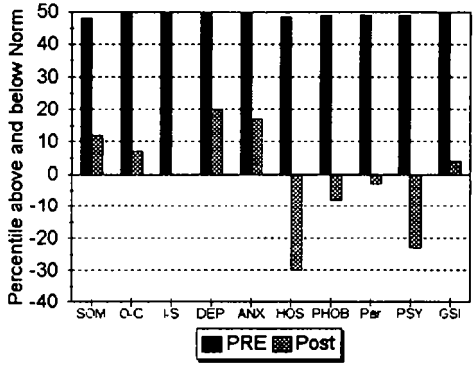

Fig. 1. Median SCL Sub-scale pre- and post-treatment percentile scores for somaticism, obsessive-compulsion, intra-personal sensitivity, depression, anxiety, hostility, phobia, paranoia, psychoticism, and global severity index.

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PRELIMINARY OUTCOME OF CUE EXPOSURE TREATMENT FOR ALCOHOL DEPENDENCE

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Ninety-one men between 18 and 65 years of age were assessed for admission to group treatment for alcohol dependence. They were assigned to groups of 4 to 12 clients and the groups were randomly assigned to one of two treatment conditions: cue exposure combined with cognitive behavioural treatment (CE +CBT) or CBT-alone. Sixty-five clients were assigned to CE + CBT and 26 to CBT-alone. Of these, 50 and 20, respectively, completed the three weeks of day-treatment. At pretreatment assessment, the clients in the two treatment conditions did not differ on demographic features, average daily consumption of alcohol, level of alcohol dependence, self-efficacy to resist drinking, alcohol expectancies or reactivity to alcohol-related cues. At the end of treatment there were significant changes in self-efficacy, expectancies and cue reactivity. Clients reported increased self-efficacy to resist drinking when in negative emotional states, during negative personal situations and positive social situations ($ts>3.2$, $df=50$, $p<.002$). They showed a decline in the expectancies that alcohol improved assertiveness and enhanced cognitive control ($ts>3.3$, $df=47$, $p<.002$ but an increase in the expectancy that alcohol produced relaxation ($t=-3.2$, $df=50$, $p<.002$). There was a significant reduction in the amount of water clients drank during a test of reactivity to alcohol cues ($t=2.75$, $df=50$, $p<.008$) hut little change in self-reported desire to drink alcohol. Self-reported confidence to resist drinking alcohol during cue exposure increased markedly (Wilcoxon test $p<.005$). Mood changed after exposure to the alcohol cue at pretreatment and posttreatment assessments. At pre- and posttreatment there was a decline in positive affect and sensation seeking. At posttreatment there was also a significant increase in dysphoria after clients saw the alcohol cue ($ts>2.5$, $df=62$, $p<.004$). At three months follow-up of 19 clients (collapsed across treatment groups), there were declines in alcohol consumption and in alcohol-related problems. Because there were 2.5 times more clients in the CE + CBT treatment condition, most of the pre- to posttreatment differences observed reflect changes in that group. High variability and low subject numbers in the CBT-alone group prevent any firm conclusions being drawn about the behaviour of these clients. In general, subjects showed improvement at three months follow-up. The decline in positive affect on the cue reactivity test at posttreatment may reflect the clients' anxiety about leaving treatment and their concerns about maintaining sobriety.

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ROLE OF EXPECTANCY IN PERSISTENT, REMITTED AND EMERGENT ALCOHOL DEPENDENCE

M. M. Kilbey, K. Downey, and N. Breslau

METHODS:

We measured the prevalence of alcohol dependence (AD) using the NIMH-DIS in a cohort of young adults randomly selected from a large HMO in the Detroit, MI area in 1989 (T1) and 1991 (T3). Drug expectancy was measured in 1990 (T2) using 40 statements, adapted from existing instruments, comprising four factor scales, representing positive and negative effects of drug use. Personality, affectivity, and alcohol use characteristics were measured also using the EPQ-R, the PANAS, and a questionnaire, respectively. Based on comparison of lifetime dependence at T1 and 3.5 year interval dependence at T3, four groups were defined: never dependent (n = 739), persistently dependent (n = 45), remitted dependent (n = 130), and newly dependent (n = 42). Expectancy, personality, and affectivity scores were analyzed using MANOVA, ANOVA, and post-hoc comparisons.

RESULTS:

The major findings of the study were: (1) Prevalence for AD is high in a population of young adults: 17.95% at T1-lifetime and 9.03% at T3 -- 3.5 year interval for a total lifetime prevalence of 22.58. (2) The AD status of young adults is not static. Over a 3.5 year interval, 4.7% of the respondents continued to meet criteria for AD, while three of four persons who were AD at T1 failed to meet criteria at T3. Of those who were not dependent at T1, 5.4% met criteria for dependence at T3. (3) Overall, the four groups classified on the basis of dependence status at Tl and T3 began regular drinking at different ages, and differed on personality and affectivity characteristics, as well as drug expectancies. (4) Persistently AD respondents are characterized by: (a) earlier initiation of regular drinking, (b) higher psychoticism scores, (c) higher expectations for alcohol enhancement of interpersonal sexual and social relations and for cocaine enhancement of pleasure, power, and confidence in comparison with never dependent and remitted dependence groups. Overall, the findings suggest that among AD young adults those with high expectancy for positive effects from drug use are less likely -- and those with high expectancy for negative effects from drug use are more likely -- to remit. Furthermore, low expectancy for negative effects is associated with the development of AD in young adults.

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EFFECTS OF FULL AND PARTIAL ALLOSTERIC MODULATORS OF GABAA RECEPTORS ON COMPLEX BEHAVIORAL PROCESSES.

J. Auta and J. Moerschbaecher

Recently, benzodiazepines(BZDs) and congeners have been classified into three main categories: 1) full allosteric modulators (for example triazolam) which act with high potency and efficacy at a great variety of recombinant GABAA receptor subtypes; 2) selective allosteric modulators (for example, diazepam), which act with high potency and efficacy at selected recombinant GABAA receptor subtypes; 3) partial allosteric modulators (for example imidazenil and bretazenil), which act with high potency but low efficacy at a great variety of recombinant GABAA receptor subtypes (Puia *et al.,* 1991; Ducic *et al.,* 1993). It is therefore not inconceivable that depending on their efficacy, BZDs and congeners may have different pharmacological profiles and associated side effects. It has been reported that in rats imidazenil, like triazolam, has pharmacological effects indicative of anxiolytic, antipanic and anticonvulsant activity but unlike triazolam, imidazenil does not produce ataxia, sedation, psychotomimetic effects, tolerance or dependence (Giusti *et al.,* 1993; Auta *et al.,* 1994). To this end, we compared the disruptive effects of imidazenil and triazolam in monkeys working on a multiple schedule of repeated acquisition and performance of discriminations. In addition, we used repeated acquisition and delayed performance to compare the effect of these two drugs on retention in monkeys. Imidazenil at a range of doses that had little or no disruptive effect on behavior when given alone, attenuated the large disruptive effects of a single dose of triazolum. This data suggest that the disruptive effect of BZDs and congeners may be a function of their efficacy at different GABAA receptor sites.

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SUPPRESSION OF MAXIMAL BENZODIAZEPINE WITHDRAWAL BY PRO-GABA-ERGIC DRUGS I. CHLORDIAZEPOXIDE, PHENOBARBITAL, SODIUM BROMIDE AND BACLOFEN

N. R. Boise, O. Amitay, and J. Leung

The neuronal mechanisms responsible for benzodiazepine withdrawal are incompletely understood. Nevertheless, electrophysiological studies of the rat spinal reflex system indicate that all withdrawal changes are rebound phenomena of the same parameters directly affected by benzodiazepines (JPET 231: 464, 1984). Since the direct actions of the benzodiazepines involve an enhancement of the effectiveness of GABA transmission, benzodiazepine withdrawal might be caused by a hypo-effective state of GABA transmission. To test this hypothesis, a maximal benzodiazepine withdrawal suppression model was developed in the rat and four pro-GABAergic drugs were initially evaluated. Rats received daily i.g. chlordiazepoxide 75 mg/kg escalated to 300 mg/kg by two weeks and maintained for three more weeks; concurrent controls received water. Three days after the last dose when rats were in maximal withdrawal, suppression drugs were evaluated for a 2x4 experimental design (two chronic treatments: chlordiazepoxide, H_20; four suppression treatments: vehicle, low, medium and high dose). Experienced, reliable raters for benzodiazepine withdrawal (2-3) blind to treatments monitored 20 different operationally defined signs for withdrawal. Withdrawal was monitored at 0, 15, 30, 60 and 120 minutes post-injection except for sodium bromide at 0, 2, 4, 8, 12, 24 and 30 hours. The highest dose of each drug produced quantifiable CNS depression. ANOVA's revealed dose-related suppression of maximal withdrawal scores for chlordiazepoxide (5, 10, 20 mg/kg), phenobarbital (15, 30, 60 mg/kg) and sodium bromide (300, 600, 1200 mg/kg); the highest doses fully suppressed chlordiazepoxide withdrawal. In contrast, baclofen (0.75, 2.0, 5.0 mg/kg), a GABA agonist at GABA-B receptors, only partially suppressed chlordiazepoxide withdrawal; the lowest dose gave the greatest and most persistent suppression of chlordiazepoxide withdrawal. Accordingly, these initial results fully support a GABA hypoeffectiveness hypothesis for benzodiazepine withdrawal at GABA-A sites.

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SEX DIFFERENCES IN SPONTANEOUS WITHDRAWAL FOLLOWING ACUTE BENZODIAZEPINE DEPENDENCE INDUCTION

J. Leung, N. R. Boisse, and O. Amitay

Epidemiological studies suggest anxiety disorders and the prescribing of benzodiazepines are more likely to occur in women than men by a factor of about 2:1. However, gender bias, psychological factors and biological factors may contribute differently to these gender differences. Since the disconcerting problem in the prescription use of these agents is the potential to induce physical dependence, it would be important to know whether there are gender differences in vulnerability to benzodiazepine dependence and withdrawal that are biologically based. The objective of this study was to test this hypothesis using a quantitative male rat model for spontaneous withdrawal following a single intragastric dose of chlordiazepoxide 450 mg/kg or water for concurrent controls (JPET 287: 775, 1986). Eight to ten females and males received each treatment in a 2 x 2 design. Spontaneous withdrawal was monitored by 2-3 trained, reliable raters for 20 different operationally defined signs. Repeat measures ANOVA for daily withdrawal scores revealed significant differences based on both sex ($P<.01$) and acute treatment ($P<.03$). Sex differences in true chlordiazepoxide withdrawal were more directly compared by calculating net withdrawal = withdrawal score of a chlordiazepoxide treated rat minus the mean value of the concurrent controls (water treated, same sex). The onset of net withdrawal occurred later for females (5 days) than for males (4 days). The peak net withdrawal scores were significantly ($P<.05$) greater for females (7.9 ± 0.6 SE) than for males (5.7 ± 0.8) despite the fact that the time to peak net withdrawal was 1-2 days later for females than for males (5 days). The total duration of net withdrawal exceeded 10 days for females whereas for males, it was only five days. The area under the curve for (+) net withdrawal was significantly greater ($P<.05$) for females than males by a factor of 1.6. Accordingly, the results overwhelmingly support the hypothesis for biologically based gender differences in vulnerability to acute benzodiazepine dependence.

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CONTINGENT ANTICONVULSANT TOLERANCE DEVELOPS TO THE BENZODIAZEPINE (BZ) PARTIAL AGONIST, BRETAZENIL (RO16-6028), BUT NOT TO CLONAZEPAM

E. I. Tietz, W. Ferencak, L. Aloe, and H. Chang

Following *continuous* BZ administration, the rate and magnitude of BZ anticonvulsant tolerance is related to BZ intrinsic efficacy (Haigh and Feeley 1988). *Intermittent* administration of anticonvulsants to amygdala kindled rats results in a sizeable degree of "contingent" tolerance, conditional upon eliciting the convulsive stimulus during drug exposure (Pinel *et. al.,* 1990). Contingent tolerance, which occurs to a variety of anticonvulsants (Mana *et. al.,* 1991), develops readily to clobazam and diazepam (Tietz 1992). The rate and magnitude of contingent tolerance development to the BZ partial agonists, clonazepam (CZP) and bretazenil (BRT) (RO16-6028) was studied to evaluate whether it relates to BZ efficacy. Rats were kindled to five stage five seizures by 2X daily amygdala stimulation (400 μAmps). Baseline seizure measures were determined 30 minutes after vehicle (VEH) injection. On the anticonvulsant pre-test, rats were administered either CZP (0.35 mg/kg) or BRT (5.0 mg/kg) 30 minutes *before* amygdala stimulation and VEH 30 minutes *after.* On test days (1, 4, 7 and 10) half received drug *before* treatment and VEH *after,* half received drug *before* and drug *after.* No tolerance was seen in rats which received drug *after* stimulation. Robust contingent tolerance developed to rats administered BRT ($p < .01$), but little to those administered CZP, *before* stimulation. CZP is particularly resistant to anticonvulsant tolerance development regardless of the pattern of drug administration. Overall, the findings suggest that mechanisms unrelated to BZ intrinsic efficacy underlie the development of contingent anticonvulsant tolerance.

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RO 15-1788 HAS AGONIST PROPERTIES IN THE PIGEON BUT NOT IN THE RAT OR SQUIRREL MONKEY IN MODELS OF WORKING MEMORY

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RO 15-1788 was studied in pigeons responding under delayed alternation of colors and titrating matching-to-sample baselines. Under the delayed alternation of colors (D-A-C) baseline accuracy was decreased at doses as low as 0.1 mg/kg. Under the titrating matching-to-sample (M-T-S) baseline, the mean delay value was decreased at doses of 0.03 mg/kg and higher. Rate of responding was decreased under both schedules at doses of 1 mg/kg and higher. In contrast, when RO 15-1788 was studied in the squirrel monkey responding under a titrating matching-to-sample baseline, no significant effects on mean delay value or rate of responding were observed at doses up to 5 mg/kg. Likewise no significant effects on percent correct responding or response latency were observed in rats responding under a delayed alternation (D-A-P) task at doses up to 10 mg/kg. The results observed in pigeons are qualitatively similar to those obtained with diazepam and suggest that in the pigeon RO 15-1788 may have agonist-like properties. This is in marked contrast to the lack of such agonist properties in the rat and squirrel monkey. Taken together, these results (summarized in Table 1) suggest that there may be a species difference in the benzodiazepine receptor found in the pigeon compared to mammalian species.

Table 1
Minimal Effective Doses (mg/kg)

		Diazepam		RO 15-1788	
Species	Procedure	Accuracy	R/Sec	Accuracy	R/Sec
Sq. Monkey	M-T-S	1.8	5.6	>10	>10
Rat	D-A-P	5.6	5.6	>10	>10
Pigeon	M-T-S	1	>3	0.03	1
Piegeon	D-A-P	1	> 3	0.1	1
Pigeon	D-A-C	1	> 3	0.1	1

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ACUTE BEHAVIORAL AND SELF-REPORTED EFFECTS OF ZOLPIDEM, TRIAZOLAM AND TEMAZEPAM IN NORMAL VOLUNTEERS

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Insomnia is reported by approximately 15-45 percent of the adult population. Benzodiazepines, including triazolam and temazepam, are effective pharmacotherapies for insomnia, but produce side effects including impairment of learning, recall and performance. The purpose of the present study was to compare the behavioral and self-reported effects of zolpidem. a newly marketed imidiazopyridine hypnotic, and triazolam and temazepam, benzodiazepine hypnotics. Subjects (N = 11) were normal, healthy male and female volunteers recruited from the community at large. The acute behavioral effects of zolpidem (5, 10 and 20 mg/70kg), triazolam (0.125, 0.25 and 0.50 mg/70kg), temazepam (15, 30 and 60 mg/70kg) and placebo were assessed across seven hour sessions. Drug effects were assessed before and 0.5, 1. 1.5. 2. 3. 4. 5 and six hours after oral administration. Subjects received all possible doses under double-blind conditions, and all drug administrations were separated by at least 48 hours. Zolpidem, triazolam and temazepam dose-dependently disrupted learning, recall and performance, and increased subject ratings of sedation and drug strength. During peak effect, the absolute magnitude of these effects were comparable across the three compounds. The time course of zolpidem, triazolam and temazepam differed. Zolpidem's, triazolam's and temazepam's effects peaked approximately 0.5, 1.5 and 2.0 hours after drug administration, respectively. These results suggest that despite the somewhat unique benzodiazepine receptor-binding profile of zolpidem, its behavioral and self-reported effects are generally similar to those of classic benzodiazepine hypnotics, triazolam and temazepam.

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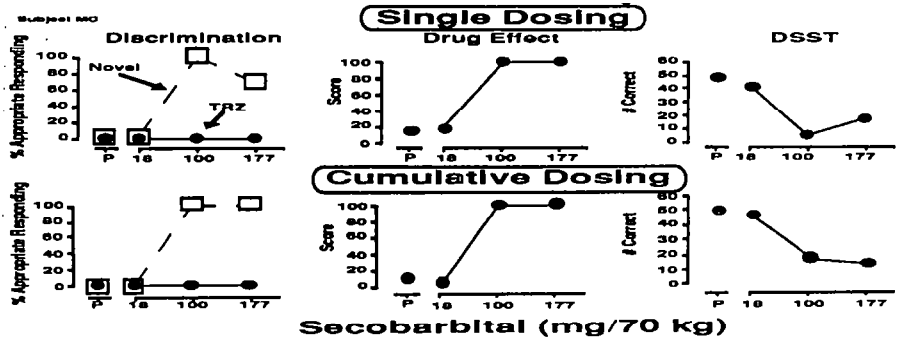
CUMULATIVE DOSING FOR HUMAN TRIAZOLAM DISCRIMINATION USING A NOVEL RESPONSE PROCEDURE

B. J. Smith, W. K. Bickel, S. T. Higgins, J. R. Hughes, and J. B. Kamien

A cumulative dosing procedure was developed for human triazolam discrimination based on animal cumulative dosing drug discrimination (DD) procedures. During the training and acquisition phases subjects received either placebo (*e.g.,* Drug A) or 0.32 mg/70 kg triazotam (*e.g.,* Drug B) capsules one hour before each assessment and each session consisted of one to four components. During the testing phase, a session always consisted of four components. Doses of triazolam (0.03, 0.1 and 0.32 mg/70 kg) and secobarbital (18, 100 and 177 mg/70 kg) were tested as single doses across sessions and cumulatively within sessions in order to compare effects. For cumulative dosing, incremental doses of the test drug were administered such that several doses were tested in a single session. A novel-response DD procedure was used where subjects were instructed that if they received a drug which was not precisely like Drug A or precisely like Drug B, respond on N (the novel-response alternative). Nine of the fourteen subjects (64%) who completed at least the first eight sessions (training and tests-of-acquisition) acquired the placebo *vs* triazolam (0.32 mg/ 70 kg) discrimination. This percentage of acquisition is similar to that obtained under our standard, single component triazolam discrimination procedure and indicates that exposure to multiple components within a single session did not disrupt drug stimulus control. Results from two subjects that have completed the testing phase indicate that the DS, self-reported and motor performance effects of triazolam and secobarbital were nearly identical whether administered in single or cumulative doses (see below for representative data). Secobarbital occasioned dose-dependent increases in novel-appropriate responding when given in single or cumulative doses, replicating previous results with single doses of secobarbital in our laboratory. There are several potential benefits of cumulative dosing for human DD research. Most importantly, this cumulative dosing procedure can dramatically increase experimental efficiency by permitting assessment of a full dose effect curve in a single session.



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ABUSE LIABILITY OF TRIAZOLAM, MEPROBAMATE AND BUTABARBITAL: A PUBLIC HEALTH ISSUE

L. Zawertailo, U. Busto, H. L. Kaplan, and E. M. Sellers

Implementation of regulations to control prescribing of benzodiazepines in New York State in 1989 resulted in a 55% decrease in benzodiazepine prescribing with a concomitant increase in prescribing rates of older sedative-hypnotic compounds such as butabarbital (30% increase) and meprobamate (125% increase) (Weintraub *et al.,* 1991). In a double-blind, crossover, placebo-controlled study, we compared the behavioral and pharmacological effects of triazolam, meprobamate and butabarbital in 14 recreational drug users who could distinguish secobarbital 150 mg from placebo and report pleasant effects during a pre-screening session. Three doses each of triazolam (0.25, 0.5, 1.0 mg), meprobamate (800, 1600, 2400 mg), butabarbital (100, 200, 400 mg) and placebo were administered to each subject in a random order. Objective tests (motor performance, concentration) and subjective response questionnaires measured drug effects. Triazolam, meprobamate and butabarbital showed comparable negative dose-response slopes on the objective measures. Using these objective data, equivalent doses for the three compounds were determined to be triazolam 0.5 mg = meprobamate 2400 mg = butabarbital 400 mg. Subjective effects data using equivalent doses show that butabarbital produces the highest peak score on Cole/ARCI Abuse Potential, ARCI PCAG and 'Drug Strength' scales. Triazolam = butabarbital on ARCI MBG, Cole/ARCI Euphoria and 'Drug Liking' scales. Meprobamate = placebo on Euphoria and Abuse Potential scales. Comparison of subjective and objective measures with serum drug levels at corresponding time points illustrate acute tolerance to some effects. Behavioral economics analysis indicate a price crossover point two times higher for butabarbital 400 mg than for any other drug condition. These data suggest that butabarbital > triazolam > meprobamate in liability for abuse and that the prescribing regulations had little net benefit on abuse risk in the population, but may have increased the risk of overdose morbidity.

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ABUSE LIABILITY ASSESSMENT OF SURICLONE: A CYCLOPYRROLONE ANXIOLYTIC

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Suriclone is a new anxiolytic belonging to the cyclopyrrolone class. This class is structurally unrelated to benzodiazepines but displaces them from binding sites. To evaluate psychoactivity and abuse potential an ascending dose-ranging study (n=6) followed by a double-blind latin square crossover study (n=12) were conducted in males with histories of substance abuse. The dose-ranging study (results not presented here) was conducted for safety and as a basis for choice of doses for the following study. For the crossover study treatments were assigned from two 6X6 Latin squares. The effects of oral placebo (negative control), diazepam 10 and 20 mg (positive control), and suriclone 0.2, 0.4. and 0.8 mg were assessed on measures of subjective, behavioral, and physiologic responses including symptoms, drug identification, Addiction Research Center Inventory Scales, signs, temperature, blood pressure and heart rate. Single doses were administered under double-blind conditions once daily in the morning. Data was collected on optical scanning forms and electronically entered into a data base. AUC and peak change scores were calculated. Data was analyzed by ANOVA using GLM and contrasts of interest (SAS). Results revealed that the time course of psychoactivity (*e.g.* "feel the drug") was similar for diazepam and suriclone. and most effects occurred within six hours. Onset of effect was more rapid for diazepam. Subjective responses were similar except that diazepam produced more sleepiness while suriclone produced more dizziness. On the Addiction Research Center Inventory Scales both drugs increased PCAG subscales and neither drug significantly altered MBG or LSD subscales. Observer responses also indicated that subjects were more "sleepy" and more likely to be "nodding" on diazepam. Physiologic responses demonstrated that both drugs reduced supine diastolic blood pressure and oral temperature. Equivalent doses for relative potency estimates were suriclone 0.4, 0.8 mg and diazepam 10 and 20 mg. Valid relative potency estimates (regression, linearity, preparations, and parallelism) were obtained for the following subjective responses to the questions: "feel the drug?" "like placebo?" "like Valium?" (AUC analyses) "like placebo?" and "a downer?" (peak analyses) and observer responses to the questions "feel the drug?" (AUC) and "like the drug?" (peak). Suriclone was 25 to 30 times more potent than diazepam. In summary the pharmacologic effects differ somewhat in that suriclone produces less sedation but more dizziness in comparison with diazepam. The abuse potential of suriclone is considered to be similar but not identical to that of diazepam at these doses.

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COCAINE INTERACTIONS WITH SEROTONIN 5-HT_3 AND DOPAMINE RECEPTORS: STUDIES OF THE 5HT_3 AGONIST 1-(*META*-CHLOROPHENYL)-BIGUANIDE (mCPB) AS A DISCRIMINATIVE STIMULUS IN THE RAT

R. De La Garza, II, P. M. Callahan, and K. A. Cunningham

Serotonin 5-HT_3 receptors modulate both DA release and locomotor stimulation (McNeish *et. al.,* 1993). However, 5-HT_3 antagonists are relatively ineffective at blocking the stimulus (Paris and Cunningham 1991) and reinforcing effects of cocaine (Peltier and Schenck 1991). To further delineate the interaction between cocaine and 5-HT_3 receptors, rats (N = 16) were trained to discriminate cocaine (10 mg/kg, IP) from saline using a standard drug discrimination task. Substitution tests with the 5-HT_3 agonist 1-(*meta*-chlorophenyl)-biguanide (mCPB: 2.5-20 mg/kg) produced, at best, a partial substitution, and mCPB (10 mg/kg) did not alter the cocaine dose-response curve. The 5-HT_3 receptors play little, if any, role in mediating the discriminative stimulus effects of cocaine.

To more fully examine the interaction between 5-HT_3 receptors and cocaine, rats (N = 16) were trained to discriminate mCPB (15 mg/kg, IP) from saline using similar procedures. Administration of the 5-HT precursor *l-5*-hydroxytryptophan (12.5-50 mg/kg) dose-dependently substituted for mCPB, whereas zacopride (0.1-10 mg/kg) partially antagonized the mCPB cue. In substitution tests, cocaine (5-20 mg/kg) elicited saline-like responding. Overall, these data demonstrate that mCPB produces distinct discriminable effects that appear to be mediated by 5-HT systems to the cue remains undetermined. Furthermore, cocaine is not perceived as similar to mCPB, and its ability to block the mCPB cue has yet to be elucidated.

While the stimulus effects of cocaine are DA mediated and 5-HT_3 receptors can modulate cocaine-induced DA release, these receptors do not appear to play a modulatory role in the cocaine cue. These findings are in contrast to the blockade of cocaine-induced hyperactivity by 5-HT_3 antagonists. Thus, the neurochemical mechanisms and/or sites of action for cocaine to produce these behavioral effects (discriminative stimulus vs. locomotor stimulatory) may not be identical.

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Available upon request.

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CHARACTERIZATION OF SEROTONERGIC INVOLVEMENT IN THE BEHAVIORAL-STIMULANT AND REINFORCING EFFECTS OF COCAINE IN THE SQUIRREL MONKEY

L. L. Howell and L. D. Byrd

The effects of cocaine and several serotoncrgic (5HT) compounds were compared in squirrel monkeys trained to respond under a fixed-interval (FI) schedule of stimulus termination and a second-order schedule of drug self-administration. Intermediate doses (0.1-1.0 mg/kg) of cocaine increased FI response rates, and higher doses (1.7-3.0 mg/kg) suppressed responding. In contrast, the 5HT uptake inhibitors, fluoxetine (1.0-10.0 mg/kg) and alaproclate (1.0-10.0 mg/kg). had little effect over a wide range of doses. The 5HT direct agonists, quipazine (0.3-3.0 mg/kg) and 8-OH DPAT (0.01-0.1 mg/kg), only decreased FI responding. Pretreatment with the 5HT uptake inhibitors or direct agonists produced an insurmountable attenuation of the behavioral-stimulant effects of cocaine as evidenced by a downward displacement of the cocaine dose-effect curve. Pretreatment with the $5HT_2$-selective antagonists, ketanserin and ritanserin, enhanced the rate-increasing effects of cocaine and attenuated the rate-decreasing effects. The $5HT_3$-selective antagonist, MDL 72222, and the non-selective antagonist, mianserin, also enhanced the rate-increasing effects of cocaine but did not alter the rate-decreasing effects. Cocaine reliably maintained self-administration behavior, and rates of responding under the second-order schedule were related directly to cocaine dose. Ritanserin enhanced rates of responding maintained by cocaine self-administration, suggesting an enhancement of the reinforcing effects of cocaine. In contrast, substitution of several 5HT uptake inhibitors for cocaine failed to maintain responding. The results indicated that the behavioral-stimulant and reinforcing effects of cocaine likely do not depend on inhibition of 5HT uptake. However, pharmacological manipulation of 5HT activity reliably altered the behavioral effects of cocaine.

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EXTRACELLULAR SEROTONIN DURING ABSTINENCE FROM EXTENDED COCAINE SELF-ADMINISTRATION: DECREASED LEVELS AND EVIDENCE FOR AN ENHANCED 5-HT/DA INTERACTION

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The role of dopamine (DA) in the reinforcing aspects of cocaine use has been well established and continues to be an area of substantial research. However, cocaine is also a potent inhibitor of serotonin (5-HT) uptake, and a growing literature implicates 5-HT in cocaine addiction and withdrawal. The experiments presented here examined the time course of change in 5-HT and DA concentrations in microdialysis samples from the nucleus accumbens (N ACC) both during, and for several hours after an extended cocaine self-administration session. The "No Net Flux" quantitative dialysis method was used to estimate the extracellular concentration of 5-HT during the abstinence period and to study alterations of the interaction between 5-HT and DA following prolonged cocaine exposure.

Dialysate samples were collected from three groups of male Wistar rats: [1] catheterized drug-naive controls (n=6), [2] animals which were trained to self-administer cocaine in daily three hour sessions (n=6). and [3] animals which were trained to self-administer cocaine, and were then allowed to self-administer cocaine for a 12 hour extended-access session (n=7). Microdialysis probes were implanted at least eight to ten hours prior to the start of dialysis sampling, and were perfused with an artificial CSF solution at 0.12 µl/min. Samples were analyzed using microbore HPLC with electrochemical detection. Dialysate levels of both 5-HT and DA were elevated to approximately 340% of baseline for the duration of the 12 hour cocaine self-administration session. Dialysate 5-HT levels were significantly decreased to 50% of pre-session baseline levels and 30% of levels from drug-naive control animals within 90 minutes after the extended cocaine session, and remained at these levels for at least six more hours. Dialysate DA levels decreased to pre-session levels within 80 min. after the session, and did not significantly differ from these levels or those from drug-naive controls for at least six more hours. Using the "No Net Flux" method, extracellular 5-HT was found to be significantly lower 6-10 hours after the extended cocaine session (0.6±0.3 nM) than in either drug-naive control animals (2.0±0.5 nM) or animals which received the daily three hour self-administration training sessions only (1.4±0.2 nM). During this time period, low levels of perfusate 5-HT (<c 10 nM) were found to elevate extracellular DA levels, an effect which was not observed in either drug-naive control animals or cocaine-trained animals which did not receive the 12 hour session.

The present data indicate that while N ACC dialysate levels of 5-HT and DA are elevated to a similar degree during an extended cocaine self-administration session, 5-HT levels decrease faster and to a greater extent than DA levels in the first hours of cocaine abstinence. Moreover, the severity of the 5-HT decrease appears to be a function of the duration of cocaine exposure. In contrast to the decreased levels of extracellular 5-HT, the ability of perfusate 5-HT to enhance extracellular DA levels appears to be potentiated after extended exposure to cocaine. As with the substantial decrease in extracellular 5-HT, this effect appears to be induced only by extended cocaine exposure. The increased sensitivity of dialysate DA to perfusate 5-HT concentrations may represent an adaptation by which relatively normal extracellular DA levels are maintained in the presence of reduced extracellular 5-HT levels. A greater decrease in extracellular DA levels at later time points of abstinence may be accompanied by a decreased effectiveness of the 5-NT/DA interaction.

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CHARACTERIZATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF BENZTROPINE, A POTENTIAL COCAINE THERAPEUTIC AGENT

J. B. Acri, A. H. Newman, M. Chider, and J. M. Witkin

Benztropine (Cogentin) is a dopamine uptake inhibitor that is used as an adjunct therapy in the clinical treatment of Parkinson's disease. Unlike other dopamine uptake inhibitors such as cocaine and GBR 12935, benztropine has low efficacy as a psychomotor stimulant, has reduced ability to enhance behavioral effects of cocaine, and does not potentiate cocaine toxicity (Acri *et al.,* 1994). From these and other data, it has been suggested that bcnztropine may be clinically useful in the treatment of cocaine addiction.

The present studies were undertaken to characterize the pharmacological basis of the discriminative stimulus effects of benztropine, which, in addition to inhibiting dopamine uptake, is a muscarinic antagonist. Rats were trained to discriminate a dose of 3 mg/kg benztropine from saline using a two lever procedure and an FR 20 schedule of food reinforcement. The discrimination was readily acquired in 36 sessions and easily maintained. Cocaine (0.1-17.0 mg/kg) dose-dependently substituted for benztropine but reached a maximum of only 30%, and reduced response rates. Atropine (0.1-10.0 mg/kg) dose-dependently substituted for benztropine without rate reductions, but was significantly less potent than benztropine. Although 10-fold more potent than benztropine in inhibiting dopamine uptake, 4-Cl-benztropine (1.0 - 10 mg/kg) dose-dependently substituted for benztropine. but was significantly less potent and reduced response rates. Data suggest that there may be an overshadowing of the discriminative stimulus effects of dopamine uptake inhibition by the anti-muscarinic actions of benztropine. This possibility was investigated further with drug mixture experiments in which doses of atropine (1, 3, or 5.6 mg/kg) were administered in addition to cocaine, and preliminary results suggest that a 1:1 mixture of atropine and cocaine at 1, 3, and 5.6 mg/kg results in maximum dose-dependent substitution for benztropine with no rate reduction or difference in relative potency. Data suggest that both muscarinic blockade and inhibition of dopamine uptake contribute to the discriminative stimulus effects of benztropine.

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ROLE OF CONDITIONING IN THE PHASIC FIRING PATTERNS OF NUCLEUS ACCUMBENS NEURONS EXHIBITED DURING COCAINE SELF-ADMINISTRATION IN RATS

R. M. Carelli and S. A. Deadwyler

A subset of nucleus accumbens (NA) neurons exhibit phasic changes in firing rate during cocaine self-administration and water reinforcement in rats (Carelli et al., 1993; Carelli and Deadwyler, in press). The emergence of NA phasic firing patterns was shown to correspond to the onset of stable self-administration behavior which followed an initial "load-up" period of 2-6 cocaine infusions (Carelli *et al.,* 1993). The objective of the present study was to examine whether NA phasic activity is related to cocaine delivery or to conditioned stimuli (CS) paired with drug infusion. NA neurons were recorded from permanently implanted multiple electrode arrays inserted bilaterally into the NA in subjects (n=14) exhibiting stable self-administration behavior. Lever depression (FR1) resulted in i.v. administration of cocaine (0.33 mg/inf, 5.8 sec) signalled by simultaneous onset of a tone-houselight CS complex (20 sec). Results indicate that the initial "load-up" period and the corresponding onset of NA phasic activity could be prolonged further in the session by decreasing the dose of cocaine per infusion, or by pretreatment with the Dl antagonist, SCH23390 (10 μg/kg, sc). In addition, NA phasic activity was not related to a direct acute pharmacological action of cocaine since such patterned discharges were absent during response independent cocaine infusion (Carelli *et al.,* 1993). However, NA neurons increased firing during CS presentation in the absence of the drug. These findings suggest that the onset of NA phasic activity during self-administration is dependent upon increased systemic levels of cocaine (and perhaps increased NA dopamine, Pettit and Justice 1989) and is also influenced by conditioned stimuli.

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THE PROGRESSIVE-RATIO (PR) SCHEDULE AS A MEASURE OF THE RELATIVE REINFORCING PROPERTIES OF THE COMBINATION OF COCAINE AND HEROIN ("SPEEDBALL") WITH EACH COMPONENT ALONE

J. Francher, C. Duvauchelle, T. Sapoznik, and C. Kornetsky

The purpose of this experiment was to compare the break points of a progressive ratio reinforcement schedule of three dose levels of the combination of cocaine and heroin and each of the three respective doses of the drugs alone. The dose levels of the cocaine/heroin combinations were .009/.15, .018/.3, and .036/.6 mg/kg, respectively. Subjects were 18 Wistar male rats. While there was a significant dose-dependent increase in the final break points completed by the rats when administered cocaine alone, no such dose dependent relationship was found with heroin alone or the combination. Also, the final break points for the self-administration of cocaine was higher and that for heroin lower than the break points for the respective combinations. These results question the validity of PR break point as an indicator of the relative reinforcing properties of abused substances.

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ADMINISTRATION IN RATS: THE EFFECT OF SCH23390

Y. Egilmez, M. W. Emmett-Oglesby, and J. D. Lane

This experiment tested the hypotheses that self-administration of cocaine would produce an increase in the dopamine (DA) oxidation current in the nucleus accumbens (n. acc.) and that this increase would be correlated to the amount of drug taken during a single experimental session. Rats trained to self-administer cocaine under a fixed-ratio 2 schedule were bilaterally implanted with a stearate-modified carbon paste electrode in each n. acc. The effect of pre-treatment with the DA (D1 subtype) receptor antagonist SCH233390 (18 ugkg s.c.) on the DA oxidation current associated with self-administration of three doses of cocaine (0.25, 0.5 or 1 mg/inj) or saline-vehicle (extinction) was investigated using a chrono-amperometry technique.

During the experimental sessions, cocaine or saline was available only for one hour. Increasing doses of cocaine produced slower rates of self-administration which resulted in approximately the same amount of cocaine-intake per unit time. The area under the time-course curve of DA signal did not differ significantly for different doses of cocaine. SCH23390 produced an approximately two-fold increase in the rate of cocaine intake, hence the total amount of drug taken per unit time. This, in turn, resulted in an approximately 1.9-fold increase in the DA oxidation current. These data show that acute cocaine produces an increase in the DA concentrations in the n. acc. and that a faster rate of cocaine intake in the presence of a D1 receptor antagonist produces a greater increase in DA levels.

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SELF-ADMINISTRATION OF THE DOPAMINE UPTAKE INHIBITOR NOMIFENSINE INTO NUCLEUS ACCUMBENS OF RATS

R. A. Wise and W. A. Carlezon, Jr.

While nucleus accumbens septi (NAS) is thought to be the trigger zone for psychomotor stimulant reinforcement, it has been reported that rats will not self-administer the dopamine (DA) uptake inhibitor cocaine (COC) into this brain structure. Rats will, however, self-administer amphetamine (AMP) into NAS and they will self-administer COC into another DA terminal field, the medial frontal cortex. Because NAS lesions disrupt intravenous self-administration of either AMP or COC, we explored the possibility that another DA uptake inhibitor, nomifensine (NOM, which lacks cocaine's local anesthetic properties), would be self-administered into NAS. Rats (n=8 per group) with injection sites located in the shell region of NAS learned to lever-press reliably by the eighth test session when given response-contingent (FR-1) microinfusions of NOM (1.7 nmoles/120 nl/infusion), but not when given similar microinfusions of vehicle. Microinfusions of NOM dorsal to NAS were less effective and non-contingent ("yoked") microinfusions of NOM into NAS were ineffective in establishing lever-pressing habits. In rats with established lever-pressing habits, responding decreased progressively when vehicle was repeatedly substituted for NOM or when the DA (D2) antagonist sulpiride (120 pmoles/infusion) was repeatedly co-infused with NOM. The reinforcing efficacy of COC (90 pmoles/infusion) was also assessed under the same conditions as were used to assess that of NOM; consistent with previous work, there were no progressive increases in lever pressing rates when rats (n=3) were tested under these conditions on 12 occasions. However, when testing continued after increasing the dosage of COC (150 pmoles/infusion), reliable increases in lever-pressing were observed in all animals by the sixteenth test session. Together, the ability of NOM and COC to reinforce lever pressing appears to confirm other evidence implicating NAS as an important site for the reinforcing action of both DA releasers and uptake inhibitors. It is not clear why COC injections into NAS are not more effective, but the fact that only the high doses are effective rules out the possibility that local anesthetic "side effects" play a significant role.

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STUDY OF DYNORPHIN A PEPTIDES *IN VITRO* PROCESSING IN HUMAN BLOOD BY MATRIX-ASSISTED LASER DESORPTION MASS SPECTROMETRY

J. Z. Chou, B. T. Chait, R. Wang, and M. J. Kreek

The biotransformation in human blood *in vitro* of Dyn A (1-17), a natural product from prodynorphin; Dyn A (1-13), the initially sequenced dynorphin A derived peptide which is frequently used in lab and more recently in clinical studies; and Dyn A (1-10) amide, a synthetic analog of Dyn A (1-17); was studied by matrix-assisted laser desorption mass spectrometry (MALDMS). Synthetically made Dyn A peptides were added to freshly drawn blood which was then incubated at 25°C for various periods of time. Many processed peptide fragments were identified from each of these peptide precursors, and the time profiles of appearance and disappearance of the major processed products were followed semi-quantitatively using MALDMS and quantitatively using HPLC for some of the processed products of the precursor peptides with the aid of an internal standard, substance P.

Dyn A (1-17) was found in significant amounts even at four hours after it was added to human blood, *in vitro*. The amount of Dyn A (2-17). one of the major processed products of Dyn A (1-17) in blood, continued to accumulate during the entire incubation period (4 hours). Both Dyn A (1-13) and Dyn A (1-10) amide were processed rapidly in human blood, *in vitro*. Most of the fragments from these two peptide precursors were also processed quickly with the exception of Dyn A (4-12) (derived from Dyn A (1-13)) and Dyn A (4-10) amide (derived from Dyn A (1-10) amide). They were detected by MALDMS for over an hour in blood, *in vitro*. Dyn A (1-6) was found as a biotransformation product from all three peptide precursors, however, the amount of Dyn A (1-6) in blood was small irrespective of the precursor peptides added *in vitro*. The identification of some of these peptide fragments is confirmed by "protein ladders sequencing" with 2-step incomplete Edman degradation and mass spectrometry. This suggests that one of the important functions of the "extra" 4 amino acids provided by "nature" in Dyn A (1-17) (as compared to Dyn A (1-13), for instance) is its ability to stabilize or protect the peptide from processing by enzymes in human blood.

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TOLERABILITY STUDY OF A DEPOT FORM OF NALTREXONE SUBSTANCE ABUSERS

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INTRODUCTION: Oral naltrexone has been associated with a high early dropout rate. A injectable depot form of naluexone could improve compliance in otherwise poorly motivated opiate addicts. A previous sustained release preparation of naltrexone using 1.5 mm diameter spheres showed opiate receptor blockade but some subjects developed tissue inflammation. In the current study, we evaluate the safety and tolerability of a depot form of naltrexone with smaller microspheres (105-150 μm). SUBJECTS: Eight cocaine dependent males (34.1 years of age, range = 23-45) with no evidence of opiate dependence and in good physical health were subjects in the study. One subject on the high dose was excluded due to adverse effect of the morphine challenge. DESIGN: The study was a double-blind, placebo-controlled two dose inpatient/outpatient study. Subjects were evaluated for 64 days. LOW DOSE PHASE (n=4, 3 drug, 1 placebo): Subjects received 1.2 cc (103 mg) of naltrexone preparation or placebo subcutaneously in triceps of each arm (one arm received placebo). When subjects did not experience severe side effects to this low dose after 64 days, the high dose phase was conducted. HIGH DOSE PHASE (n=4, 3 drug, 1 placebo): Subjects received 2.4 cc (206 mg) of naltrexone preparation or placebo in a similar fashion to the low dose group. Plasma naltrexone levels were obtained during both phases. RESULTS: Subjects generally reported mild injection site pain; erythema was observed in most subjects, but was not severe and subsided over the course of the study. Induration without pain or discomfort was the most persistent side effect. Blood chemistries and CBC did not change significantly over the course of the study. Morphine challenge: Subjects in the high dose group were challenged with 10 mg IV morphine on days 8, 15, 22, and 29 of the inpatient stay. Opiate receptor blockade was observed although physiologic and subjective responses were variable. CONCLUSIONS: The depot formulation of naltrexone used in this study appeared well-tolerated and resulted in plasma levels of 1 ng/ml or greater for more than three weeks. Higher doses of opiate agonists may better assess efficacy of this depot formulation of naltrexone. Future studies to assess the acceptability, tolerance, and efficacy of depot naltrexone in outpatient detoxified opiate addicts appear indicated.

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A COMPARISON OF BUPRENORPHINE'S AND NALTREXONE'S OPIOID BLOCKADE ABILITIES

K. J. Schuh, S. L. Walsh, and M. L. Stitzer

Buprenorphine is an opioid partial agonist proposed for treatment of opioid dependence. It is long-acting which may allow dosing on a less-than-daily basis when used for opioid maintenance. A therapeutic benefit of opioid maintenance is the development of cross-tolerance which blocks the effects of other opioids. This study examined the development of buprenorphine's opioid blockade effects and compared the magnitude and duration of these effects with those of naltrexone, a long-acting opioid antagonist.

Eight non-dependent opioid abusers participated in this ten week inpatient study. Using double-blind and double-dummy controls, each subject was maintained for one week on each of five maintenance conditions: placebo, naltrexone (25 and 100 mg p.o.), and buprenorphine (2 and 8 mg s.l.). Each maintenance week was followed by a washout week when the subjects were maintained on placebo. The subjects participated in three hydromorphone challenge sessions each week. Thus, we examined the blockade development after 1, 3, and 5 maintenance drug treatments (maintenance weeks) and the blockade duration 1, 3, and 5 days after maintenance treatment was discontinued (washout weeks).

Both naltrexone and buprenorphine greatly attenuated hydromorphone's subjective effects. Attenuation was nearly complete at all doses from the first day of maintenance. Naltrexone blockade of the miotic effects was less complete than its blockade of the subjective effects. When low dose maintenance was discontinued, blockade of both subjective and physiological effects was quickly lost. Hydromorphone's effects had returned to placebo levels by 3 days after discontinuation of either 2 mg buprenorphine or 25 mg naltrexone. High doses of both maintenance drugs produced long-lasting blockade; hydromorphone's effects were attenuated for up to five days after the last dose. However, five days after the last maintenance dose blockade produced by 8 mg buprenorphine was incomplete (resulting in 50% of control hydromorphone response) while blockade produced by 100 mg naltrexone was still nearly complete. These results suggest that both naltrexone and buprenorphine produce potent and long-lasting opioid blockade. In addition, 8 mg buprenorphine may produce blockade of a sufficient potency and duration to accommodate a less-than-daily maintenance schedule.

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THE PHARMACOKINETICS STUDIES OF LAAM: CLINICAL CORRELATES

M. Beckson, W. Ling, F. Vocci, W. Pickworth, P. Fudala, J. Wilkins, and K. Clagett-Carr

This study was conducted to determine the safety and pharmacokinetics of LAAM in male and female opioid-dependent patients transferred from methadone maintenance treatment. The absorption, distribution, metabolism and elimination of LAAM, and the formation, distribution, metabolism and elimination of the metabolites, nor-LAAM and dinor-LAAM, were determined for a single initial dose of LAAM, trough levels during two weeks of dosing, a single maintenance dose at steady state conditions, and trough levels once weekly during the three-week outpatient follow-up phase. The only reported adverse event, moderately severe cellulitis at the site of angiocatheter insertion, was related to the study procedure itself rather than to LAAM.

The patient was treated with antibiotics and recovered without sequelae. Laboratory results, including hematology, chemistry, urinalysis, and ECGs at pre-treatment and discharge, were reassuring. The only systematic change observed was hematology. All patients showed a slight decrease in RBC. hemoglobin, and form pre- to post-treatment; the magnitude of these changes was small and did not result in adverse clinical consequences. No statistical association was found between QT prolongation and age. gender, race/ethnicity, clinical site, or use of adjunct medication. No consistent signs of withdrawal or excessive dosing were reported, and most reported symptoms were mild and of short duration. The most commonly reported symptom was constipation (37.5%). Insomnia was also reported (18.8%). No patient withdrew from the study for complaints relating to underdosing. No clinically significant abnormalities were noted at admission or termination physical examination. In conclusion, it was demonstrated that LAAM was safe under the conditions of this study.

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BUPRENORPHINE AND NALOXONE INTERACTIONS IN HEROIN DEPENDENT VOLUNTEERS

R. T. Jones and J. Mendelson

Sublingual buprenorphine appears useful for the treatment of opiate dependence. A sublingual combination dose formulation of buprenorphine and naloxone should have less potential for parenteral use by heroin-dependent individuals since injection of the combination dose should precipitate opiate withdrawal. Because of naloxone's relatively low sublingual bioavailability it would have no effect by the sublingual route.

Healthy opiate-dependent daily users of heroin were recruited by newspaper ads. Self-reported daily opiate use was 0.3 gm ± 0.1 gm. Opiate dependence was confirmed during the screening process by confirming precipitated withdrawal after 0.4 and 2 mg intravenous doses of naloxone. Ten hospitalized heroin users were given on four separate occasions at weekly intervals buprenorphine (2 mg), or naloxone (2 mg), or buprenorphine and naloxone combined (2 mg of each drug), or placebo. Drugs were administered under double blind conditions as a single intravenous dose injected over 60 seconds. Self and observer reports of opiate agonist and antagonist signs and symptoms were obtained for four hours after each injection. Data was analyzed by ANOVA.

Buprenorphine alone produced moderately intense opiate agonist effects with increased ratings of global opiate intoxication and good drug effect. The subjective effects of buprenorphine and naloxone in combination resembled naloxone given alone. Cardiovascular effects, pupil diameter changes and skin temperature did not differ between, treatments. Two subjects left the study after their first exposure to naloxone, one after naloxone alone and one after the combination dose. About half of the subjects were unable to distinguish naloxone alone from the combined medications during the first hour after injection. Buprenorphine effects were significantly altered by naloxone with diminished opiate agonist effects and increased opiate antagonist effects throughout the four hour testing session. Subjects on average valued the buprenorphine dose at $10 ± 8 and the combination dose at $1 ± 4. They typically spent $35 per day on heroin.

Our findings suggest that buprenorphine and naloxone in combination has a relatively low parenteral abuse potential in daily heroin users not enrolled in or seeking a treatment program.

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THE EFFECT OF CLONIDINE ON NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

M. I. Rosen, T. J. McMahon, F. A. Hameedi, and T. R. Kosten

Introduction: The effect of a pre-treatment, medication (compared to placebo) on serial naloxone challenge tests (NCTs) in the same opiate-dependent individual is an efficient way to test new medications for their effects on opiate withdrawal. The validity of this method was assessed by determining the effects of a well-studied treatment for opiate withdrawal, clonidine, in this paradigm.

Method: Four opiate-dependent subjects were hospitalized and stabilized on the opioid levorphanol, 6 mg po tid, for at least five days. NCTs were then done on four consecutive days. In a balanced, randomized 2X2 design, pre-treatment for the three hours prior to naloxone was with either clonidine 0.5 mg in divided doses or placebo; and naloxone doses were either 0.2 mg or 0.4 mg intravenously. Outcome measures for the hour after naloxone included vital signs, pupillary size, subject and observer ratings of opiate withdrawal, and plasma ACTH levels.

Results: Preliminary analysis for the first four subjects show that four of four, when given active clonidine pre-treatment. had lower observer-rated withdrawal scores after 0.4 mg of naloxone for opiate withdrawal signs shown by prior studies to be clonidine-responsive. Blood pressure and pulse were lower after active clonidine before naloxone and this persisted after naloxone. Subjective withdrawal ratings did not appear to be different with clonidine pre-treatment.

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ABUSE LIABILITY EVALUATION OF BUPRENORPHINE IN BUPRENORPHINE-TREATED PATIENTS

E. C. Strain, S. L. Walsh, K. L. Preston, I. A. Liebson, and G. E. Bigelow

Buprenorphine is an opioid partial agonist being developed as a new treatment agent for opioid dependence. Currently, all buprenorphine dispensing is at opioid treatment clinics, and no take-home buprenorphine is permitted. The abuse potential of buprenorphine in buprenorphine-maintained patients is not known. The purpose of this study was to characterize the acute effects of buprenorphine in comparison to hydromorphone and placebo, in opioid-dependent volunteers maintained on buprenorphine. Participants were eight inpatient opioid abusers maintained (>2 weeks) on sublingual buprenorphine (8 mg per day). Testing was twice per week. Each test session consisted of baseline data collection, followed by double-blind IM injection of either buprenorphine (4, 8, or 16 mg), hydromorphone (9 or 18 mg), or saline, followed by two hours of data collection. Injections were 16 hours after the last dose of buprenorphine. Measures included physiologic monitoring, and subject and observer ratings of drug effects. Buptenorphine and hydromorphone each produced significant opioid agonist-like effects: pupillary constriction, increased blood pressure, subject-rated and observer-rated increases on opioid agonist adjective scales and increased subject visual analog scale ratings of drug effect, high, good effect, and liking. Hydromorphone effects were generally greater than those of buprenorphine, but not significantly so. These results indicate 8 mg of daily sublingual buprenorphine does not produce complete cross-tolerance to high doses of buprenorphine or hydromorphone. This suggests that buprenorphine treatment doses may need to be higher than 8 mg, and that supplemental buprenorphine doses may have abuse liability in buprenorphine-maintained patients.

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LAAM LABELING ASSESSMENT STUDY: RETENTION, DOSING, AND SIDE EFFECTS IN A 64 WEEK STUDY

S. Herbert, A. Montgomery, P. Fudala, F. Vocci, J. Gampel, J. Mojsiak, J. Hill, and R. Walsh

Six hundred and twenty-three methadone maintenance patients and street addicts (419 males, 204 females) were dosed with LAAM in an open label, non-randomized study at 26 outpatient methadone maintenance clinics. Four hundred and forty-one (70.8%) of the patients completed the 12 week initial treatment Phase I, 300 (71.8%) of the male patients and 141 (69.1%) of the female patients. 57% of those who terminated in Phase I did so in the first three weeks of treatment. Of those who completed 12 weeks, 216 or 49.0% completed the 52 week continuation phase: 146 males (34.8%) and 70 females (34.3%). As with gender there was no difference in retention rates among the racial/ethnic groups or by methadone status at study entry (methadone maintained patient who transferred to LAAM vs. street addict seeking treatment and inducted directly onto LAAM vs. street addict stabilized on methadone < 30 days and then switched to LAAM).

Study dosing guidelines were established through review of literature on LAAM. with the final decision on dosing levels left to the discretion of the treating physician. The average LAAM dose was 72.5 mg for males and 77.3 mg for females at week 12 and 65.8 mg for males and 73.2 mg for females at week 64. The slightly higher average dose for females continued throughout the study. As methadone maintained patients transferred to a LAAM dose equivalent to 1.2-1.3 times their methadone dose, and street addicts started at a LAAM dose between 20-40 mg, the dose of the former group was considerably higher during the early part of the study. By the end of the study, however, the difference in doses among the groups narrowed and the dose of the methadone transfers was only about 5mg above the street addicts.

LAAM was generally well tolerated. The most frequently reported side effects were similar in Phases I and II and included feeling bad, difficulty sleeping, constipation, aching bones and joints, sweating, and low energy/fatigue. Insomnia and nervousness were seen as possibly unique to LAAM while many of the others were expected effects of either opiate use or withdrawal.

This study, designed to provide additional information about the current opiate addict population to the historic database on LAAM studies of the 1970's and 1980's, showed similar dosing and retention patterns, and no new or unexpected reactions or side effects.

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ROUTES OF PRIOR OPIATE ADMINISTRATION: EFFECTS ON OUTCOME VARIABLES IN THE NIDA/MDD #999a BUPRENORPHINE MULTICENTER STUDY

D. L. Segal and J. L. Hill

NIDA's Medications Development Division in cooperation with the Los Angeles Addiction Treatment Research Center, sponsored a randomized, double blind, one year multicenter clinical trial in which 733 subjects were dosed to study the safety and efficacy of buprenorphine in the treatment of opiate dependence. This paper focuses on several outcome measures from the 16-week maintenance phase of the study according to subjects' preferred route of opiate administration at baseline.

We compared the results from 464 intravenous injectors (IV) with 2 16 snorters (N=204)/smokers (N=12) (S/S). Not included in this analysis were 38 oral abusers, at least 26 of which were addicted to prescription analgesics--Percocet being the most common, and 15 subjects claiming preference for "other" routes.

Results: The most dramatic results were seen in the very sharp decrease in heroin craving on a visual analog scale near 80 (with 0 being no craving and 100 the worst craving ever experienced),. After being on buprenorphine maintenance therapy for four weeks, craving dropped to about 36 in the IV group and to 26 in the S/S group. Craving for cocaine, however, decreased only slightly. Regarding retention in treatment, 44% of the IV users completed the 16 week study while 63% of the S/S completed. When comparing the percent of subjects with 13 consecutive opiate-free urines, 14.4% of the IV users and 18.5% of the S/S were "clean" for that time period. At baseline, however, *all*
subjects were using opiates on a daily basis--one of the entrance criteria.

Based on these results, we suggest that: 1) Heroin craving can be reduced significantly within four weeks of initiating buprenorphine maintenance therapy; 2) Heroin addicts who prefer the IV route of administration are probably more heavily addicted and have a longer history of substance abuse than are S/S. The IV users in this study had a prior history of having been enrolled in about 4.6 times as many methadone maintenance programs as the S/S; 3) The ritual of injecting may have its own separate reward and is thought to be a potent reinforcer even in the tolerant addict. Therefore, we believe it is necessary to identify primary routes of administration in future treatment settings as well as research studies.

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CORRELATES OF MATERNAL SMOKING AMONG BLACKS AND WHITES

P. Andreski and N. Breslau

Data from a large study (n=801) on the sequelae of low birth weight at six years of age were used to identify potential risk factors of maternal smoking in blacks and whites. It was hypothesized that maternal smoking will vary by race, age, education, psychiatric history, marital status, burden of child care, and employment. Multiple logistic regressions were used to estimate the association between smoking and potential risk factors in whites and blacks separately. Results: Low education, young age, current psychiatric disorder, and an index child with a psychological/physical illness predicted current smoking, regardless of race. For blacks, employment status was an additional predictor of smoking. For whites, current smoking was also associated with being a single mother and caring for more than one pre-school child. For whites, the combined effect of being single and caring for an ill index child was a particularly strong predictor of smoking, odds ratio=5.3 (95% CI, 2.2-13.3). Conclusions: This study identified common and race-specific predictors of maternal smoking. It highlights the importance of burden of child care as a factor in maternal smoking.

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CALORIC RESTRICTION INCREASES SMOKING IN NICOTINE-DEPENDENT ADULTS

L. J. Cheskin, J. Hess, L. Wiersema, J. E. Henningfield, and D. A. Gorelick

Food deprivation in animals increases self-administration of abused drugs such as ethanol and nicotine (Carroll & Meisch 1984; Lang *et al.,* 1977). A related phenomenon is the weight gain commonly associated with smoking cessation (U.S. Surgeon General 1988). There have been no controlled studies reporting an effect of caloric or carbohydrate (CHO) restriction on drug use by drug-dependent humans. This study measured the effect of diet on cigarette smoking, in 16 (8 male), non-obese, healthy, nicotine-dependent (DSM-IIIR criteria) volunteers, 21-55 years old, who regularly smoked 20-40 cigarettes daily, scored >7 on Fagerstrom tolerance questionnaire, and had afternoon expired breath CO of >20 ppm. Subjects were housed on a metabolic research ward for four weeks, during which, using a Latin square, single-blind, random assignment design, they were cycled through each of four diets for six days apiece (Sunday through Friday, with Saturday a washout day): normal calorie; low calorie (700 kcal/day balanced deficit); normal calorie, low CHO (ketotic); and low calorie, low CHO. Subjects' preferred cigarette brand was available ad lib. Cigarette counts, craving for cigarettes and food (100-mm visual-analogue scales, mood, body weight, and urinary ketones were measured daily; expired breath CO seven times daily. Data from the last day of each diet were analyzed by a repeated measures ANOVA or by ANOVA on ranks when assumptions of normality were not met. Two-tailed alpha level=0.05.

The low calorie (balanced) diet resulted in 8% more cigarettes smoked ($p<0.02$) and 10% higher breath CO ($p<.01$) than the normal diet. The low calorie, low CHO diet produced 12% higher breath CO ($p<.04$) than the normal 'diet. The normal calorie, low CHO (ketotic) diet produced no significant effects. While these effects are of small magnitude, they are consistent with animal studies. Since drug abuse often alters the diet of the drug abusers (usually by decreasing intake), these findings raise the possibility that the dietary effects of drug abuse could result in further drug use (i.e., a positive feedback). There may also be consequences of this effect in patients seeking to quit smoking cigarettes.

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ASSESSING SEVERITY OF NICOTINE DEPENDENCE

K. L. Sees, D. T. Hartz, R. F. Muñoz, and S. M. Hall

We report differences in categorization of nicotine dependence severity as a function of criteria used. The Diagnostic Interview Schedule (DIS) is a widely used research instrument for making DSM-III-R diagnoses. For nicotine dependence, however, the DIS excludes two of the DSM-III-R criteria (3 & 4), on the basis that they do not apply, and operationalizes others (5 & 7) in an overly restrictive manner. Consequently, the DIS neither makes a completely accurate DSM-III-R diagnosis of nicotine dependence, nor reliably qualifies the severity of nicotine dependence. Using the DIS, 14.9% of 154 subjects were diagnosed with mild dependence, 70.8% with moderate dependence, and 14.3% with severe dependence. Due to concerns with the diagnosis of nicotine dependence using the DIS criteria, we developed an alternate instrument, the Nicotine Dependence Scale (NDS). The NDS is based on all nine of the DSM-III-R criteria and is more liberal in interpreting criteria five and seven. Using the NDS, 74.3% of subjects endorsed the third DSM-III-R criterion, 90.8% endorsed the fourth DSM-III-R criterion, and 6.6%, who did not meet the DIS tolerance requirement (DSM-III-R criteria 7), were classified as nicotine tolerant. Using the NDS, 7.1% of subjects were diagnosed with mild dependence, 71.4% with moderate dependence, and 21.4% with severe dependence. We correlated the two methods of assessing nicotine dependence with the Shiffman Withdrawal Scale and various baseline mood measures. Psychometric analysis of the NDS suggests convergent, concurrent, and predictive validity and, further, that the associations involved are of higher magnitude for the NDS than for the DIS. Therefore, although the DIS has been widley used as a smoking cessation research instrument, its continued use may not be justified.

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EFFECT OF CUE-TYPE AND CIGARETTE AVAILABILITY ON CRAVING AND SMOKING BEHAVIOR

A. Droungas, R. Ehrman, A. R. Childress, and C. P. O'Brien

It has been suggested that Pavlovian conditioning mechanisms underlie the maintenance of substance abuse and relapse. Consistent with this idea, we showed that smokers report greater craving for cigarettes in response to smoking cues compared to affectively neutral or unpleasant nonsmoking cues (Droungas *et al,* 1993). The current study examined whether the differential reactivity to smoking cues, compared to affectively neutral or unpleasant nonsmoking cues, is affected by expectations regarding the opportunity to smoke. Twenty-six smokers viewed a video and then engaged in a task in each of three sessions. Half of the subjects (group SMOKE) were told ahead of time that they could smoke following each session and the remaining half (group NO SMOKE) were told that they could not smoke. In the "smoking" session the video showed individuals smoking, and the subject handled cigarettes and matches or lighter. In the "unpleasant" session the video showed people getting injured in an industrial setting, and the subject sorted pictures of people with severe physical deformities. In the "nonsmoking" session the video was a nature documentary, and the subject sorted children's playing cards. The dependent variables in each session were: a) subjective ratings of mood, b) subjective ratings of drug-related states (DRSs), namely, "desire to smoke", "nicotine-like high", "nicotine-like withdrawal", and c) latency to initiate smoking only in group SMOKE. Statistical analyses of the mood-ratings showed that subjects in both groups rated the unpleasant cues as affectively more negative compared with the neutral cues. Statistical analyses of the DRSs-ratings showed that only subjects in group SMOKE responded differentially to the three types of cues. These subjects reported a greater "desire to smoke" and stronger "nicotine-like withdrawal" in response to the smoking cues, compared with the unpleasant and the neutral cues. Group SMOKE smoked faster after the smoking cues than after the neutral cues. These data support the notion that perceived availability of a drug determines the impact of drug-cues on craving and subsequent drug-use.

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Available upon request of senior author.

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CUE REACTIVITY IN SMOKING CESSATION: CAN REACTIVITY PREDICT OUTCOME?

V. W. Rees, J. D. Greeley, and R. F. Westbrook

It is now widely recognized that drug craving can be elicited in the presence of stimuli that have been paired with the effect of a drug. The Pavlovian conditioning theory of drug cue reactivity suggests that exposure to drug cues can trigger subjective and physiological reactivity. This study examined the relationship between cue reactivity and treatment outcome, as reactivity may, through the elucidation of conditioned responses, be implicated in the relapse process. Evidence for changes in cue reactivity following treatment, without active cue-exposure procedures was also sought. Twenty-five moderate-heavy smokers commencing intensive cognitive-behavioral treatment were tested for cue reactivity before and after treatment. Both groups were followed up at three months. A significant reduction in cue-elicited urge to smoke was observed over the treatment period [$t(22) = 4.001 p<.05$], but no changes in reactivity were observed on the skin conductance response, suggesting that involvement in a treatment program was effective in reducing cue-elicited urge responses but not physiological reactivity. At three month follow-up, only five subjects were abstinent, although most subjects had reduced daily cigarette consumption [38% mean reduction].

Physiological cue reactivity was most important in determining reduction in cigarette consumption. Pre-treatment skin conductance reactivity was found to correlate significantly with smoking reduction [r = .457, p, .05], but self-reported urge reactivity did not [r = .147]. When incorporated into a multiple regression model, skin conductance and change in self-efficacy from pre- to post-treatment accounted for a significant 36% of the variance of daily cigarette consumption [$F(4,17) = 4.755$, p, .01]. That is, greater physiological reactivity and poorer improvement in self-efficacy were associated with poorer outcome. The findings point to the importance of cue reactivity in mediating changes in smoking behavior, and suggest that cue exposure for reducing physiological reactivity would be an important addition to treatment interventions for smokers.

AFFILIATIONS:

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STAGES OF CHANGE AND CIGARETTE SMOKING AMONG CHRONIC PSYCHIATRIC PATIENTS LIVING IN SUPERVISED LIVING SETTINGS

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Most chronically psychotic patients smoke. We had observed clinically, that chronic patients who had quit, seemed to function better than those who had not. We hypothesized the patients who had been able to quit on their own, would have fewer drug or alcohol problems, be less likely to have guardians, and more likely to live independently.

METHOD: We interviewed 300 chronically psychotic patients using the Stages of Change Questionnaire and verified their smoking status with Residential Cam Home operators and the patient's clinician. Then we checked the charts for diagnosis, living situation, and guardianship status. These findings were confirmed or modified to the current status by consulting with the patient's clinician. To assess drug and alcohol problems, the clinician was asked to identify the patients in their case load for whom they had established a treatment plan to intervene with a drug or alcohol problem.

RESULTS: There were 10.67% patients who had never smoked, and 14% who had quit for six months or longer (maintenance + termination). Hence slightly over 75% of the sample smoked although six percent were actively trying to quit (preparation and action). Mean age of the sample was 56.6 years (SD=12.8) with a range of 27 to 85. Males accounted for 288 of the 300 patients interviewed. Schizophrenia accounted for 65%, SchizoAffective Disorder for 22%. and Bipolar Disorder for 8% of the sample. The remaining 5% of diagnoses included Major Depression, organic syndromes, Delusional Disorder and one case of Generalized Anxiety. Alcohol/Drug problems were found in 25% of the sample. Patients who were conserved of person (a guardian who has control over where the patient lives and can order the patient taken to a treatment facility) constituted 11% of the sample. Most patients had a guardian of their funds (51%), and 38% had no guardian or conservator. Most lived in Residential Care Homes (84.7%), 13% lived independently, and 2.33% lived with their families. The remaining analyses compare former smokers and current smokers. Never smokers are omitted except were noted. Former smokers were more likely to live independently ($p<.026$) and were far less likely to have a drug or alcohol problem ($p<.013$). Former smokers were more likely to have no guardian and not be conserved. This finding only approaches significance ($p<.08$). When Never Smokers are added to the analysis of guardianship and smoking status, the results are statistically significant ($p<.02$).

DISCUSSION: Our hypotheses were confirmed. Attempts to aid quitting in this population will likely be rewarded by assisting the more functional patients. Some caution should be exercised in that most of the sample were older men.

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AFFILIATION: VAMC, Palo Alto, California, UCSF, and San Francisco VAMC

IMPACT OF INPATIENT SUBSTANCE ABUSE TREATMENT ON CIGARETTE SMOKING

R. I. Kim, K. L. Sees, and K. L. Delucchi

The present study is PHASE I of a two-part study on cigarette smoking levels during a short-term inpatient substance abuse treatment. Using one-group pre-post-test design, we were interested in (1) exploring whether a short-term inpatient substance abuse treatment program affects cigarette smoking rates; and (2) examining the relationship between patients' psychosocial functioning in relation to cigarette smoking. The pre-assessment occurred 24-72 hours prior to hospital admission for the substance abuse treatment, and the post-assessment occurred on the 10th-13th day of the treatment. The pre- and post-assessments included a breathalized Carbon Monoxide (CO) test and sets of self-report measures. Subjects were 38 male veterans, age range of 29 to 60 (m=44.8, SD=7.6); predominantly unemployed (92%); ethnic-makeup of white (45%), African-American (42%). and Hispanic-American (13%); smoking range of 3 to 40 cigarettes per day (m=18.2, SD=11.6); over half (6 1%) reported alcohol as their main drug of choice, and 28% reported cocaine as their main drug.

Matched-pair t-tests between subjects' pre- and post-assessments revealed no significant difference in their CO levels but did reveal a significant difference in subjects' self-reported measures (number of cigarettes smoked per day) of their smoking ($t=-4.67$, $p<.001$). Other t-tests resulted in significant decreases in depression levels ($r=-7.53$, $p<.001$) and stress levels ($t=6.10$, $p<.001$) at post-assessment. Among the correlational findings, the larger the decrease between pre- and post-assessment CO levels, (1) the higher the subjects' post-assessment depression ($r=35$, $p<.05$) and (2) the more number of years of 'a pack per day' smoking rate ($r=.35$, $pc<05$). Furthermore, subjects with alcohol as their primary drug appeared less interested in quitting smoking ($r=.33$, $p<.05$). Although self-reported smoking significantly decreased at the post-assessment, this was not biologically verified by the CO measures. Short-term inpatient substance abuse treatment, therefore, does not appear to impact levels of cigarette smoking, but may distort patients' perceptions of smoking. This study was an important first step prior to implementing a smoking cessation/education research intervention (PHASE II). Since no difference in subjects' cigarette smoking at pre- and post-assessment was found, any differences that we may find in the PHASE II study can be attributed to the smoking intervention. Moreover, variables related to cigarette smoking, substance abuse, and other psychosocial characteristics found in the present study can be examined during PHASE II for comparative purposes.

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AFFILIATIONS:

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COMBINING INDIVIDUAL RELAPSE PREVENTION COUNSELING WITH A TRANSDERMAL NICOTINE PATCH FOR SMOKING CESSATION

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Introduction:
Although transdermal nicotine replacement therapy appears to be quite effective for short term smoking cessation, limited success rates have been reported at long term follow-up. Concurrent cognitive/behavioral relapse prevention interventions may be an effective adjunct to the nicotine patch for the maintenance of abstinence following smoking cessation.

Objectives:
The purpose of this study is to investigate whether the addition of 16 weeks of individual cognitive behavioral relapse prevention counseling enhances the effects of a medically based intervention consisting of ten concurrent weeks of transdermal nicotine replacement therapy in combination with brief advice and education about smoking consequences.

Methods:
Eighty-one nicotine dependent study subjects, smoking at least 20 cigarettes per day and having at least one previous attempt to quit were randomly assigned to one of two treatment conditions: A) Transdermal nicotine replacement therapy plus advice and education about smoking consequences; or B) Transdermal nicotine replacement therapy plus advice and education about smoking consequences plus manual guided individual cognitive/behavioral relapse prevention counseling. The outcome criterion selected was abstinence, measured by self-report and confirmed by exhaled CO concentration and urine cotinine analysis.

Preliminary findings:
This study is in its preliminary stages of development, and our small n's do not allow us to draw definitive conclusions. However, preliminary results show a trend consistent with higher abstinence rates (54% vs. 22%) at one year follow-up when individual cognitive/behavioral relapse prevention counseling was added to the medically based intervention. Relapse prevention counseling seemed to be especially effective in those smokers with heavy nicotine dependence (Fagerstrom scores between 8 and 11).

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VALIDITY OF THE SACHS OPTIMUM DOSING ALGORITHM (SODA) FOR DETERMINING NICOTINE PATCH DOSE TO OPTIMIZE TOBACCO DEPENDENCE TREATMENT

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At the 1993 CPDD meeting, we presented a statistically significant pair of regression equations, the Sachs Optimum Dosing Algorithm (SODA®, patent pending), for determining the nicotine patch dose required to attain an optimum target serum nicotine replacement level during treatment. This SODA was a function of five variables for men and six for women. We now report initial results from a clinical trial to validate these two regression equations.

Eighty-four subjects are being randomly assigned in double-blind fashion to receive nicotine patch treatment (Nicotrol; 30 cm^2 delivering 15 mg nic/16 hours) to replace 0% (placebo), 50%, or 100% of the venous serum cotinine (se cot) obtained by each subject's regular cigarette smoking. Sixty-seven/eighty-four subjects have sufficient data to enable initial analysis for determining the validity of the SODA. Each subject had his or her optimal patch dose computed using the SODA, with the designated number of patches (up to 3, 30 cm^2 patches, delivering 45 mg nic/16 hours) applied each morning, starting on Target Quit Date (TQD), for six weeks. Venous blood was drawn three days later, and the patch dose adjusted at the next visit, ten days after TQD, based on the deviation of the measured se cot value from the target cotinine value predicted by the SODA. One week later (~2 weeks after TQD) a second blood specimen was drawn to determine the final se cot level. Results from the 0% replacement group are not reported here. For all subjects randomized to each of the active dose treatment conditions, the ***measured %*** cotinine replacement after the first SODA-computed patch dose was, 50% group (n=24): 39±22% (Mean±1SD) (95% CI: 30-49%) and 100% group (n=25): 90±33% (95% CI: 76-103%). The measured cotinine replacement after the second SODA-computed patch dose was, 50% group: 58±17% (95% CI: 50-66%) and 100% group: 87±34% (95% CI: 72-103%). Since the study design allowed only a maximum of three patches, some patients had their nicotine patch dose artificially capped. This was so for 9/28 (32%) in the 100% replacement group, and for 1/28 (4%) in the 50% replacement group. Computing the % cotinine replacement only on the subjects who, ***in fact,*** received the dose calculated by the SODA was as follows: 50% group (n=23): 39±22% (95% CI: 30-49%) and 100% group (n=16): 86±35% (95% CI: 70-103%). The measured cotinine replacement after the 2nd SODA computation was. 50% group: 58±17% (95% CI: 50-66%) and 100% group: 93±35% (95% CI: 74-112%). There were no moderate, severe, or serious adverse events in any of the subjects. We conclude that this first version of the SODA is valid and reasonably accurate in assigning the appropriate number of nicotine patches to achieve a 50-100% target replacement cotinine level during treatment. Moreover, use of doses up to 45 mg nic/day for six weeks to achieve 100% replacement would appear to be safe and well-tolerated, producing no significant side effects.

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EFFECTS OF NICOTINE ON COOPERATIVE RESPONDING IN ABSTINENT MALE AND FEMALE SMOKERS

M. Broitman, R. Spiga, J. Schmitz, R. Elk, and R. H. Bennett

The effects of ad *libitum* smoking, abstinence, and 0, 2 and 4 mg nicotine gum on human, male and female, cooperative responding were examined. In a free-operant laboratory procedure, subjects were provided the opportunity to respond cooperatively or independently to episodes initiated by a computer-simulated other person. Subjects could also initiate episodes which ostensibly provided the other person the opportunity to respond cooperatively or independently of the subject. Working cooperatively added points to both the subject's and other person's counters. Working independently added points only to the subject's counter. Doses were administered over five consecutive laboratory days. For females, doses were administered during the luteal phase. Results demonstrated that abstinence decreased cooperative responses during self- and other-initiated episodes. *Ad lib* smoking increased cooperative responding relative to abstinence and placebo gum conditions in seven of ten subjects. Gum containing either 2 or 4 mg of nicotine increased responding in six of the ten subjects. No gender differences were observed. Decreases in cooperative responding may set the occasion for smoking relapse.

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SELEGILINE FAILS TO ALTER CIGARETTE CONSUMPTION IN COCAINE-DEPENDENT SUBJECTS

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Selegiline (SEL), which increases brain DA via its selective irreversible inhibition of MAO-B, is currently used to treat Parkinson's Disease. Because of its ability to elevate CNS DA, SEL is being examined by several research groups as a treatment for cocaine abuse. The present study was undertaken primarily to verify the safety of administering SEL to cocaine users. Nicotine-induced increases in mesolimbic DA are thought to mediate the addictive effects of cigarettes (like other abused drugs). We therefore also used this study to test the hypothesis that administration of a medication which increases CNS DA would substitute for cigarettes and decrease cigarette consumption. Eight cocaine users who smoked at least 20 cigarettes per day participated in this 17-day double-blind study. All subjects received placebo for the first seven days, SEL (10 mg po) for the next five days, and placebo for the final five-day wash-out period. End-points included daily EKGs, vital signs, blood samples for hormone levels, subjective-effect scales, cigarette consumption, reaction times and carbon monoxide levels in exhaled breath. Sclegiline had no effect on reaction times, EKG, vital signs and produced no clinically significant side effects. There were no significant changes in cigarette consumption or carbon monoxide levels. There were no alterations in plasma prolactin levels. These data indicate that short-term administration of selegiline does not decrease cigarette consumption and does not appear to produce any significant motor or other side-effects in cocaine users.

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EFFECTS OF TARGET CRITERIA AND REINFORCEMENT MAGNITUDE IN REINFORCING REDUCED BREATH CO LEVELS IN SMOKERS NOT SEEKING TREATMENT

R. J. Lamb, M. Y. Iguchi, and K. C. Kirby

Numerous studies show that contingency management procedures can facilitate abstinence. However, little is known about their optimal parameters. In two studies designed to examine the parameters of contingency management, smokers not planning to quit in the next year gave breath CO samples each weekday. In the first study, smokers were paid for delivering breath CO samples $\leq$ 4 ppm (a level indicating no or very little smoking in the past day). Subjects could earn \$0, \$1, \$3, \$10, or \$30 for meeting criteria. The amount subjects were paid varied from week to week. The second study was similar except that the payment criterion was delivery of samples equal to or less than half their median daily CO level in the week preceding the payment portion of this study. In both studies the probability of producing breath samples meeting payment criteria generally increased as payment amount increased from \$1 to \$30. In the first study, four of five subjects were abstinent for the entire week at the \$30 payment level. In these subjects, smoking was often decreased in the \$0 payment condition following the \$30 payment condition, and one subject was still abstinent at follow-up some months later. These studies indicated 1) reinforcement magnitude can influence the effectiveness of a contingency management program; 2) abstinence initiated through the use of arbitrary reinforcement can be maintained beyond these contingencies: and 3) the half baseline CO criterion is more useful for an analog procedure designed to study parameters of contingency management than the $\leq$ 4 ppm criterion.

There are several implications of these results. The first is reinforcement magnitude influences the effectiveness of a contingency management program in initiating abstinence. The second is the importance of reinforcement magnitude fades as the reinforced behavior comes under the natural contingencies of reinforcement associated with it. For some individuals these natural contingencies may come into effect in as short a time as a week. A third implication is that clinically appropriate behavior may on occasion need to be shaped. In subject four, for instance, no criterion behavior occurred when the criterion was $\leq$ 4 ppm breath CO, but the less stringent criterion of used in the second experiment was met and the frequency of the target behavior increased following payment. Whether even lower breath CO levels could be shaped with such "resistant" individuals is an empirical question, but the clear implication is that an individual's "motivation" can be changed through the use of external contingencies. The fourth and final implication of these results is that for analog studies examining contingency management interested in the momentary control of behavior the less stringent criterion is more useful, but for studies interested in the "carry-over" effects of behavior the abstinence criterion is more useful.

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EFFECTS OF D1- AND D2-DOPAMINE RECEPTOR AGONISTS ALONE AND COMBINED ON LOCOMOTOR ACTIVITY OF CAFFEINE-TOLERANT RATS

B. E. Garrett and S. G. Holtzman

A_{2A} adenosine receptors and D_2 dopamine receptors are co-localized on basal ganglia neurons where the former may inhibit the latter (Ferré *et al.,* 1991). According to this model, caffeine, by blocking adenosine receptors, removes that inhibitory influence on dopamine receptors, resulting in behavioral stimulation. Compensatory changes in the dopamine system might then account for caffeine tolerance. Animals tolerant to the locomotor stimulant effect of caffeine are cross-tolerant to other drugs that block adenosine receptors, such as theophylline and CGS-15943, but are not cross-tolerant to psychomotor stimulant drugs that do not block adenosine receptors, such as d-amphetamine and cocaine (Finn and Hltzman 1987). Drugs that release or potentiate released dopamine presumably activate both D_1 and D_2 dopamine receptors. Perhaps caffeine cross-tolerance develops only to drugs that activate a single type of dopamine receptor. As a test of this model, we evaluated the effects of D_1 and D_2 dopamine agonists alone and combined on locomotor activity in control rats and rats made tolerant to caffeine-induced stimulation of locomotor activity by chronic treatment with caffeine (86 mg/kg/day, orally, in four divided doses).

The selective D_2 dopamine agonists quinpirole (0.1-3.0 mg/kg, s.c.) and R(-)-propylnorapomorphine (NPA, 0.03-1.0 mg/kg, s.c.) dose-dependently increased activity in control rats. Cross-tolerance developed to these effects in rats receiving chronic caffeine treatment. SKF-77434 (1.0-30 mg/kg. s.c.), a partial agonist at D_1 dopamine receptors, produced increases in activity in control rats, but completely failed to stimulate locomotor activity in rats treated chronically with caffeine. Doses of the partial Dl dopamine agonists SKF-38393 (10 mg/kg, s.c.) and SKF-77434 (1.0 mg/kg, s.c.), had no locomotor effects on their own, but significantly potentiated the locomotor response to NPA and quinpirole. In most cases, cross-tolerance was not seen to these potentiating effects. The lack of cross-tolerance to the synergistic interaction between D_1 and D_2 dopamine agonists may explain why caffeine cross-tolerance does not extend to non-xanthine psychomotor stimulants.

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Available upon request of senior author.

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QUANTITATIVE EEG CHANGES DURING CAFFEINE WITHDRAWAL

R. R. Reeves, F. A. Struve, G. Patrick, and J. A. Bullen

Although many studies have shown the occurrence of withdrawal symptoms with the cessation of caffeine intake, there is still debate as to whether a caffeine withdrawal syndrome occurs. Neurophysiological correlates of the caffeine withdrawal process have not been previously demonstrated. Quantitative EEG provides a uniquely sensitive measure of neurophysiological change. To study changes occurring during caffeine withdrawal, 13 subjects were recruited who had caffeine intake of 300 mg or more daily and no medical or psychiatric history. A series of tests were conducted on each subject including quantitative EEG. neuropsychological testing, caffeine level and drug screens, performed at baseline and again during days 1. 2, and 4 of abstinence from caffeine. Results obtained during the withdrawal phase were compared to baseline and statistically significant changes noted. The preliminary results indicate a generalized increase of alp\ ha and theta voltage primarily over the frontal central cortex during withdrawal. This is often easily visualized on analog EEG. Topographic mapping of alpha power was statistically significantly increased in 38.5% of the subjects on day one, and 76.9% on days 2 and 4. Theta power was increased in 38.5% of the subjects on day one and 76.9% on day two. Fully 92.3% of subjects showed statistically significant increases of theta voltage of the frontal cortex at some point during caffeine withdrawal. In over 50% of the subjects, the quantitative EEG changes were reversible within 20 to 30 minutes of resuming caffeine intake. The above described changes and the rapid reversal of voltage increase in certain subjects suggest that caffeine may act as a chronic suppressor of electrical activity, possibly secondary to cerebral vasoconstriction.

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DOES CAFFEINE CESSATION INCREASE FIRING RATES OF PAROXYSMAL EEG DYSRHYTHMIAS? A SERENDIPITOUS OBSERVATION

G. Patrick, R. Reeves, and F. Struve

In a study of quantitative EEG effects of caffeine withdrawal, a subsample of six subjects had EEGs containing DIFFUSE PAROXYSMAL SLOWING (a minor waking EEG dysrhythmia found in less than 10% of the normal population) at baseline during caffeine use. These subjects showed marked increases in the number of paroxysmal slow bursts per unit time (increased "firing rate") during caffeine withdrawal. This increase paroxysmal burst firing rate was then reversed to baseline levels within 15 minutes following reintroduction of caffeine.

For all subjects, 21 channel EEGs were secured at baseline and on days 1, 2, and 4 of caffeine withdrawal. Verification of caffeine abstinence was accomplished by obtaining blood levels at each test day. Urine drug screens were obtained on each testing day to verify absence of abuse drug use. Subjects were all normal volunteers free of medical or psychiatric illness. All EEGs were an hour or more in duration. For each EEG the amount of alert wake EEG. measured in seconds, was determined. The amount of alert wake EEG ranged from 916 seconds (15.3 minutes) to 4,380 seconds (73.0 minutes) with 96.3% of the EEGs containing from 25 to 73 minutes of wake activity. The "firing rate" of paroxysmal slow bursts was expressed as the number of bursts per 10 minutes of wake EEG.

Across all six subjects, day one of caffeine abstinence was associated with nearly a 90% average increase in paroxysmal burst firing rate and this peaked at over a 100% increase on day two of caffeine abstinence. For the six subjects the percent increase in paroxysmal firing rate (average over days 1, 2, and 4 of caffeine withdrawal) ranged from around 20% to over 160%. Caffeine resumption produced return of firing rate to initial baseline levels.

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EFFECTS OF CAFFEINE ON COOPERATIVE RESPONDING

S. Rafieha, R. Spiga, and M. Broitman

The effects of acutely administered placebo, 1.5 mg/kg, 3.0 mg/kg and 6.0 mg/kg caffeine on cooperative responding in caffeine users (50-450 mg/day) was investigated. Subjects were instructed that via a computer their and another person's responses could produce points exchangeable for money. The Other person was fictitious. Throughout an experimental trial two schedule components repeatedly alternated. During the first, work alone, component button presses added points to the subject's counter on a random interval, RI, 30 second schedule. Points were added to the other person's counter on a random time, RT, 30 second schedule. During the second, choice, component independent responses were maintained by points added only to the subject's counter on a random interval, RI, 30 s schedule and cooperative responses were maintained by points added simultaneously to the subject's and other person's counters. The proportion of cooperative responses increased in four of six subjects at the 1.5 mg/kg dose. These subjects differed in the pattern of changes in cooperative and independent response rate that produced differences in the proportion of cooperative responses. The three profiles of response rate changes observed in this study included increased cooperative response rate accompanied by decreased independent response rate, only decreased independent response rate and only increased cooperative response rate. Subjects reported greater shakiness at the 3.0 and 6.0 mg/kg doses than at placebo and the 1.5 mg/kg dose.

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INTERACTIONS OF ALPRAZOLAM AND CAFFEINE: EFFECTS ON DRL PERFORMANCE

C. E. Lau and J. L. Falk

The interaction between BZs and xanthines may involve many receptors, *e.g.,* BZ receptors, GABAA receptor-channel complex and adenosine receptors. In order to characterize BZ-xanthine interaction, both additive and independent relations should be considered. We used a dose-response curve (DRC) method which enabled the calculation of the theoretical additive and independent curves proposed by Poch *et al.,* (1990). The observed values for the drug combinations were compared to the calculated values to study the interaction of alprazolam and caffeine on DRL 45-sec behavior in rats.

Male Holtzman rats performed in 3 hour daily sessions. Performance was evaluated in the 45-55 second inter-response time (IRT) bin. When baseline behavior was established, the DRCs for i.p. alprazolam and i.p. caffeine by themselves and their combination were determined by a 4-parameter logistic function. Alprazolam was more potent than caffeine in disrupting DRL behavior with potency ratios of alprazolam-to-caffeine ranging from 41 to 2.3 from 1 hour to 3 hour. Although the interaction between the BZs and methylxanthines is commonly antagonistic, the present results indicate that additivity or independence occurs.

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SEROTONIN (5HT) INVOLVEMENT IN THE DISCRIMINATIVE STIMULUS EFFECTS OF BENZODIAZEPINES (BZ)

H. C. Chen and M. E. Bronson

A growing body of evidence suggests that 5HT may be involved in anxiety and in the mechanism of action of benzodiazepines. The purpose of the present study was to examine the role of seiotonin (5-HT) in the discriminative stimulus effects of benzodiazepines (BZs). Two groups of male Sprague Dawley albino rats were trained to discriminate either 7 mg/kg of a BZ full agonist, chlordiazepoxide (CDP), or 7 mg/kg of a partial BZ agonist, bretazenil. from water (n=7/group). During substitution tests, CDP, bretazenil and a novel beta-carboline anxiolytic, abecarnil, produced >80% responding on the drug-appropriate lever in both groups. Bretazenil was more potent than CDP and abecamil, in that 1 mg/kg bretazenil resulted in full substitution in both groups of rats, whereas 7 mg/kg CDP and 7-10 mg/kg abecarnil were required for substitution in the same rats. In contrast, the BZ antagonist, flumazenil, the selective 5-HTIA agonist, (+)8-hydroxy-(di-N-dipropyl-2-amino)tetralin (8-OH-DPAT) and the selective 5-HT2 antagonist, ketanserin, did not substitute for either training drug. When administered either before or after the training dose, flumazenil dose-dependently attenuated the discriminative stimulus effects of both CDP and bretazenil. 8-OH-DPAT did not attenuate the discriminative stimulus effects of the training dose of CDP or bretazenil but decreased responding in both groups, and the effects on response rate were supra-additive at the 0.32 mg/kg dose of 8-OH-DPAT. 8-OH-DPAT also produced a short-lived immobility when administered in combination with a low, non-discriminable, dose of bretazenil (0.1 mg/kg) or CDP (1 mg/kg) in rats trained on each respective drug. If rats were allowed to recover, however (*i.e.,* tested 30 min later), 8-OH-DPAT potentiated the discriminative stimulus effects of the low, non-discriminable, dose of both bretazenil and CDP. Interestingly, 8-OH-DPAT did not potentiate the effects of a low (0.1 mg/kg) dose of abecamil in either group, nor did it potentiate the effects of bretazenil in CDP-trained rats or CDP in bretazenil-trained rats. When administered before, but not after, the training dose of CDP or bretazenil, ketanserin attenuated the discriminative stimulus effects of CDP and bretazenil. Unlike 8-OH-DPAT, ketanserin did not potentiate the discriminative stimulus effects of a low dose of CDP or bretazenil in rats trained on each respective drug. Ketanserin also did not potentiate the effects of a low dose of abecarnil. These results suggest that CDP, bretazenil and abecarnil share discriminative stimulus properties, but the role of 5-HT in these effects is minimal and appears to depend upon the training drug. Because of the supra-additive effects on response rate in certain 5-HT/BZ combinations - an effect also noted by Gauvin *et al.,* 1994 - some caution may be necessary if these drugs are used simultaneously in other species.

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CONTEXTUAL STIMULI AND REVERSAL LEARNING: INTERACTION IN A DRUG DISCRIMINATION TASK

T. U. C. Järbe and D. A. Mathis

Drug discrimination learning is the process whereby one or more drugs acquire differential control over behavior of organisms. Training is done in much the same way as when studying more conventional, exteroceptive stimulus control of behavior. However, only limited work has been devoted to the interaction of these two clsasses of stimuli. To further investigate the commonalties and interaction between the two classes of stimuli, we examined contextual stimuli and reversal of drug discrimination behavior using two groups of rats: one group was reversal-trained in the same context as for the original training; and, for the other group, a contextual change was introduced in the reversal phase. The drug stimulus was 1375 mg/kg ethanol (ETOH). A T-maze procedure was used and the exteroceptive context variable was the presence and absence of light in the experimental room. In this three-alley shock-escape maze the center start alley was 15 cm wide X 30 cm long. A choice section (15 cm X 15 cm) was at the junction of the center start alley and the left and right side alleys (each 15 cm wide X 30 cm long). An exit alley (15 cm wide X 2.5 cm long) was connected to each side alley. An acrylic lid covered the maze. The distance from the grid-floor to the lid was 7 cm. Midway through either side alley a moveable fluorescent paper was attached to the lid for recording the response; thus the paper hung down from the roof and was brushed aside when the rat touched it. Barrier doors that were not visible from the choice point could be inserted into either of the exit alleys. The rat could escape from the maze by jumping off the grid floor into a cage placed just beneath the grid floor at the end of the exit alley. During light sessions a 60W light bulb was placed 30 cm above the choice area. During dark sessions all lights were turned out. (Thus an entire session was conducted either in the presence or absence of light, analogous to the sustained presence of the drug stimuli). Half the rats were originally trained in the lighted maze condition; the other half was trained in the dark maze. We found that the speed of original training and the resulting drug-dose generalization gradients (i.e., the dose-response curve determined prior to reversal) were as described previously in the literature and did not differ for the two groups. Reversal learning took longer for both groups as compared to the original training. However, the group subjected to a contextual change during reversal acquisition mastered the reversal faster than the group not experiencing a contextual change. Incorrect responding during ETOH sessions seemed mainly responsible for the slower acquisition in the reversal phase. When tested after reversal in the original training context, dose-generalization gradients were affected differentially depending upon the conditioning history of the animals: dose generalization to the training stimulus was reduced for animals experiencing a context change during reversal training, but not for animals not experiencing contextual change. Thus, drug stimuli and contextual stimuli interact in the control of behavior.

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TOLERANCE AND CROSS-TOLERANCE BETWEEN ETHANOL AND DIAZEPAM IN RATS TRAINED TO DETECT ETHANOL

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The present experiment tested the hypothesis that cross-tolerance between ethanol (EtOH) and diazepam (DZP) would occur in an EtOH discrimination. Rats were trained to detect EtOH (1.0 g/kg, i.p.) from saline using a two-lever choice procedure where food was available under a fixed-ratio 10 (FR10) schedule of reinforcement. Subsequently, dose-effect curves for EtOH (0.1 - 1.78 g/kg) and DZP (0.32 - 10 mg/kg) substitution for EtOH were performed. Chronic administration of EtOH (5.0 g/kg/12 hours) resulted in three-fold tolerance to EtOH and a six-fold cross-tolerance to DZP substituting for EtOH. Conversely, chronic administration of DZP (20 mg/kg/8 hours) did not result in tolerance to DZP nor cross-tolerance to EtOH. The degrees of tolerance to EtOH and cross-tolerance to DZP following chronic administration of EtOH suggests that tolerance to EtOH is mediated in part by changes at the GABA/BZD complex. Previous reports have demonstrated that the chronic dose of DZP used in this experiment confers tolerance to benzodiazepines (BZD) substituting for other BZDs (Pugh *et. al.,* 1992). The lack of tolerance to DZP substituting for EtOH following this same regimen of DZP suggests that the mechanism of DZP substituting for EtOH is different than the mechanism that mediates DZP substitution for BZD.

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PREFERENCES FOR ETHANOL AND DIAZEPAM IN ANXIOUS INDIVIDUALS: AN EVALUATION OF THE SELF-MEDICATION HYPOTHESIS

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The self-medication hypothesis of addictive disorders postulates that individuals with high levels of psychiatric symptoms use drugs to alleviate their symptoms, thus, placing these individuals at risk for drug abuse. Although widely used to explain the etiology of drug abuse, the self-medication hypothesis has not been empirically validated. This study evaluated one version of the self-medication hypothesis by formulating it into two testable hypotheses: i) that two purportedly anxiolytic drugs, ethanol and diazepam. would decrease anxiety in highly anxious volunteers and; ii) that highly anxious volunteers would be more likely to self-administer these drugs than non-anxious controls.

Preferences for and subjective effects of ethanol and diazepam were tested in two separate experiments, each using a choice procedure. Anxious (ANX, N=22) and control (CTL, N=23) subjects participated in two double-blind placebo-controlled experiments, one testing ethanol and the other testing diazepam. Subjects were tested in groups of four, during the evening, and in a comfortable laboratory environment. Subjects sampled and then chose between ethanol (0.8 g/kg) and placebo in one experiment, and diazepam (20 mg) and placebo in the other. Choice of drug over placebo and subjective responses to each substance were measured.

Ethanol decreased anxiety in the ANX group, but the ANX subjects did not choose the ethanol more often than CTL subjects (52% vs 48% ethanol choice, for ANX and CTL respectively; difference ns). Diazepam did not measurably reduce anxiety, but there was a trend for ANX subjects to choose diazepam more often than CTL subjects (65% vs 45% diazepam choice, for ANX and CTL respectively; $p<.10$). Thus, anxious subjects were more likely to choose diazepam but not ethanol. However, preference for these drugs was not associated with their anxiolytic effects. Other measures suggested that drug preference may be related to subjective drug effects such as euphoria. These data provide mixed support for the self-medication hypothesis: Drug choice may not be related to the acute effects of the drug on psychiatric symptoms. However, these data do suggest that greater preference for diazepam by anxious individuals indicate a higher likelihood of diazepam use in nonmedical contexts.

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EFFECTS OF PENTYLENETETRAZOLE (PTZ) ON ANXIETY AND ETHANOL SELF-ADMINISTRATION IN MALE WISTAR RATS

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Alcohol dependence frequently co-exists with anxiety disorders. However, the interrelationship between these two disorders is unclear. Tension reduction theory of alcoholism suggests that anxiety may lead to alcohol consumption for the purpose of tension relief. The aim of this study was to compare the effects of pentylenetetrazole (PTZ) at subconvulsant doses on exploratory (Hole Board), anxiety (Elevated Plus Maze) and ethanol self-administration (Limited Access Paradigm) behaviour. PTZ is an antagonist at GABA\Benzodiazepine\Cl^- ionophore receptor complex and at subconvulsant doses has been reported to induce anxiety in laboratory animals and man. PTZ (5.0-15.0 mg\kg i.p.) showed no effects in the hole board but significantly suppressed open arm exploration in the Plus Maze (50-67%) demonstrating an anxiogenic profile as predicted. In the 40 minute Limited Access Procedure, during which rats were presented with 12% ethanol and water, acute treatment with PTZ (5.0-15.0 mg\kg) produced a mild but non-significant increase in ethanol intake (30%). However, upon chronic treatment (8 days), PTZ (15 mg\kg i.p.) significantly increased ethanol intake (15-91%). These results show that at anxiogenic doses PTZ increased alcohol consumption. Therefore, PTZ may be useful as a pharmacological tool to assess the interrelationship between anxiety and alcohol drinking.

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EFFECTS OF ORAL TRIAZOLAM PRETREATMENT ON DRINKING IN BABOONS: DIFFERENTIAL EFFECTS DEPENDING UPON SELF-ADMINISTRATION HISTORY

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In a study of the reinforcing efficacy of oral triazolam (TRZ), three baboons consumed higher volumes of TRZ than of vehicle. Although these results typically would be interpreted as demonstrating that TRZ was serving as a reinforcer, the unconditioned effect of TRZ itself on drinking (*i.e.,* benzodiazepines have been shown to increase drinking in rodents) remained a possible confound. That is, high volumes of TRZ consumption could have been a direct effect of TRZ that was ingested at the beginning of the self-administration session. Therefore, we assessed the effect of pretreatment with TRZ on the amount of the TRZ vehicle consumed by the same baboons from the drinkometer spout used during the self-administration procedure. Except for the fact that the baboons were pretreated with a TRZ dose or its vehicle, the experimental sessions were identical to the oral drug self-administration sessions conducted previously. (Oral dosing was accomplished by mixing the triazolam suspension in an orange-flavored drink and letting the baboon lick it off the end of a syringe held by the technician at the front of the cage.) TRZ (0.6 - 19.2 mg total dose) produced a dose-dependent increase in consumption of TRZ vehicle from the drinkometer spout for all baboons, suggesting that, indeed, the high volume of TRZ self-administration found earlier might have been a direct effect of ingested TRZ on drinking per se. However, when the TRZ dose-response function was redetermined on tap water consumption from the regular drinking spout in these same baboons, there was no systematic change in volumes consumed. This suggested that the increased drinking from the drinkometer (the device used in the self-administration study) might have been a "priming" or reinstatement phenomenon analogous to that reported in i.v self-administrations studies. In those studies, pretreatment with a dose of a drug previously self-administered reinstated lever pressing that had been maintained by the drug but which now only produced saline injections. Therefore, as a final condition of the present study, the TRZ dose-response function was determined for TRZ vehicle consumption through the drinkometer device in three baboons without histories of oral benzodiazepine self-administration. Reliable increases in drinking were not produced in these baboons. Taken together, these results suggest that (1) the oral TRZ self-administration results likely were not confounded by direct effects of TRZ on drinking per se, and (2) the dose-related increase in consumption of vehicle from the drinkometer spout after TRZ pretreatment by the baboons experienced in oral benzodiazepine self-administration was most likely an example of a priming or reinstatement phenomenon because the same result did not occur in baboons without such a history. This phenomenon can most parsimoniously be interpreted as the TRZ pretreatment's serving a discriminative stimulus function for making the response of drinking through the drinkometer that previously had been maintained by oral TRZ delivery.

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THE ACUTE EFFECTS OF BETA-CARBOLINE-3-CARBOXYLATE-ETHYL ESTER (B-CCE) ON ACQUISITION IN SQUIRREL MONKEYS

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Benzodiazepines are agonists and some beta-carboline esters are inverse agonists at benzodiazepine receptors. Benzodiazepines have anxiolytic, sedative-hypnotic and anti-convulsant properties and are also known to induce impairments of learning and memory. Inverse benzodiazepine agonists have pharmacological properties that are opposite to those of the benzodiazepines and have been shown to be anxiogenic and pro-convulsant or convulsant. There is evidence that beta-carboline benzodiazepine inverse agonists may enhance learning under some behavioral procedures. The present experiments were conducted to determine whether B-CCE might enhance acquisition under two different schedule conditions which maintained low rates of learning. Responding in squirrel monkeys was maintained by food presentation under a repeated acquisition procedure using either chain strained-ratio or tandem strained-ratio schedules. Under both procedures, subjects were required to acquire a different three-response chain each session. Sequence completions were reinforced under a high fixed-ratio schedule producing pausing and a high level of errors. Under both schedules, B-CCE produced rate-decreasing effects only at the higher doses tested. Similarly, B-CCE did not increase or decrease errors at any of the doses tested under both schedule conditions. The effects of B-CCE were blocked by flumazenil indicating that the effects of B-CCE are mediated by an action at the benzodiazepine receptor. These data would suggest that under these conditions B-CCE does not enhance acquisition in squirrel monkeys at sub-convulsant doses.

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PENTOBARBITAL AND DIAZEPAM HAVE SIMILAR EFFECTS ON VISUAL AND SPATIAL MEMORY IN PIGEONS

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Pigeons were trained under two different visual memory tasks (titrating matching-to-sample and delayed alternation of colors) and a spatial memory task (delayed alternation of position). Under control conditions total percent correct responses under the delayed alternation of color and position were 79.6 ± 2.6 and 82.7 ± 4.2, respectively. Percent accuracy under the titrating matching-to-sample baseline was maintained at approximately 80% by the titration schedule. Pentobarbital at doses of 3 mg/kg and lower was without significant effects on accuracy under all three behavioral baselines. Doses of 5.6 and 10 mg/kg decreased accuracy under the two alternation baselines and decreased the mean delay value under the titrating matching-to-sample baseline. The performance decreases under the three baselines at these higher doses were approximately equal. The effects of diazepam were likewise similar under the three baselines. Diazepam doses of 0.03 - 0.3 mg/kg were without effect, and doses of 1 and 3 mg/kg produced similar performance decrements. These results show that pentobarbital and diazepam affect spatial and visual memory in the pigeon similarly, and they suggests that the control of visual and spatial memory in the pigeon may not be mediated by different systems. Alternatively, these results might suggest that these drugs may be acting on reference memory (schedule control) rather than working memory (stimulus control).

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PHYSICAL DEPENDENCE ON NORDIAZEPAM IN RATS

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The present study was conducted to characterize the dependence-producing properties of nordiazepam (ND) in rats chronically exposed to ND slowly released from silastic capsules (SC). Six female Sprague-Dawley rats (225-250 g) were implanted subcutaneously at weekly intervals with 3SC containing 200 mg/cap of ND. ND was released *in vitro* from the SC with a constant rate equal to 0.1 mg/day (Jing *et. al.,* 1993). During stabilization on ND the rats gained weight ($p < .05$). ND did not produce any overt signs of sedation. After the fourth or fifth implant, rats were administered bolus intravenous injections of 40 mg/kg of flumazenil (FL) followed a week later by DMSO vehicle. The rats were observed for two five minute epochs before and for eight five minute epochs after injections of FL or DMSO and signs of precipitated abstinence (PA) and behavioral states were recorded on standard observation forms. The Precipitated Abstinence Score (PAS) and Behavioral Score (BS) were calculated (Martin *et. al.,* 1993). FL-evoked clonic (two rats) and tonic-clonic (three rats) seizures emerged rapidly, whereas no seizures were observed after DMSO. The PAS was significantly ($p < .005$) higher within five minutes after FL than after DMSO and thereafter rapidly decreased to a stable level. FL produced statistically significant tachypnea ($p < .05$), increased writhing ($p < .05$) and decreased rearing ($p < .025$). Furthermore, FL induced a significant depression of several behavioral states. FL-PA in ND rats differed from that previously observed (Wala *et. al.,* 1993) in rats implanted with SC containing diazepam (DZ) (3 X 180 mg/cap/week). In ND dependent rats, the time-course of PAS was shorter than in DZ dependent rats which was also the case in dogs (Martin *et. al.,* 1990). Also marked differences in signs of abstinence and behavioral states were observed in ND and DZ dependent rats. The present data indicate that the capsule implantation technique is an efficient way of producing physical dependence on ND in rats and that in rats ND and DZ produce different types of dependence.

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ETHANOL INHIBITS FORSKOLIN-STIMULATED cAMP FORMATION IN HUMAN NEUROBLASTOMA CELLS

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Ethanol has been shown to have a stimulatory effect on adenylate cyclase (AC) and potentiate the cyclic AMP (cAMP) response to receptor stimulation. It is suggested that ethanol causes an increase in membrane fluidity and thereby facilitates the coupling between the subunits of AC. Also, several reports indicate that acute ethanol (ETOH) increases extracellular adenosine by blocking its reuptake. Thus, adenosine, by stimulating A2 adenosine receptors, may be responsible for enhanced cAMP responses in the presence of ETOH. More recent evidence supports the hypothesis that ethanol acts directly on the catalytic subunit of AC or on regulatory G proteins.

The studies described here were designed to clarify whether ETOH directly modifies the AC system independent of its effects on extracellular adenosine levels. The ATP pool of human SK-N-SH neuroblastoma cells was radioactively labeled by preincubating the cells with ^{3}H-adenine for two hours in serum-free DMEM followed by a ten minute incubation in fresh medium containing the phosphodiesterase inhibitor, Ro 20-1724 and adenosine deaminase (2U/ml). Under these conditions, negligible extracellular adenosine is present. Intracellular cAMP accumulation was stimulated by ten minute drug challenges followed by Dowex-alumina column chromatography to isolate ^{3}H-ATP and ^{3}H-CAMP. Forskolin (FSK) stimulates AC activity by promoting Gs-catalytic subunit coupling. In SK-N-SH cells, FSK increased cAMP levels 30-40 fold with an EC50 of 6 μM. Ethanol (> 80 mM) inhibited FSK- stimulated cAMP synthesis in a concentration-dependent manner. Cyclic AMP accumulation was significantly stimulated in SK-N-SH cells by the selective A2 adenosine agonist CGS 21680 (CGS) and the ß-adrenergic receptor agonist isoproterenol (ISO). However, neither the potency nor the efficacy of these agonists was affected by the presence of 160 mM ETOH. In the presence of 1 μM FSK, receptor-dependent stimulation of cAMP synthesis by either CGS or ISO was markedly potentiated. ETOH (160 mM) significantly inhibited the response to both CGS and ISO measured in the presence of 1 μM FSK. The inhibitory effect of ETOH was not attenuated after pre-exposure of cells to ETOH (160 mM) for 24 or 48 hours, an indication that tolerance does not develop to this effect. Thus, ETOH inhibits FSK-dependent, but not receptor-dependent, AC activity in a model neural cell line and tolerance does not develop to this pharmacologic effect. These results suggest that ETOH may alter the interaction between Gs and the cyclase catalytic subunit.

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A RAT MODEL OF 'ANTICIPATORY' DRUG-SEEKING FOR ETHANOL

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The incentive-motivational value of drug-related environmental stimuli is one of the most important determinants of drug-craving and their experimental manipulation is crucial for the development of animal models. In this study, we describe a rat model of 'anticipatory' drug-seeking for ethanol determined by stimuli previously paired with the drug. Adult male Long Evans rats were trained to self-administer oral ethanol (ethanol 0, 2, 4 and then 8% w/v) under a schedule of food-induced polydipsia. After discontinuation of within-session feeding, rats were gradually trained up to the following schedule: 30 minute session, FR5 for 8% ethanol contingently paired with a tone (BS). When responding for ethanol was stable, rats were tested under a tandem-schedule consisting of firstly a five minute component, [FI5 min (FR5:BS)], followed by a 30 minute component, (FR5: 8% ethanol + BS). Rats showed a high level of responding during the first component for the first three sessions. However, on the following days, lever pressing for BS presentation decreased, even if responding for ethanol in the second component did not show any change. Based on these results, rats were tested under a different tandem-schedule, where the duration of the second component was reduced from 30 minutes to 5 minutes. The new tandem-schedule was: [FI5 min (FR5:BS)] → (FR5: 8% ethanol + BS) five minutes. The rate of responding for BS during the first component and responding for ethanol during the second component did not decrease and they remained stable over several days. During the first component, BS presentations = 7.4±1.6, active lever presses = 51.7±10.3; during the second component, ethanol deliveries = 17.2±3.5, active lever presses = 95.2±22.2 and ethanol intake (g/kg) = 0.32±0.06 (mean ± SEM of two stable sessions, n = 6 rats). Discontinuation of BS during the first component caused a significant decrease in responding, which was reversed by the reintroduction of the BS. Exposing the rats to extinction induced a decrease of responding during both components. Reintroduction of BS during the first component caused a partial reinstatement of responding during both components, even if ethanol was not available. Using this tandem schedule, it is possible to distinguish two discrete phases: i) an 'incentive' phase where responding is maintained by the presentation of an ethanol-related cue (i.e. BS); a 'consummatory' phase, where ethanol is available upon responding for a limited period of time. The behavior observed during the 'incentive' phase may be defined as an 'anticipatory' drug-seeking for ethanol due to the incentive-motivational value of the BS.

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DEVELOPMENT AND VALIDATION OF A NEW QUESTIONNAIRE TO ASSESS CRAVING FOR ALCOHOL

E. G. Singleton, S. T. Tiffany, and J. E. Henningfield

A series of new questionnaires have been developed to provide valid and reliable self-report formats to assess urges and desires to smoke cigarettes [(Questionnaire of Smoking Urges (QSU)], cocaine craving [Cocaine Craving Questionnaires (CCQ-Now and CCQ-Gen)], and craving for heroin [Heroin Craving Questionnaire (HCQ-Now)]. Thus far. three validation studies have revealed that drug craving is a multidimensional rather than a one-dimensional construct. In this investigation, responses from 219 alcohol users who completed the Alcohol Craving Questionnaire (ACQ-Now) were factor analyzed. Similar to findings from the previous validation studies, current craving for alcohol consisted of an amalgam of urges and desires, intent to use alcohol, anticipation of positive benefits of drinking, anticipation of relief from withdrawal and negative moods, and lack of control over alcohol use.

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THE RELATIONSHIP BETWEEN CRAVING AND NEUROPSYCHOLOGICAL FUNCTIONING

T. E. Douglas, E. G. Singleton, and J. E. Henningfield

Many investigations of neurological functioning and substance abuse examine the relationship between drug use and cognitive performance. Some theories (*e.g.,* automatic thinking) suggest that drug craving is a cognitive function, yet little is known about the relationship between craving and neuropsychological impairment. Neuropsychological profiles of 75 users of alcohol were developed from responses to a 90 item neurological screening instrument [Neurological Impairment Scale (NIS)] measuring general cognitive impairment; history of neurological illness or injury; attention and concentration; memory, expressive speech, learning, and academic abilities; and frustration and other affective disturbance. Canaonical analyses of the NIS profiles with craving for alcohol as assessed by the Alcohol Craving Questionnaire (ACQ-Now) indicated that all signs of neurological impairment were associated with this aspect of alcohol use. Thus, neuropsychological evaluation may have some practical value in addiction research but there are limitations to self-reports and screening instruments should never substitute for more robust neurological testing.

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SCREENING THE PLASMA OF LIGHT AND HEAVIER SOCIAL DRINKERS FOR POTENTIAL BIOCHEMICAL MARKERS OF CUE-INDUCED CRAVING FOR ALCOHOL

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Isolation of heightened cue-induced biochemical responsivity to alcohol would raise the possibility of precisely targeted pharmaceutical early-interventions. Clearly, the earlier diagnoses of at-risk drinkers can be made the better. Typically, however, the search for biochemical markers has centered on populations of clinically dependent drinkers; but cataloging differences in end-process functioning of chronic users is unlikely to tell us much about early-markers or the processes by which dependence evolves. This research focuses on differenes in the biochemical responsivity of light and heavier *social* drinkers to the expectation and ingestion of a small dose of alcohol. Reliable biochemical differences between classes of social drinkers in this low-dose range would hold out the hope of early diagnosis of problems and more precise targeting of early interventions.

Volunteers suffering from medical or psychiatric problems, taking medication and/or using drugs other than alcohol or cigarettes more than three times per month were excluded from the study. Following a control period to establish baseline psychological and biochemical parameters, subjects were exposed to visual cues for their favorite alcoholic beverage. After 20 minutes of cue exposure, they consumed the beverage over ten minutes. A total of 13 plasma samples were obtained across baseline, anticipation and consumption phases. The data demonstrate clear differences in cue-induced biochemical responsivity between light and heavier *social* drinkers. Distinctive and specialized biochemical changes are observed in heavier drinkers in both the anticipation and consumption phases. Heavier drinkers showed a disinctively modulated prolactin response when anticipating alcohol. They also showed uniquely elevated glucose levels immediately after consumption of a single standard alcoholic drink. Assays in progress strongly suggest heightened cue-specific adrenalin and noradrenalin responsivity in heavier drinkers. The data suggest the possibility of isolating reliable early-onset biochemical markers of alcohol-related problems in non-clinical drinkers.

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CARDIOTOXICITY IN ASYMPTOMATIC FEMALE ALCOHOLIC INPATIENTS

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Cardiovascular complications are known to contribute to early morbidity among alcoholics with an increased risk of hypertension, stroke, and cardiac dysfunction. The course of alcohol-related cardiomyopathy is relatively long with few early symptoms. Although women have a higher bioavailability of alcohol than men, few researchers have considered gender differences with regard to alcohol-related myocardial involvement. Based on data from our labs, male alcoholics with the highest blood pressures during the first two days of withdrawal had the greatest evidence of cardiotoxic effects of alcohol consumption. These patients reported the greatest consumption of hard liquor, had the most severe withdrawal symptoms, and had elevated liver enzyme status. Women alcoholics show similar alcohol-blood pressure relationships during withdrawal, although elevations are less marked than those of men. This suggests that female alcoholics may have similar functional deterioration from chronic ethanol abuse. In order to examine if there is a relationship between elevated blood pressures during withdrawal and asymptomatic cardiovascular dysfunction in recovering female alcoholics, we will test two subgroups of inpatients defined by level of admission resting blood pressures: *normotensive (NT; BP<140/90mmHg) or transiently hypertensive (tHT; BP≥140/90mmHg).* These subjects will be compared to a group of nonalcoholic controls at three to four weeks post admission on various cardiovascular responses to a speech stressor and isometric handgrip exercise. Impedance cardiography will be employed to assess the underlying hemodynamic and vascular stress responses, allowing for noninvasive measures of cardiac output, stroke volume, and peripheral resistance. With information regarding the pattern and severity of alcohol abuse in these women, along with the pattern of abuse of other drugs; this study should allow us to identify differential risk factors which appear to modify the toxic effect of ethanol on the female cardiovascular system and conceivably contribute to gender differences in developmental rates of alcoholic cardiomyopathy.

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THE RELATIONSHIP BETWEEN SPIRITUAL EXPERIENCE AND ALCOHOL USE

M. M. Arias, T. E. Douglas, E. G. Singleton, and J. D. Kass

In the treatment of addiction, clinical observations sometimes suggest a relationship between spiritual experience and key concepts such as alcohol use and abstinence. This study was designed to explore this hypothesized relationship. The Alcohol Craving Questionnaire (ACQ-Now) and a mood questionnaire were administered to 55 male and female alcohol users. Spiritual experience was defined as the experience within the person that transcends and connects the personal self to a Higher Self and it was assessed by the INSPIRIT-R. Regression analysis was performed. There was a significant relationship for certain aspects of craving for alcohol were associated with enhanced spiritual experience: a) Increased anticipation of positive benefits, b) Decreased dysphoria, and c) Decreased intent to drink alcohol. Three specific moods were also related to the concept of spiritual experience: 1) Increased levels of happiness, 2) Increased frustration, and 3) Decreased anger and hostility.

AFFILIATION:

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PREDICTORS OF OUTCOME FOR PERSONS COMPLETING INPATIENT TREATMENT FOR ALCOHOL DEPENDENCE

D. Presti, S. L. Tunis, M. Young, and K. L. Delucchi

Efforts to identify predictors of outcome following inpatient treatment for alcohol dependence have had limited success. Most have focused exclusively on pre-treatment subject characteristics. This study was conducted on the Substance Abuse Inpatient Unit of the San Francisco Veterans Affairs Medical Center. The purpose was to identify pre-treatment and post-treatment variables predictive of short-term outcome for a sample (N=75) completing the program for alcohol dependence.

Information was obtained through in-person interviews at treatment entry, and by telephone at one week and one month post-discharge. Categories of pre-treatment predictors were a) severity of alcohol dependence, b) social stability (employment and family problems), and c) affective symptoms. Categories of post-treatment predictors were a) social stability (cmploymcnt, and family support at one week post-discharge), and b) continued participation in alcohol treatment. We used the entire set of variables to predict reported alcohol use (corroborated by a contact person) at one month post-discharge. We used all but the one week treatment variables to predict whether or not the subject had participated in alcohol treatment by the one month interview.

Subjects were predominantly Caucasian, unemployed, separated, and in their late forties. Follow-up rates were 77% at one week and 66% at one month, with no differences between those reached and those lost to follow-up. Of the 49 subjects reached at one month, 12% reported alcohol use. In general, subjects who had better outcome at one month tended to have greater need for treatment at program entry (*i.e.,* were unemployed, had more affective symptoms), but had family support for recovery immediately upon discharge. Continuation of intensive alcohol treatment (e.g., inpatient, residential, outpatient) was related to a more severe alcohol problem at program entry and to the absence of family support. The examination of both pre-treatment and post-treatment variables appears to be promising for predicting short-term outcome of patients completing inpatient treatment for alcohol dependence.

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RISK AND PROTECTIVE FACTORS IN ALCOHOL USE AMONG AFRICAN AMERICAN COLLEGE STUDENTS

W. A. Rhodes and E. G. Singleton

Considerable attention is paid to the concept of risk in addiction research; however, some persons succeed despite the predisposing conditions that have placed them at risk for developing drug problems. So-called protective factors shield and counteract against dysfunctionality associated with vulnerable conditions. In this investigation, 100 college students were given a new questionnaire that identifies and isolates vulnerability, resiliency, and invulnerability factors among groups at high-risk for alcohol abuse. Both unique and shared aspects of personal characteristics, family experiences, environmental circumstances, evaluation, and adaptation determine responses to dysfunctionality among this high-risk group, and serve to shield some individuals from developing substance use problems and laying the groundwork to help others recover from problem use.

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CONDUCT DISORDER AND RELATIVE RISK OF VIOLENCE, EMOTIONAL PROBLEMS, AND ALCOHOL AND OTHER DRUG USE IN ADOLESCENT FEMALES

G. Dale and E. G. Singleton

This investigation reviews the case records of African American, adolescent females with conduct disorder to examine the relative risks for co-occurring violence, emotional disorders, and alcohol and other drug problems. With regards to relative risk *(i.e.* unadjusted odds ratios), the patterns of comorbidity of alcohol and other drug use were higher than either alone. There were not enough indications of emotional problems to evaluate the extent of comorbidity with mental disorders.

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PERSONALITY DISORDERS, ALCOHOL USE, AND FAMILIAL RISK STATUS IN COLLEGE-AGE MEN

J. D. Bedrick and A. I. Alterman

As part of a larger study of drinking behavior in college-age men deemed to be at either high or low risk for alcohol abuse, based on whether or not there was a history of heavy alcohol use in the fathers of the subjects, a sample of 251 high-risk and 242 low-risk men were administered the PDQ-R. Men in the high-risk group were found to have significantly higher levels of 7 of the 13 personality disorders. Specifically, they had significantly higher incidence of schizotypal, histrionic, narcissistic, borderline, antisocial, obsessive-compulsive, and sadistic personality disorders. There was a trend towards higher incidence of schizoid, paranoid, and self-defeating personality disorders. There were no significant differences between the groups for avoidant, dependent, and passive-aggressive personality disorders. Men in the high-risk group also drank more. Having any personality disorder was associated with greater drinking in the low-risk group but not in the high-risk group. When the individual personality disorders were looked at differences in effect were noted and it was not simply the case that having any personality disorder was associated with greater drinking. Some personality disorders were associated with higher levels of drinking whereas others were actually associated with lower levels of drinking. Thus it was not simply a case of psychopathology *per* se being associated with greater drinking. Further, these results would suggest that the population with alcohol use disorders is a heterogeneous one.

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DRUG DEPENDENCE AND OBSESSIVE COMPULSIVE PERSONALITY (OCP)

M. K. Romach, H. L. Kaplan, G. Somer, and E. M. Sellers

The interrelationship between drug dependence, particularly alcohol dependence, and anxiety has received considerable attention (Kushner *et al.,* 1990). Alcohol may exert anxiolytic properties via effects on cognitive processes *e.g.* attention allocation, self-evaluation and attributions. Individuals with all types of anxiety disorders may have concurrent personality disorders. Numerous attempts have been made to link particular personality characteristics to risk to substance dependence. Antisocial personality disorder has been a constant association (Hesselbrock et al., 1986). We have noted a high prevalence of obsessive compulsive personality disorder (OCPD), one of the anxious (C) cluster of personality disorders, in patients dependent on benzodiazepines and alcohol.

Among chronic therapeutic dose benzodiazepine users (N=131; mean age 47 years; 58% male) many self-reported OCP traits on the SCID II, a structured psychiatric interview, with males endorsing significantly more traits than females ($p<0.03$). Twenty-two percent of the individuals were diagnosed with OCPD, the most common personality disorder in the group. A further 21% of the patients were rated as subthreshold for this diagnosis. OCPD patients had higher scores on the obsessive compulsive sub-scale of the HSCL-90 ($p<0.02$). Fifty-two percent of the OCPD patients had a past history of alcohol dependence, compared to 35% in the non-OCPD group. OCPD subjects overall showed a trend to drinking greater amounts of alcohol. There were no differences in dose of benzodiazepines used. OCPD patients had a greater prevalence of concurrent generalized anxiety disorder ($p = 0.06$) and higher scores on several anxiety scales.

In a separate sample of 47 alcohol dependent individuals (mean age 43 years; 72% male) OCPD traits were prominently endorsed on self-report. SCID interviews diagnosed OCPD in 12 (26%) subjects with another 10 (21%) almost meeting diagnosis (subthreshold). There were no significant differences in alcohol consumption between the OCPD versus non-OCPD patients. OCPD patients had greater overall impairment in their level of general functioning ($p = 0.006$). Significant and interesting differences between the two groups were noted on several subscales of the Inventory of Drinking Situations.

These data suggest that OCPD traits are common in subgroups of patients dependent on certain substances. Understanding such personality differences, the cognitive processing and affective states around issues of control and how these relate to substance use may be important in designing treatment interventions that meet specific individual needs. Our results provide an initial empirical data set which can serve as a basis for hypothesis generation and prospective detailed studies.

REFERENCES: Available upon request of senior author.

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SEX DIFFERENCES IN TWIN-PAIR CLOSENESS AND CONCORDANCE FOR ALCOHOLISM

M. C. LaBuda and R. W. Pickens

Within-pair emotional closeness was assessed in 169 same-sex twin pairs ascertained through an alcohol and drug treatment program in order to assess the impact of the closeness of the twin relationship on concordance for alcohol abuse and/or dependence. In general, identical twin pairs reported closer relationship than fraternal twin pairs, and female twin pairs reported closer relationships than male twin pairs. The data did not indicate an overall effect of closeness on concordance for alcohol abuse and/or dependence. In contrast, closeness was significantly related to co-twin risk for drug abuse and/or dependence; however, the MZ/DZ concordance difference for drug abuse remained significant when the effects of within-pair closeness were controlled. These results are important because there is at least some evidence to suggest that twins who separate from one another later in life and who maintained closer social contact, are behaviorally more alike with respect to alcohol consumption (Kendler *et. al.,* 1992). To the extent that environmental factors operate differentially in identical and fraternal twin pairs and to the extent that these same environmental factors are significantly related to behavioral outcome, traditional twin studies will overestimate the importance of genetic factors. The results of the current study demonstrate that the initial zygosity and sex differences in concordance for alcohol abuse and/or dependence reported by Pickens and colleagues (1991). cannot be explained solely on the basis of differences in twin relationship.

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EFFECTS OF FAMILIAL ALCOHOLISM ON FEMALE MARIJUANA USERS

B. W. Lex, S. K. Teoh, J. H. Mendelson, K. Kissell, and S. Peters

We hypothesized that different physiological, behavioral, or subjective responses to marijuana could distinguish between women with (FHP) and without (FHN) a family history of alcoholism. Subjects (16 FHP and 17 FHN) (X = 22.5 years) smoked either a 0.8 g cigarette containing 2.02 mg Δ^9-THC (FHP = 8; FHN = 7) or a placebo cigarette (FHP = 8; FHN = 10) in a within-group double-blind repeated measures design. Tests occurred 30, 90, and 120 minutes after smoking.

Δ^9-THC levels after marijuana were almost identical for FHP and FHN women, and none was detectable after placebo. Peak pulse rate increases for FHP women occurred at 15 minutes (27 bpm), but at 30 minutes (24 bpm) for FHN women. At 30 minutes after marijuana smoking, a performance decrement for FHN women was seen for the Digit Symbol Substitution Test (p = .0380). FHP subjects had more body sway than FHN subjects in the "eyes closed" condition (p = .0344) 120 minutes after marijuana. No significant differences occurred in the "eyes open" condition. There were no significant differences among groups for performance on a Divided Attention Task.

Subjective responses were greater for FHN women at 30 minutes (p = .0075) and 90 minutes (p = .0059) after marijuana for feeling "uncomfortable," and at 30 minutes (p = .0452) for feeling "confused." Results for feeling "high" and feeling "marijuana effects" showed no significant differences among groups. In this study, decreased performance and increased subjective responses occurred mainly at 30 minutes after marijuana for FHN women, when pulse rate increases were greatest.

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THE EFFECTS OF MARIJUANA HISTORY ON THE REINFORCING, SUBJECTIVE AND BEHAVIORAL EFFECTS OF NITROUS OXIDE IN HUMANS

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In past studies conducted in our laboratory, we have been unable to demonstrate that nitrous oxide functions as a reinforcer in healthy volunteers (Dohm *et al.,* 1993a,b). However, reinforcing and other behavioral effects of psychoactive drugs may be modulated by drug history. We hypothesized that subjects with a drug history of marijuana use may find the effects of nitrous oxide to be more reinforcing than subjects without such a history, due to the putative similarities in some of the subjective effects of these drugs (Block *et al.,* 1990). In the present study, the reinforcing, subjective and psychomotor effects of nitrous oxide, and the choice rate of nitrous oxide (40% in oxygen) over placebo (100% oxygen) were compared across marijuana smokers and non-users in a double-blind, discrete-choice paradigm. Group One consisted of nine current marijuana users (mean: 1.3 joints/week; range: 0.25-3) while Group Two consisted of nine non-users. Subjects were exposed to 30-min trials of nitrous oxide and placebo over four sampling sessions and then chose between the two in three subsequent sessions. Distribution of choice rates did not differ significantly between marijuana users and in non-users [37% and 30% respectively; $X^2(3)=0.54$, ns]. The same degree of nitrous oxide-induced psychomotor impairment was noted in both groups. Nitrous oxide increased VAS ratings of "drunk," "stimulated," and "tingling" and decreased ratings of "in control of thoughts" and "in control of body" in both users and non-users. Both groups also showed increased ratings of "coasting," "carefree," and "high," but the magnitude of these effects was significantly higher in the marijuana users group. Marijuana users also had marginally higher euphoria ratings than non-users (History X Dose: $p=0.06$) on the Inhalant Drug Effects questionnaire. We conclude that at the concentration tested, some of the subjective effects of nitrous oxide differed as a function of drug history, but reinforcing effects of the gas did not.

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DOES SMOKING MARIJUANA CAUSE REVERSIBLE RETINAL VASCULAR CHANGES?

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The unique patterns and spatial stability of human retinal blood vessels have provided a means for individual indentification analogous to fingerprinting. This ongoing study is using the Ibex 90 retinal reader (Eyedentify, Inc., Baton Rouge, LA) to determine if smoking marijuana results in retinal vasculature changes, preventing a positive identification of previously enrolled subjects. Delta-9-tetrahydrocannabinol (THC) has previously been reported to produce vascular changes. The Ibex 90 scanner is operated using an IBM PS/2 personal computer for data handling. The subjects (N = 5) were three males and two females, 18 - 35 years old, who smoked marijuana cigarettes (placebo, 1.77% and 3.58% THC) according to a randomized dosing design. Blood and urine specimens are collected and retinal scans taken for a pre-smoke baseline and five minutes, one hour and four hour post-smoking periods. Concentrations of cannabidiol, cannabinol. THC and selected metabolites are quantitated in plasma and urine using gas chromatography/mass spectrometry (GUMS). Preliminary results indicate that changes in the spatial patterns of retinal blood vessels may be changing following acute exposure to marijuana. Data from one subject is shown in the table below to illustrate the changes being observed. Additional subjects have been enrolled to increase the number of subjects and the number of temporal observation points after smoking.

	Scanner Readings*			
dose	**baseline**	**5 min**	**60 min**	**240 min**
placebo	80.5	88	83	77.6
3.58% THC	73.6	43	22.6	93.6
*35 y.o. female				

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STRUCTURAL CHARACTERIZATION OF CANNABINOID RECEPTOR GENES

A. Chakrabarti, E. S. Onaivi, and G. Chaudhuri

The cannabinoid receptors are members of the G-protein linked super family of receptors. Two subtypes of cannabinoid receptors, brain type, CB1 and peripheral type CB2, have been cloned from rat and human origins. Studies from several laboratories suggest the possible role of genetic factors in drug addiction and toxicity. We have found significant differences in the neurobehavioral pattern in different strains of mice after the administration of tetrahydro cannabinol (Δ^9-THC), the primary psychoactive constituent of marijuana. The aim of this study is to characterize these receptor genes and apply that knowledge to determine the genetic basis of these observed differences in cannabinoid-induced neurobehavioral changes in mouse model.

Nucleic acids were isolated from the brain tissues of male C57BL/6 (Black), DBA/2 (Gray) and ICR (White) mice, from the brain and testes of Long Evans Hooded rats and from human blood cells using standard protocols. Oligonucleotide primer sets were designed from the published cDNA sequences. PCR amplification was done with these primer sets using genomic DNA (500 ng) or cDNA (-10 ng) templates. The PCR products were analyzed on 2% agarose gel. The identity of the amplified DNAs was verified by Southern hybridization. Purified PCR products from mouse genomic DNA were cloned in pCR-Script SK(+) (Stratagene) using standard protocols. Behavioral assessments with the mice were done by measuring catalepsy (Pertwee ring test), tail-flick, rectal temperature and spontaneous locomotor activity.

The differential sensitivity following the administration of Δ^9-THC to these mouse strains suggested that some of the neurobehavioral changes may be attributable to genetic differences. Amplification of identical bands in both DNA-PCR and reverse-PCR with human DNA templates suggests that the coding regions of human CB1 and CB2 genes are intronless. Similar experiments show that the rat and mouse CB1 genes are also intronless. These structural characteristics of the coding regions of CB1 and CB2 genes conform with the general feature of intronlessness in the genes of the G-protein linked super family of receptors. Two additional bands for CB1 gene were found with the reverse PCR product from C57BL/6 mouse brain. We have also found additional bands hybridizable with CB2 genes from both DNA- and RNA-PCR for human CB2 gene. These findings may indicate the possibility of subtypes of cannabinoid receptor genes. The sequence obtained for the mouse CB1 gene shows significant homology with the cDNA sequences of both rat and human CB1 gene.

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DOUBLE-BLIND TRIALS WITH ORAL COCAINE AS COCA TABLETS (CTA), USED FOR COCAINE DEPENDENCE TREATMENT

T. Llosa

Lately, have appeared some references on use of oral cocaine for cocaine dependence treatment, and there are evidences that the use of 20 mg of cocaine by oral route, in controlled trials, do not carry to cocaine dependence, and could reach levels of ≤15,000 ng/ml of benzoylecgonine (BE) in urine (Baselt 1992; Llosa 1994). and showed evident psychological differences with subjects that use cocaine by other routes and for addiction goals (Llosa 1993). Eight volunteers, males, Spanish, mean age 27.8±6.3. Coca Paste (CCP) dependents (DSM-IIIR criteria), mean CCP cigarettes (CCPC) per binge 22.7±16.3, mean 3344 mg of CCP/2090 mg of cocaine per binge, mean 4.3±1.3 relapses per week in the last three months, mean 3.25±0.83 days of largest abstinence in the last three months, mean 11.5±5.5 years of CCP use, enter in a double-blind, double dummy design, in out-patient clinic, at Lima, Peru, during five weeks. Subjects took daily eight CTA (20 mg of cocaine), plus placebo (Alfalfa/ALF or Thiamine/TH); Carbamazepine (CBZ) 400 mg plus ALF or ALF plus TH, in the second and third week; then, two subjects continued with CTA, and the other six with ALF, during the last two weeks. CTA matched in color and form, with ALF, and CBZ with TH. During the study all subjects were controlled with toxicological urine tests (Abuscreen Ontrak, Cut-off 300 ng/ml), Cocaine Craving Scale/CCS, Hamilton Anxiety Scale/HAS, and vital signs, two times a week. Urines collected were kept frozen (20°C) in order to be analyzed after with TDxFLx (Abbott) tests.

Preliminary results suggests that subject that were under CTA trials dropped their average in relapses, craving, CCPC use, and CCS/HAS scores, while they used CTA. Subjects that changed CTA and CBZ. by ALF, increased, after 6/11 days (CBZ/CTA), their weekly scores in positive urine Ontrak, relapse, CCPC number use, CCS, and CCS/HAS scores, and showed positive while subjects intake CTA. Subjects that used CTA during the four weeks, showed the largest abstinence and the lowest scores in relapse average, CCS, HAS, and CCPC use, even their urine tests showed positive for cocaine.

With TDxFLx tests, at entry, all subjects showed levels of BE up to 50,000 ng/ml. Subjects that intake CBZ, TH, and ALF showed during the study levels up to ≥30,000 ng/ml. Subjects that intake CTA dropped their average levels of BE from >50,000 ng/ml to 12,000±5,458 ng/ml, since the third week of treatment until discharge of study. Average levels of BE in subjects that intake CBZ, TH, and ALF, showed >35,000, >50,000, and >50,000 ng/ml respectively, during the study. Statistical analysis of the results suggest that CTA>CBZ>Placebo ($p < 0.01$), had effects in control craving, relapse and CCPC number use, at least during the four weeks; and that the prescription of controlled oral cocaine could be an efficient alternative for cocaine dependence treatment.

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DIETHYLPROPION THERAPY FOR INPATIENT TREATMENT OF COCAINE DEPENDENCE

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INTRODUCTION: Dicthylpropion (DEP) is a psychostimulant approved for the treatment of exogenous obesity. It is reported to have a low abuse potential. Animal studies indicate that DEP maintains self-infusion behavior with somewhat lower potency than cocaine as a reinforcer. Because of these properties of DEP, we examined the potential anti-craving efficacy of DEP in cocaine addicts.

SUBJECTS: Fifty subjects (38 men, 12 females; mean age 32.8 years) who met DSM-III-R criteria for cocaine dependence served as subjects. Subjects had no history of a major psychiatric or medical disorder. Mean duration and amount of cocaine use was 6.6 years and 2.52 grams each week, respectively.

PROCEDURE: The study design was a randomized, double-blind, placebo controlled parallel groups comparison on an inpatient unit. Subjects (n = 10 per group) were given either 25 mg QD, 25 mg BID, 25 mg TID, or 75 mg sustained release of DEP, or placebo daily for two weeks. Cue-induced craving was assessed once during the premeditation phase and daily throughout the medication phase. Blood pressure, heart rate, temperature, respiration were assessed daily. EKGs were obtained weekly.

STIMULATED CRAVING PROCEDURE (SCP): SCP involved subjects viewing five slides of cocaine and cocaine-related paraphernalia. A 100 mm visual analog scale (VAS) was completed prior to viewing the first slide (preslide), and once after each slide was presented (postslide). Change scores for the VAS were calculated by subtracting the preslide VAS score from the mean of the postslide VAS score.

RESULTS: There were no dose-related differences for any vital sign measure. There were no clinically dose-related differences in EKG parameters (QRS, PR, QTc) as a result of DEP treatment. However, DEP was associated with a number of adverse effects. 12% (n=8) of subjects on DEP were withdrawn secondary to medication side effects; two of whom developed coronary vasospasm and atrial fibrillation. There were no significant differences between groups on the VAS. Although craving increased with the SCP, stimulated craving decreased over the course of the study ($F_{(2,90)} = 8.33$, $p < 0.001$).

CONCLUSIONS: DEP was not superior to placebo in anti-craving efficacy. Because of the lack of demonstrated anti-craving efficacy and the emergence of side effects, DEP lacks a rationale for outpatient studies in the investigational treatment of cocaine dependence.

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SAFETY AND EFFICACY OF BUPROPION IN COMBINATION WITH BROMOCRIPTINE FOR TREATMENT OF COCAINE DEPENDENCE

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Bupropion and bromocriptine have been used separately for treatment of cocaine dependence. This eight week open-label ongoing study tested two medication schedules of the combination of bupropion and bromocriptine with the goal of obtaining an enhanced therapeutic effect with less side-effects. The first group (n = 12) (Slow Dose Escalation [SDE]) received a slow dose induction and stayed a short time at the highest dose of both medications. This group had significant ($p < .01$) reductions between pre-treatment and post-treatment for patients' self-reported weekly grams used and money spent on cocaine, but no significant changes in urine toxicology tests for cocaine (qualitative and quantitative).

To examine if this partial improvement was due to the medication, a second group (n = 5) that received a rapid dose escalation (RDE) of both medication achieving the highest dose for longer time was studied. All patients in both groups received weekly individual standardized counseling. No serious adverse events were reported. One patient was discharged for non-medication-related medical reasons.

The RDE showed longer retention time in treatment, lower percent of urines negative for cocaine, greater reduction of urine cocaine concentration, and self-reported cocaine use in grams and dollars. These results suggest that the combination of bupropion and bromocriptine is safe and that a higher dose for longer time may be more effective for treatment of cocaine dependence.

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IMIPRAMINE FOR THE TREATMENT OF COCAINE AND METHAMPHETAMINE DEPENDENCE

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At the Drug Detoxification, Rehabilitation, and Aftercare Program of the Haight-Ashbury Free Clinics, we conducted a double-blind, controlled, randomized clinical trial of imipramine in the treatment of cocaine and methamphetamine abusers. The purpose of the trial was to test the efficacy of imipramine as a treatment for stimulant dependence and to establish the feasibility of conducting a controlled clinical trial at the clinic under conditions that approximated usual clinical practice. Subjects were randomly assigned to receive either 10 or 150 mg/day of imipramine. Imipramine 10 mg/day was the control condition. Subjects could receive study medication for up to 180 days. One-hundred eighty-three subjects participated in the study: 151 who were cocaine dependent and 32 who were methamphetamine dependent. In addition to receiving study medication, all subjects were assigned to intensive drug abuse counseling, which included an HIV education component. Using an intention-to-treat analysis, we found that retention in treatment was significantly longer for subjects who were treated with 150 mg of imipramine compared to control. However, we found no consistent difference in percent of urine samples positive for stimulants, Beck Depression Inventory scores, or stimulant craving between the two groups of subjects. The feasibility of conducting a controlled, randomized clinical trial of medication for treatment of drug abuse was established for this community clinic setting.

REFERENCES:

Available upon request of senior author.

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COMPARISON OF PLACEBO AND DUAL TREATMENT AGENTS FOR COCAINE AND METHAMPHETAMINE DETOXIFICATION

F. Tennant

Our group has sequentially tested a large number of single agents for cocaine withdrawal, but none has shown clear superiority to placebo control groups. Included among tested agents for cocaine dependence have been amantadine, bromocriptine, bupropion, fluoxetine. mazindol, nifedipine, pentoxifylline, and selegiline. Some previous reports suggest that multiple treatment agents, when simultaneously administered, are more successful than single agents in stimulant detoxtfication. To this end, we have selected some of the single agents we have identified to be possibly effective in previous controlled studies, combined them, and compared them to placebo on an open trial basis. Subjects were cocaine and methamphetamine addicts who met DSM-III-R criteria for stimulant dependence, volunteered for treatment and demonstrated metabolites in their urine. The six evaluation criteria were percentage of subjects who dropped out in the first week of treatment, percent who left treatment with a negative urine, mean days in treatment, mean reduction in urine metabolite concentration between the day of admission and day of discharge, percent who remained in treatment over 30 days, and percent who achieved temporary detoxification by submitting at least one negative urine test. Agents which were simultaneously administered to cocaine addicts include amantadine and oxazepam, selegiline and tyrosine, nifedipine and pentoxifylline, fenfluramine and phentermine, and bupropion and nifedipine. Results indicate that some agent combinations may be more effective for stimulant detoxification than single agents or placebo. The combined use of agents may be superior to single agents possibly because cocaine and methamphetamine affect multiple biochemical and metabolic systems. In our hands, some agents and combinations appeared to have an early treatment effect in that first week dropouts were minimized while others may be superior in long term retention and elimination of cocaine metabolites from body fluids. For example, the combination of pentoxifylline and nifedipine demonstrated the lowest first week dropout rate while amantadine and oxazepam demonstrated the longest mean days in treatment and the highest percentage to leave treatment with a negative urine test. The agents pentoxifylline, nifedipine, and carnitine, which increase microcirculatory flow and/or produce a hemorheologic effect, appear to have therapeutic benefits. The combined use of agents should be further investigated for treatment of cocaine and methamphetamine dependence.

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COMBINED USE OF FENFLURAMINE AND PHENTERMINE IN THE TREATMENT OF COCAINE ADDICTION: A PILOT CASE SERIES

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Hitzig recently reported successful treatment of alcoholism with a combination of fenfluramine and phentermine (Maryland Medical Journal February: 153-157, 1993). Dr. Hitzig predicted that combined serotoneric and dopaminergic drugs which suppress craving for food would also suppress craving for alcohol, cocaine, ampethamines and treat depression and obsessive-compulsive disorders. The present study reports on the open-label treatment of six of the first seven cocaine addicts treated by Hitzig with these medications. Patients were retrospectively evaluated shortly after entering treatment and at three additional weekly visits thereafter. In addition to a clinical interview with a trained psychiatrist, the patients were assessed with a variety of instruments including the POMS, SCL-90R, Beck depression inventory, a cocaine craving questionnaire and a drug use survey. At the time of entry into the program, all the patients were suffering from moderate-to-severe depression and strong craving for cocaine. Within three hours after the onset of treatment, and lasting throughout the study, all patients experienced highly significant decreases in cocaine craving, cocaine use and abatement of their depression. Contemporaneous with the marked decrease in cocaine use, there was considerable improvement in their level of psychosocial functioning. The power of environmental triggers was substantially reduced. The two subjects who used cocaine while on medication did not experience any adverse effects. These findings support the hypothesis that the combined use of serotonergic and dopaminergic drugs is an effective treatment for depressed cocaine addicts who are motivated to seek treatment. Appropriately designed double-blind placebo-controlled clinical trials should be done as soon as possible in order to determine the efficacy of this treatment.

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TYROSINE FOR TREATMENT OF COCAINE DEPENDENCE: A HISTORICALLY CONTROLLED TRIAL

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Cocaine dependence continues to be a major public health problem and efforts to develop pharmacotherapies have been generally disappointing. Chronic cocaine use is believed to cause catecholamine depletion and similarities exist between cocaine withdrawal and major depression. Tyrosine is the dietary precursor to catecholamines and has yielded positive results in small trials of its antidepressant efficacy. Tyrosine 2 g every eight hours was administered on an open-label basis to 49 cocaine dependent individuals, as an adjunct to intensive outpatient drug abuse counseling. Data on retention in treatment at 90 days were compared to data from a control group of 80 subjects who had received 10 mg of imipramine per day in an earlier trial. Survival curves did not differ between the two groups (p=0.47, Breslow-Gehan). Median retention was 17 days in the tyrosine group and 17 days in the control group (p=0.48, Mann-Whitney U); 22% of the subjects receiving tyrosine were still in treatment at day 90, compared to 7% in the control group (p=0.015, chi-square). No side effects were reported by the subjects receiving tyrosine. While these data are limited by the historical design, small sample size, and lack of data concerning cocaine use, they provide little support for the hypothesis that tyrosine is a useful adjunct in the treatment of cocaine dependence.

REFERENCES:

Available upon request of senior author.

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DESIPRAMINE AND COUNSELING FOR TREATMENT OF COCAINE DEPENDENCE: A CONTROLLED STUDY

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A double-blind, random-assignment, parallel-group study comparing desipramine escalating dosages up to 300 mg/day (n=14) and inactive placebo (n=15), for a 12-week outpatient treatment of cocaine dependent (DSM-IIIR criteria) individuals, was conducted at the NIH-NIDA-IRP. They were males or females (ages 21 to 50 years) who self-reported at least 1 gram of current cocaine use per week during the past three months. Exclusions were: concurrent dependence on other psychoactive substances except caffeine or tobacco, unmanageable psychiatric or medical symptoms, illiteracy, pending incarceration. Patients attended the clinic twice a week and received counseling once a week. Evaluable patients stayed in treatment and received active medication or placebo for two weeks or more. Completers stayed in treatment at least 11 weeks. Treatment outcome measures were retention time in treatment, urine toxicology results, self-reported cocaine use and craving. Mean (SD) survival in the study was 8.14 (3.7) weeks for the desipramine group and 10.3 (2.4) for the placebo group (t=-1.87, df=27, p=.07). The percent of weekly urines positive for cocaine decreased from 85.7% to 57.1% for the desipramine group and from 7 1.4% to 60% for the placebo group; this decrease was close to significance for both groups of p=.07 ($\_^2$=3.21). The mean (SD) craving score decreased from 10.4 (5.7) to 6.3 (6.3) for the desipramine group and from 8.8 (6.6) to 5.2 (6.4) for the placebo group. There was a significant overall reduction across time in cocaine craving (F=10.23, df=1,27, p=.004), but there was no significant difference between groups in this reduction (F=0.05, df=1, p=0.82). A significant group by time interaction was found in self-reported cocaine use in grams during the past week (F=4.75, df=1,27 p=.04). In the current study, the decrease in use between intake and treatment is followed by a further significant ($p< .05$) decrease for the desipramine group but not the placebo group. While the desipramine group decreased reported use of 37.5%. the placebo group increased by 47.3%. The range of maximum desipramine dose achieved was 150 to 300 mg/day. The highest dose (300 mg/day) was achieved by 10 (71.4%) of the 14 patients treated with desipramine. While desipramine subjects showed more side-effects than placebo subjects, this was not statistically significant (66.7% vs. 33.3%, p=.09). This study supports desipramine as a useful component of the ambulatory treatment program of cocaine dependence.

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FLUOXETINE EFFECTS ON COCAINE RESPONSE: A DOUBLE-BLIND ASSESSMENT

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Fluoxetine (FLX), a selective serotonin reuptake inhibitor, has been proposed as a treatment for cocaine abuse. Clinical trials have assessed the effects of FLX on cocaine use and produced mixed results. Our laboratory has previously reported that treatment with FLX (40 mg, p.o./day) attenuates the subjective and mydriatic effects of intravenous cocaine administered to human volunteers under controlled laboratory conditions. The present study was designed to replicate and extend those findings by examining the effects of FLX, at doses up to 60 mg/day, on the physiologic and subjective response to cocaine.

METHODS: Current intravenous users of cocaine participate in this double-blind, placebo-controlled study while residing for nine weeks on a closed research unit. Volunteers receive oral capsules each morning as follows: Group 1 receives placebo (PLA) throughout the study, while Group 2 receives capsules containing either PLA or ascending doses of FLX (0 mg for Weeks 1, and 5 through 9; and 20, 40, and 60 mg for Weeks 2, 3. and 4, respectively). In twice weekly challenge sessions, three intravenous cocaine injections (0.20 & 40 mg) are given one hour apart. Physiologic and subjective indices are monitored before and after each injection.

RESULTS: Preliminary analyses (PLA n=4; FLX n=5) indicate that cocaine alone dose-dependently increases pupil diameter, blood pressure, heart rate, and subjective ratings of positive drug effects (i.e., “liking for the drug,” and “rush”). When given in combination with cocaine, all doses of FLX decrease the subjective response to the 20 mg, but not the 40 mg, cocaine challenge. FLX mildly potentiates the heart rate increasing effects of cocaine in a dose-dependent fashion, but produces no accompanying effect on blood pressure. The greatest heart rate increase observed was -10 beats/minute following treatment with 40 mg cocaine in combination with 60 mg FLX. FLX blunts the mydriatic response to cocaine, possibly because FLX itself produces mydriasis. FLX alone produced no other significant physiologic or subjective effects.

CONCLUSIONS: Preliminary data indicate that FLX decreases the subjective effects of cocaine under some dose conditions. The limited magnitude of the cardiovascular interaction between the two drugs suggests that they can be administered safely in combination across a range of doses. These data support continued investigation of FLX as a potential pharmacologic treatment for cocaine abuse.

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INTERACTION OF SELEGILINE AND COCAINE IN HUMAN COCAINE ABUSERS

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Selegiline (L-deprenyl), an MAO-B inhibitor, is currently being considered as a potential pharmacological therapy for cocaine withdrawal and craving. Selegiline blocks dopamine metabolism in the brain. Understimulation of the dopamine system during cocaine withdrawal has been speculated to be involved in cocaine craving. This study was conducted to evaluate the safety of selegiline and cocaine given concurrently, and to assess potential alteration of cocaine's subjective and cardiovascular effects and cocaine craving. Five male inpatient volunteers, ages 22-39, with histories of recent i.v. cocaine use, received placebo or 10 mg sustained-release selegiline (p.o.)(Pharmavene, Inc., Gaithersburg, MD) per day. Urine samples were collected daily for analysis to confirm the presence of selegiline metabolites, l-amphetamine and l-methamphetamine. Each subject participated in two i.v. cocaine challenge sessions, one during placebo treatment and one following 2 days of selegiline treatment. Ascending doses of cocaine (0, 20, 40 mg, i.v.) were administered at 60 min. intervals, while assessments were made on cardiovascular, pupil diameter, and subjective measures and craving. Repeated measures ANOVAs revealed significant increases ($p<0.05$) of heart rate, systolic blood pressure, diastolic blood pressure and a significant increase in pupil diameter, with increasing cocaine dose. Subjects' ratings of "drug effect," "rush" and "good effects" on visual analog scales increased as cocaine dose increased. "Desire for cocaine," indicative of cocaine craving, also increased significantly as cocaine dose increased. "Bad effects" ratings were unaffected and "drug liking" ratings tended to increase (non-significantly) as cocaine dose increased. Thus, this human laboratory procedure was sensitive to cocaine-produced effects on cardiovascular parameters, on subjective effects and on desire for cocaine. In contrast, there were no significant between-session differences in cardiovascular parameters, subjective effects or desire for cocaine as a result of selegiline versus placebo pretreatment. Selegiline significantly decreased pupil diameter, but did not interact with cocaine-induced mydriasis. In conclusion, co-administration of selegiline with cocaine is safe under these dose conditions as assessed by cardiovascular indices. However, the present study provides no evidence suggestive of therapeutic benefit of selegiline. Further evaluations under other conditions may be useful.

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AN ANALYSIS OF FACTORS INFLUENCING SUBJECT PARTICIPATION IN A TRIAL OF CARBAMAZEPINE FOR COCAINE-DEPENDENCE TREATMENT

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Data was gathered from a 10-week outpatient trial of carbamazepine vs placebo for cocaine-dependence treatment. Discriminant analysis was used to look for factors predictive of subject survival; cocaine use (past 30 days and lifetime), education, number of previous drug and alcohol treatments, Beck Depression Inventory scores, treatment (carbamazepine or placebo), and Addiction Severity Index composite scores. One hundred and eighty-six subjects were recruited into the study. Thirty-two subjects were consent forms only, 21 were screened out prior to randomization, 116 subjects were randomized, 95 subjects were dosed, 46 dropped after dosing, 43 completed. Baseline data was used for all analyses. Four models were selected; (1) weeks one through nine (drop outs) versus completers, (2) weeks three through nine (steady drug state) versus completers, (3) week one through two versus week three through ten, and (4) consent form only versus randomized (treatment assigned). In all four models there was little difference between groups. In model 1, priors were 48% (completers) and 52% (drop outs). Overall classification was 58.4%. Group percentages were 62.8% and 54.3% respectively. In model 2, overall classification was 68.12%. Priors were 38% (3-9) and 62% (completers). Group percentages were 38.5% and 86% respectively. In model 3, overall classification was 73.7%. Priors were 27% (weeks 1-2) and 73% (weeks 3-10). Group percentages were 11.5% and 97.1% respectively. For model 4, priors were 22% (CFO's) and 78% (randomized). Group percentages were 0% and 98.2% respectively. Overall classification was 76.2%. The results for the variables used in these analyses did not substantiate evidence of pre-treatment indicators useful to predict treatment survival.

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A QUANTITATIVE ASSESSMENT OF URINARY BENZOYLECGONINE LEVELS AS INDICATORS OF CARBAMAZEPINE EFFICACY FOR COCAINE-DEPENDENCE TREATMENT

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We conducted a ten week double-blind, placebo-controlled pharmacotherapy trial of carbamazepine for cocaine dependence. Urine specimens were collected for each subject and analyzed for the cocaine metabolitc. The data was then graphed and screened for patterns of urinary excretion of benzoylecgonine. We found that the graphs could be grouped into five categories based upon the patterns of excretion. These categories are: **Theoretical** (positive values at baseline that decrease to zero during the initial weeks and stay there for the duration of the study), **Negative** (zero values at baseline and throughout the study), **Negative to Positive** (zero values at baseline and a steady increase for the remainder of the study), **Positive** (positive values at baseline and throughout the study), and **Others** (no consistent pattern of benzoylecgonine excretion). All urine specimens were analyzed using (FPIA). There were no differences in the pattern of urinary excretion of benzoylecgonine between groups. Although the **Theoretical** pattern is the desired excretion looked for in response to effective treatment where the subject reaches abstinence and remains drug-free. it is expected that some subjects will relapse during treatment. Hypothetically, an all negative or all positive subject will not make a good research subject because they generally do not show a treatment effect. The positive group, however, may represent the most "hard core" patient because the response to a minimal-to-moderate therapeutic effect may not be seen. It is advisable to collect several urine specimens over an extended baseline period to identify such subjects in order to show a treatment effect.

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NIMODIPINE PHARMACOTHERAPEUTIC ADJUVANT THERAPY FOR INPATIENT TREATMENT OF COCAINE DEPENDENCE

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INTRODUCTION: Emerging literature suggests a role for voltage sensitive calcium channel blockers (VSCCBs), such as nimodipine, in the treatment of cocaine addiction. For instance, nimodipine suppresses cocaine-induced dopamine release in ventral striatum, and cocaine-induced motor stimulation, place preference, and self-administration. Nimodipine also appears to have mood stabilizing properties that may be useful in an anti-craving agent.
METHOD: Thirty-five male and female crack cocaine abusers who met criteria for cocaine dependence completed the study. Subjects were admitted to an inpatient treatment ward and randomly assigned to receive either nimodipine (60 mg po QID) or placebo for 21 days. The efficacy of nimodipine to in reducing cocaine cue-induced craving was assessed with a "stimulated craving paradigm". Subjects completed 100 mm visual analog scales (VAS) immediately prior to and after viewing five slides of cocaine and cocaine-related paraphernalia and handling realistic "demos". Craving was assessed twice in the premeditation phase and every other day during the medication phase.
RESULTS: **Pre- and poststimuli craving:** Prior to the medication phase, placebo subjects showed significantly more cue-associated craving than did nimodipine subjects (ANCOVA [using prestimuli values as covariates], $F_{(1,32)} = 8.11$, $p < 0.008$). Pre- and post-stimuli craving decreased over the course of the study (2 [group] x 3 [week] ANCOVA [using premeditation pre- and post-stimuli VAS scores as covariates]; $F_{(2.66)} = 26.6$, $p < 0.001$). There was also a significant group x week interaction ($F_{(2.66)} = 3.94$, $p < 0.03$), such that placebo subjects showed greater decreases in craving from week one to week two than nimodipine subjects showed. **Change from pre-stimuli scores:** During the premeditation phase, placebo subjects showed significantly greater changes in craving following the cocaine stimuli than did the nimodipine subjects ($F_{(1,33)} = 6.1$, $p < 0.02$). Medication phase data (2 [group] x 3 [week] ANCOVA using baseline premedication phase change scores as covariates) showed no significant main effects or interactions.
CONCLUSIONS: Subjects in the placebo group demonstrated significantly greater cue associated craving than the nimodipine group during the baseline premedication period, suggesting that the two groups were different prior to the medication phase of the study. The baseline differences limit any conclusions that can be drawn from the medication phase of the study. Pre-stimuli craving levels were not effected by nimodipine treatment.

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SUBACUTE CARDIOVASCULAR EFFECTS OF IV COCAINE IN HUMANS WITH 24 HOUR HOLTER AND BP RECORDINGS

L. L. Weinhold, R. A. Nelson, W. R. Lange, and D. A. Gorelick

To evaluate the subacute effects of cocaine on blood pressure (BP), heart rate (HR), and occurrence of cardiac ectopy in humans, this study retrospectively analyzed the 24 hour ambulatory BP and Holter monitor recordings from an inpatient cocaine administration study. After a one week baseline, 18 cocaine-dependent (DSM-IIIR) subjects (15 men; mean age 32.9 years; cocaine use 8.4 years; average cocaine use 3.2 grams per week) with no other cardiovascular risk factors (except cigarette smoking) received three doses (at about 0930, 1130, and 1330) of either cocaine (25 mg IV) or saline (1 mg IV) administered over ten seconds in a counter-balanced double-blind procedure. Data from the second week (two cocaine days and one saline day) were compared.

BP and HR were significantly ($p < .05$) higher on cocaine days only from 0900 to 1500. The mean elevations during this six hour interval on cocaine days were HR: +11.8 bpm, SBP: +8.1 mmHg, DBP: +6.2 mmHg.

For isolated supraventricular (SVT) and ventricular (VT) beats, there were no significant differences between cocaine days and saline days either from 0900-1500 or for the entire 24 hour period, nor did ectopy rates from 0900-1500 on cocaine days significantly differ other time periods. Mean (SE) ectopy rates (per 24 hours) on cocaine vs. saline days were 15.2 (7.5) vs. 6.9 (2.6) for SVTs and 31.5 (29.9) vs. 82.3 (81.7) for VTs. For 25 patients, representing 1487 hours, one four-beat ventricular run, one ventricular couplet, four supraventricular runs, zero bigeminy, and zero pauses were recorded. No significant association between ectopy rate or type and later study disqualification was found.

These findings suggest that low-dose IV cocaine has transient effects on BP and HR, and that low levels of ectopy may not be a significant risk factor for cocaine-associated adverse cardiovascular events.

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RISK FACTORS FOR ADVERSE CARDIOVASCULAR EVENTS IN COCAINE-DEPENDENT RESEARCH SUBJECTS

D. L. Frankenfield, D. A. Gorelick, L. L. Weinhold, C. S. Contoreggi, and W. R. Lange

The temporal relationship between cocaine administration and adverse cardiovascular events (ACEs) and identification of risk factors for experiencing an ACE were investigated in 31 cocaine-dependent research volunteers (87% male, 61% African-American) receiving intravenous cocaine (25 mg IV over ten seconds three times a day twice weekly) while undergoing 24-hour ambulatory electrocardiographic monitoring. Seven subjects (all males) experienced an ACE: four not temporally associated with acute cocaine administration (asymptomatic Wenckebach atrio-ventricular (AV) block, first degree AV block, ventricular tachycardia and unifocal premature ventricular contractions, including bi- and tri-geminy) and three after acute cocaine exposure (ST depressions > 3 mm and a heart rate of 120 beats per minute (BPM) within four minutes of cocaine exposure, asymptomatic ventricular tachycardia 15 hours after cocaine exposure and a heart rate of 145 BPM and serial systolic blood pressures of 150-180 mm Hg three days after cocaine exposure).

Demographic, physiologic, family history, and drug use history variables were examined for an association with a subsequent ACE. Top quartile of body weight, and body mass index (BMI), and elevated baseline diastolic blood pressure (greater than the median, 74 mm Hg) were significantly associated with experiencing an ACE. Although not statistically significant, persons in the top quartile of age distribution experienced 43% of the ACEs.

A similar analysis was conducted on eight applicants excluded from protocol participation due to evidence of pre-existing cardiac abnormalities and on 24 randomly-selected applicants excluded for non-medical reasons. There were no statistically significant differences between groups.

All identified events resolved uneventfully without medical intervention. Nonetheless, investigators and clinicians should be aware of the possibility of spontaneous ACEs in association with cocaine use. Consideration should be given to exclusion of those at possibly higher risk: persons older than 35 years, with elevated baseline diastolic blood pressure, and with elevated weight or BMI. Careful monitoring of subjects receiving cocaine is required, as well as readily accessible resuscitative equipment and trained personnel. Prospective studies with greater numbers of subjects are needed to confirm the validity of the potential risk factors identified in this study.

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CARDIOVASCULAR EFFECTS OF COCAINE USE IN OUTPATIENTS TAKING ANTI-DEPRESSANT MEDICATION

R. A. Nelson, R. M. Keenan, D. A. Gorelick, G. N. Carmona, N. J. Carriero, and L. Covi

To investigate the subacute cardiovascular effects of cocaine both alone and with medication, this study retrospectively analyzed standing and sitting blood pressure (BP) and heart rate (HR) measurements from 91 cocaine-dependent (DSM-IIIR) patients in two outpatient cocaine-abuse pharmacotherapy trials.

At study entry, patients with cocaine-positive urines (> 300 ng/ml, N = 55) had significantly (by one-way ANOVA), higher standing diastolic BP (81.9 mmHg vs. 75.4 mmHg, respectively, p = .008), standing mean arterial pressure (97.8 mmHg vs. 91.5 mmHg, p = .018), and greater systolic orthostatic BP changes (-2.8 mmHg vs. +2.5 mmHg; p = .043) than patients with cocaine-negative urines (N = 36). No significant differences were found for systolic BP, sitting BPs or HR. A multivariate ANOVA controlling for age. gender, and alcohol use produced similar results. The only significant group difference in demographic or drug use characteristics was admitted cocaine use in the past 48 hours (64.8% vs. 19.4%, p < .001). Reanalyzing the data with self-reported cocaine use in the past 48 hours (divided into: 0 grams (g), N = 48; 0.25-1.00 g, N = 24; 1.50-15.0 g, N = 18) as the independent variable produced significant differences only for systolic orthostatic blood pressure changes.

Of 47 patients on treatment medication (desipramine, N = 10; fluoxetine, N = 20; diphenhydramine. N = 9; or inactive placebo, N = 8) who had serum medication levels indicative of treatment compliance and had both a cocaine-positive and a cocaine-negative urine within a two week period, a two-way mixed ANCOVA found no significant association between a cocaine-positive urine and BP, HR or orthostatic changes. Desipramine itself was associated with a significant increase in sitting HR. The only cocaine-medication interaction found was accentuated orthostatic pulse changes in patients taking desipramine and diphenhydramine. These data suggest that cocaine has minimal subacute effects on the cardiovascular functioning of otherwise healthy cocaine-dependent patients, which are not significantly accentuated by treatment with anti-depressants.

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RAPID ARTERIAL KINETICS OF INTRAVENOUS AND SMOKED COCAINE: RELATIONSHIP TO SUBJECTIVE AND CARDIOVASCULAR EFFECTS

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This study was designed to directly compare arterial and venous cocaine plasma concentrations following both smoked and intravenous cocaine, while measuring standard physiological and subjective effects. Nine healthy male volunteers, who were current users of smoked and intravenous cocaine, participated. Each volunteer was tested under all conditions without an arterial catheter (Phase I) to determine if subjects could. tolerate each cocaine dose before proceeding to Phase II. Phase II consisted of two test days; each day consisted of either four smoked cocaine sessions (sham, 12.5, 25, 50 mg) or four intravenous cocaine sessions (0, 8, 16, 32 mg) in ascending order spaced 90 minutes apart. For the two highest doses of each route, arterial and venous blood samples were taken simultaneously before drug administration, during drug administration, and multiple times after drug administration. At the same time, heart rate, blood pressure and visual analog ratings of subjective effects were measured. Preliminary analyses indicate that the onset of subject and cardiovascular effects was rapid, paralleling the rapid peak in arterial cocaine concentrations. The administration of intravenous and smoked cocaine produced substantially higher arterial cocaine concentrations than venous cocaine concentrations and these effects were dose-dependent. After either smoked or intravenous cocaine, peak arterial cocaine concentrations were, on average, 13 times higher relative to peak venous cocaine concentrations regardless of route of administration or dose. Arterial concentrations peaked within 15 seconds after the completion of drug administration, whereas venous concentrations peaked 5.7 minutes after drug administration; there were no significant dose or route effects. No arterial kinetic differences were observed as a function of route of cocaine administration suggesting that any greater addictive effects attributed to smoked cocaine over intravenous cocaine may be related to nonpharmacologic factors, such as ease of administration.

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EFFECTS OF CARBAMAZEPINE ON EEG ACTIVITY AND MOOD IN COCAINE-DEPENDENT OUTPATIENTS

L. O. Bauer and H. R. Kranzler

Electroencephalographic, autonomic, and subjective reactions to cocaine cues were evaluated in 33 cocaine-dependent outpatients and 17 non-drug-dependent controls. None of the subjects met DSM-IIIR criteria for dependence on any other drug (exc. nicotine). They were also screened to exclude individuals with major psychiatric, neurological, or cardiovascular disorders, head injuries, seizures, or medication usage. Their reactions to three five minute videos (cocaine-associated, neutral, and erotic) were evaluated twice, with an interpolated one week interval. Between evaluations, patients received either carbamazepine (200 mg tid) or matching placebo in double blind fashion. The results of multivariate and univariate ANOVAs suggested the following conclusions: (1) CBZ treatment had no effect on subjective measures of the desire for cocaine among cocaine-dependent patients. This null finding is consistent with the demonstrated absence of a CBZ effect on the treatment outcome of these patients (Kranzler *et. al.,* submitted). (2) Quantitative analyses of EEG activity recorded from T3, T4, F3, F4, and Pz leads revealed no significant differences between patients and controls. Differences between these groups have been detected in evoked EEG responses (e.g.. Bauer 1993b; Bauer 1994; Amass *et. al.,* 1989; Herning *et. al.,* 1990; Branchey *et. al.,* 1993). However, we have repeatedly failed to detect abnormalities in on-going activity among cocaine-dependent patients with minimal psychiatric, neurological, polysubstance abuse, and medication histories (Bauer and Kranzler in press; Bauer 1993a; Bauer 1994). (3) The cocaine-associated and erotic videos evoked similar increases in the self-rated desire for cocaine, and similar decreases in total EEG power. CBZ-treated patients exhibited a greater decrease in respiratory sinus arrhythmia (vagal tone) in response to these videos than the other groups, but only during the first laboratory session (cf. Kranzler and Bauer 1992). (4) The increase in desire for cocaine evoked by the cocaine-associated and erotic videos was not significantly greater among patients than among controls, Future studies of cue reactivity should include a non-drug-dependent control group. Otherwise, it will be impossible to determine whether an increase in desire reported by patients reflect their abnormal status or the demand characteristics of the setting.

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REPLICATION OF QUANTITATIVE EEG DEVIATIONS IN COCAINE ABSTINENT SUBJECTS

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A purpose of this project is to test, in abstinent humans, the extent to which to chronic drug abuse, or DSM-III-R diagnoses of anxiety disorder or mood disorder are associated with central nervous systems alterations as indicated by EEG activity. Alper *et. al.,* (1990) using quantitative EEG analyses (QEEG) found increased absolute and relative alpha and decreased frontal delta power in cocaine abusers. In a population of hospitalized neuroleptic-treated patients, Dhuna *et. al.,* (1991), found decreased relative alpha over the fronto-temporal and temporo-parietal areas in those with cocaine-related psychoses. Roemer *et. al.,* (1994) reported independent confirmation of Alper *et. al.,* finding of hypofrontal delta activity in a sample of 25 cocaine-dependent polydrug abusers. Here, we combined the original 25 with 66 new subjects as the QEEGs of the two samples did not differ to yield a sample of 91 subjects. The larger sample permited testing of the relationships between comorbidity and QEEG features and the application of multivariate methods to evaluate relationships between polydrug abuse and residual QEEG alterations during abstinence.

Reduced Delta, Theta and Beta absolute power was found globally. Repeated measures ANCOVA (gender as covariate) comparing QEEG features in four groups of subjects: 1) without Mood Disorder or Anxiety Disorder (N=29); 2) with Mood Disorder and without Anxiety Disorder (N=19); 3) without Mood Disorder and with Anxiety Disorder (N=20); 4) with Mood Disorder and with Anxiety Disorder (N=23) yielded no main effects for Mood, main effects for Anxiety in 6% of the analyses and Mood by Anxiety interactions in 6% of the analyses; the latter approximates chance levels. This indicates the deviations of QEEG features are not secondary to other Axis I disorders.

Using multiple partial correlation analysis to partial out the effects of gender and any two of three measures of lifetime exposure to cocaine, alcohol or THC revealed that alterations in QEEG features were: Negatively related between lifetime exposure to cocaine and absolute power in all frequency bands; Negatively related between lifetime exposure to ETOH and, both, Theta and Beta absolute power; and not related to duration of THC dependence. The results indicate that chronic exposure to cocaine or alcohol does have a lasting effect on QEEG measures which can be observed during extended abstinence whereas exposure to THC does not.

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COGNITIVE FUNCTION IN ABSTINENT CRACK-COCAINE USERS

C. Ollo, T.N. Alim, and S. I. Deutsch

Concentration and memory are effected in cocaine abusers abstinent for about 1 month; (O'Malley *et. al.,* 1992). To determine whether cognitive deficits are more severe in early abstinence, we compared control subjects (N=7) and crack-cocaine dependent patients (N=36) who were abstinent for 9.4 (± 4.2) days. A sixth grade reading level on the WRAT-R was required. Patients were younger than controls (30.4 ± 6 years vs. 37 ± 6.1) and less educated (11.9 ± 1.5 years vs 14.1 ± .9), so an ANCOVA was used to compare groups. Test scores were correlated with abstinence (days), duration (years) and amount (grams/week) of use. Average duration of cocaine use was 6.1 years (± 4.4), an average amount used was 4.9 (± 5.9) grams/week. Fourteen patients were retested after 17.3 (± 1.6) days on memory (alternate forms) and concentration/speed tests.

RESULTS: Full Scale IQ was lower in patients (see Table; unadjusted means and standard deviations; p values $\leq .05$). but not on the WRAT-R. The WRAT-R reading score was highly correlated with Full Scale IQ ($r=.48$, $p<.007$) and Verbal IQ ($r=.62$, $p<.0003$) but not Performance IQ ($r=.21$). Immediate and delayed memory and concentration/speed performance did not differ. A pattern suggestive of frontal lobe dysfunction emerged; on the WCST, patients completed fewer categories and failed to maintain set, and were more susceptible to distraction on Stroop interference. Grams/week of cocaine was associated with more perseverative errors on the WCST ($r=.41$), and longer duration of use was associated with failure to maintain set ($r=.42$). At follow-up testing, there were improvements in concentration/speed tests only (* = $p < .05$). Amount of cocaine used now was positively correlated with verbal learning and recall, but negatively correlated with Stroop color-word naming and interference (all r's $> .55$, $p < .05$).

	Cocaine	Controls
Full Scale IQ	88.8 (8.2)	97.7 (7.8)
WRAT-R Reading	86.8 (10.5)	90.4 (15.0)
Conceptual Reasoning: Wisconsin Card Sort		
# categories	3.7 (2.1)	5.1 (1.9)
Perseverative errs	24.7 (15.2)	15.0 (7.1)
Not maintaining set	1.3 (1.9)	.9 (.9)
California Verbal Learning and Memory Test:		
Trial 5#	12.6 (2.7)	11.3 (1.7)
Total trials 1-5 T	39.8 (14.3)	35.4 (8.8)
Long term recall #	11.2 (2.9)	8.3 (2.8)
Complex Figure delayed recall #/36	19.1 (6.3)	19.3 (6.7)
Concentration/Psychomotor Speed:		
Digit Span SS *	10.1 (2.7)	11.3 (1.9)
Digit Symbol SS *	7.9 (1.9)	9.7 (2.1)
Stroop Words #	89.9 (14.6)	98.7 (13.4)
Colors # *	68.9 (10.3)	74.4 (9.0)
Color-word # *	36.6 (7.1)	43.1 (7.3)
Interference	-2.4 (7.3)	2.4 (3.9)

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EVALUATION OF COCAINE WITHDRAWAL USING THE COCAINE SELECTIVE SEVERITY ASSESSMENT

K. Kampman, D. McGinnis, A. Alterman, J. Volpicelli, R. Weinrieb, L. Epperson, and L. D'Angelo

BACKGROUND: A reliable and valid measure of cocaine withdrawal does not exist and such a measure may be useful in assessing treatment efficacy and predicting treatment outcome. This study presents preliminary reliability and validity data on the cocaine Selective Severity Assessment (CSSA), an 18 item clinician administered, cocaine withdrawal scale.

METHODS: Charts from all admissions to an outpatient substance abuse treatment research center over 12 months were reviewed. In addition, test-retest reliability was assessed in 60 other cocaine dependent patients by repeat interviews within two hours. All patients were routinely administered the CSSA at their first detoxification appointment. Cocaine dependent patients had the scale administered to them at each subsequent detoxification appointment. A psychiatric evaluation was conducted on each patient during the first week of treatment. Patients with concurrent axis I disorders were eliminated from evaluation. The remaining patients were grouped into three main groups: primarily cocaine dependent (70), primarily alcohol dependent (27), and mixed cocaine/alcohol dependent (31). An Addiction Severity Index (ASI) was obtained from each patient during the first week of treatment. Urine toxicology screens were obtained two to three times per week and analyzed on an ADX machine.

RELIABILITY: Test-retest reliability was high (r=.89). Cronbach's alpha was high in cocaine dependent patients (.79), and cocaine/alcohol dependent patients (.83), but not in alcohol dependent patients (.46).

FACE VALIDITY: Mean initial CSSA scores were significantly higher in cocaine dependent patients and mixed cocaine/alcohol dependent patients than in alcoholics (27, 28, 12 respectively). CSSA scores declined over one week only in patients who maintained abstinence. Initial CSSA scores were highly correlated with amount and frequency of recent cocaine use and with measures of addiction severity from the ASI.

PREDICTIVE VALIDITY: Mean initial CSSA scores were significantly higher in cocaine dependent and mixed cocaine/alcohol dependent patients who failed to detoxify than in those who were able to detoxify (32 vs. 19 and 33 vs. 12 respectively). Detoxification was defined as three consecutive urines negative for benzoylecgonine within the first month of treatment. Initial CSSA scores were negatively correlated with duration of treatment.

CONCLUSIONS: 1) Cocaine withdrawal is a distinct and measurable syndrome. 2) The CSSA is a reliable measure of cocaine withdrawal. 3) The CSSA is a valid measure of cocaine withdrawal. 4) High CSSA scores are associated with poor outcomes in outpatient cocaine detoxification.

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GROWTH HORMONE RESPONSES TO DOPAMINE ANTAGONISTS IN COCAINE ADDICTS AND ALCOHOLICS

C. K. Farren, C. McDougle, L. Price, D. Ziedonis, F. Hameedi, and T. Kosten

The dopaminergic system has been implicated in both alcohol withdrawal and cocaine abstinence. We measured the GH response to the dopamine agonist bromocriptine (1.25 mg orally) in post withdrawal (2 weeks) alcoholics and healthy controls, and the GH response to the dopamine agonist Sinemet (250mg L-dopa and 25mg carbidopa orally) in post abstinence (2 weeks) cocaine addicts and in healthy controls. The measurement was carried out over a three hour period.

The normal controls had a similar rise in GH in response to both dopamine agonists ($t=0.14$, $df=15$, p=ns), but the rise in response to Sinemet occurred earlier and fell earlier than the rise in response to bromocriptine, (group by time interaction $F=4.4$, $p<0.01$). The GH response in abstinent cocaine addicts was similar to that in controls, ($t=0.47$, $df=13$, p=ns), and there was no difference in timing of response (group by time interaction $F=1.4$, p=ns). There was a significant difference between post withdrawal alcoholics and controls in their response to bromocriptine, with a significant diminution in the alcoholics' response($t=2.9$, $df=14$, $p=0.01$). There was a significant difference in GH response between the alcoholics and cocaine addicts when compared directly(one tailed $t=-1.8$, $df=12$, $p<0.05$), with the alcoholics' response earlier and lesser than the cocaine addicts' response, (group by time interaction $F=2.13$, $p<0.05$).

Sinemet and bromocriptine thus equivalently stimulate a GH response but may have different pharmacokinetics and dynamics, with Sinemet having a quicker onset and shorter time of action than bromocriptine. There may be a relative dopaminergic subsensitivity in post withdrawal alcoholics relative to abstinent cocaine addicts. There may be a down regulation of dopamine receptors in the post withdrawal period in alcoholics, and these receptors are most likely post synaptic. There may be a post synaptic dopamine receptor supersensitivity in abstinent cocaine addicts, or an increase in presynaptic dopamine turnover.

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DOPAMINERGIC RESPONSIVITY AND PROLACTIN LEVELS IN COCAINE AND HEROIN DEPENDENT MEN: A PILOT STUDY

S. K. Teoh, J. H. Mendelson, N. K. Mello, S. Springer, M. Eros-Sarnyai, L. Goldstein, A. Skupny, and J. W. Sholar

Deregulation of prolactin secretion has been reported in cocaine dependent men. Acute abstinence from cocaine may be associated with increased dopaminergic responsivity. which normalizes over time. Since prolactin secretion is under inhibitory dopaminergic control, oral aministration of L-dopa 250 mg/ carbidopa 25 mg (Sinemet) was used to assess dopaminergic responsivity in twelve men who fulfilled DSM-III-R diagnostic criteria for concurrent cocaine and opioid dependence. The reported average duration of cocaine and heroin use was 10.2 ± 1.6 and 9.1 ± 1.3 years respectively. These men reported using an average of 3.0 ± 0.8 grams of cocaine intravenously per week and an average of 9.1 ± 2.3 bags of heroin per day. All subjects were in good physical health and the study was conducted between six to eight days following drug abstinence under controlled research ward conditions. Following an overnight fast, three baseline bolus blood samples were collected via an i.v. catheter. After oral Sinemet administration, bolus blood samples were collected at 15 minute intervals for 480 minutes for subsequent analysis of prolactin. Urine drug screens were negative for all subjects on the study day. Sinemet challenge study was also carried out in eight age-matched controls. Baseline prolactin levels were within normal limits (<20 ng/ml) and averaged 6.1 ± 0.5 ng/ml and 8.3 ± 1.4 ng/ml for the cocaine and opioid dependent men and controls respectively. Plasma prolactin levels were significantly suppressed between 30 to 270 minutes following Sinemet administration. A significant rebound in prolactin levels was detected between 330 to 480 minutes in both the cocaine and opioid dependent men and controls which exceeded the baseline. Suppression of plasma prolactin levels were significantly less in the cocaine and opioid dependent men compared to controls, though the degree of rebound prolactin secretion was similar between groups. These studies are still ongoing in cocaine abusers and controls. It is possible that chronic cocaine use may lead to down regulation of lactotroph responsivity to dopaminergic inhibitory control of prolactin secretion.

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SEROTONERGIC FUNCTION DURING ACUTE AND CHRONIC COCAINE ABSTINENCE

F. A. Hameedi, M. I. Rosen, L. H. Price, C. K. Farren, S. W. Woods, and T. R. Kosten

We conducted a preliminary study using mCPP as a neuroendocrine probe to explore serotonergic function in abstinent cocaine abusers. In this pilot study with five subjects who met DSM-III-R criteria for cocaine dependence, the subjects participated in two test days during acute and two test days during chronic cocaine abstinence. On two separate days during the acute and chronic abstinence phases the subjects received mCPP, .1 mg/kg, or placebo intravenously over a 20 minute period in a double blind random design. Behavioral ratings and blood samples for prolactin and cortisol levels were done over 180 minutes. The data from these subjects was compared with normal control data from another study. Baseline delta mean prolactin level over two weeks but did not reach the prolactin levels found in normal controls (Baseline prolactin 1-3 days > 2 weeks > normal controls). The prolactin response to mCPP was blunted in both one to three days and two weeks abstinence as compared to normal controls (prolactin levels; normal controls > 2 weeks > 1-3 days). The cortisol response to mCPP was blunted in both one to three days and two weeks abstinence as compared to normal controls (cortisol levels; normal controls > 2 weeks > 103 days). These data indicate dopaminergic and serotonergic dysfunctions during one to three days cocaine abstinence, which tends to return to normal following two weeks of abstinence but does not reach normal over a two week period. Our data support the findings from other studies by Dackis *et. al.,* 1985 and Buydens *et. al.,* 1993. The increased baseline prolactin could be due to decreased dopamine function and the blunting of prolactin and cortisol response to mCPP could be due to decreased serotonergic function. A larger sample is needed to confirm these findings.

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PLASMA BUTYRYLCHOLINESTERASE ACTIVITY IN SUBSTANCE ABUSERS

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Plasma butyrylcholinesterase (BChE) is the major cocaine-metabolizing enzyme in humans, and metabolizes heroin *in vitro,* but little is known about factors that might influence BChE activity and its stability over time in substance abusers. We evaluated these issues in 41 substance-dependent (DSM-IIIR criteria) subjects (20 cocaine, 14 tobacco, seven other) on a closed research ward by drawing blood at three day and one month intervals when subjects were drug/medication-free and had normal liver function (AST/ALT $\leq$ twice normal). All subjects had BChE activity (1.56-5.19 U/1) within the range of published norms for non-substance abusers. There were no significant differences in BChE activity by drug group or race (29 black vs. 12 non-black), nor any significant correlations between BChE activity and age (mean [SD] 34.8 [5.5] years), height (1.73 [0.094] m), weight (72.8 [11.5] kg), or body mass index (24.3 [2.7]). For the entire group, BChE activity did not change significantly over three day (mean change = -0.13 U/1, n = 40) or one month intervals (mean change = 0.08 U/1, n = 19). Cocaine addicts showed a significant three day increase (0.45 U/1, p = 0.03). These findings confirm earlier reports that cocaine addicts have normal BChE activity, extend this to other types of substance abusers, and suggest that cocaine addicts may have short-term fluctuations in BChE activity even when drug-free.

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SELF-REPORTED DRUG USE COMPARED WITH HAIR ANALYSIS AND URINALYSIS

J. A. Hoffman, E. D. Wish, J. J. Koman III, S. J. Schneider, P. M. Flynn, and J. W. Luckey

As part of a drug abuse treatment study conducted in Washington, D.C., 107 clients provided a self-report of drug use, a hair sample, and a urine sample at intake. Clients were 57% male and predominantly African-American (94%). These clients were referred to methadone programs or therapeutic communities for heroin and cocaine addiction treatment. Hair analysis detected higher percentages of opiate and cocaine use than both self-report and urinalysis. Greater concentrations of drug metabolites were found in the hair of clients who reported higher usage frequency during the past month. Additionally, hair analysis found that of 98 clients who tested positive for opiates, 95 (97%) also tested positive for cocaine. During a post-discharge follow-up 33 different clients provided a self-report of drug use and a hair sample. Follow-up clients were 56% male and mostly-African American (88%). The follow-up data indicated substantially lower concordance rates between self-report and hair analysis than the intake data, especially when lower concentrations of the drug were detected in the hair.

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HAIR ANALYSIS - A METHOD OF VALIDATION FOR SELF REPORT OF COCAINE USE

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Self reporting of cocaine use has proven to be an unreliable source of information and in an attempt to use an empirical objective test, hair analysis has been found to be a much more reliable source of information. Drugs and their metabolites appear in detectable levels in hair approximately one week after ingestion; once a drug and its metabolite are embedded in the hair shaft they remain there permanently. As the hair shaft grows, it forms a longitudinal record of the compounds it has absorbed. We report on hair analysis of the cocaine metabolite -benzoylegonine (BZ) in 32 subjects enrolled in a Toronto study. All claimed to have been current or former (within the past two years) regular cocaine users. However, in all subjects urine tested negative for BZ. In an attempt to validate their self report, a hair sample cut as close to the root as possible was obtained from each subject; at the same time a detailed account of cocaine use (monthly use in grams for min one year) was recorded. Five mm clippings from both ends (root and distal) were combined and analyzed for BZ using Roche Abuscreen RIA. For each subject, the hair clippings showed measurable levels of BZ. therefore confirming that they were indeed cocaine users. An attempt to correlate hair concentrations of BZ with the average use of cocaine per month, at the root and distal ends, resulted in a linear fit with an $R^2 = 0.0567$ when all 32 subjects were included. However, when only the subjects with a "reliable history" (as assessed by interviewer) were included the linear fit had an $R^2 = 0.633$ for $n = 21$ ($p < 0.001$). In an effort to obtain a more detailed time relationship, in 17 subjects with a "reliable self report" the hair shaft was sectioned in 1.5 cm sections (approx. monthly hair growth) and in each section BZ concentration (average of all the sections) with the average cocaine use corresponding to the time frame analyzed resulted in a linear fit with an $R^2 = 0.77$ ($n = 17$; $p < 0.001$). Also, in order to see how well the two measures related the average sectional BZ concentrations was correlated with the average BZ concentration measured from clippings from the root and distal ends ($R^2 = 0.41$; $n = 15$). Sectional analysis may provide the means to corroborate or refute self-report information although further investigation to better understand the relationship, quantify the uncertainties and discern if the degree of improvement is worth the additional labour is necessary.

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THE UTILITY OF QUANTITATIVE URINALYSIS FOR BENZOYLECGONINE IN CLINICAL TRIALS FOR THE ASSESSMENT OF COCAINE USE

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Urinalysis is a primary outcome measure in clinical trials for the evaluation of the efficacy of medications for drug abuse treatment. Qualitative analysis for urine benzoylecgonine (BE) levels has typically been employed to assess cocaine use. Recently, there have been increasing reports of the use of quantitative urinalysis for assessing cocaine use levels. The purpose of this study was to evaluate the utility of quantitative urinalysis versus qualitative approach based on simulated BE data from a set of simple clinical models.

Urine BE levels were simulated to mimic a 12-week clinical trial using a one-compartment model for cocaine disposition. The individual subjects' pharrnacokinetic (PK) parameters were randomly generated such that the mean and standard deviation of the group parameters matched those of an actual clinical PK study. The route of administration was assumed to be the IV dose and no intra-subject variations in PK parameters were used. The BE levels were calculated for 9:00AM samples on Mondays, Wednesdays and Fridays. The only variable for each subject was the dosing time which was randomly assigned between 6:00 and 24:00. Three groups of urine BE levels were simulated: A (control)--assumed cocaine use of 100 mg once daily, B (reduction in dose)--assumed cocaine use of 50 mg once daily, and C (reduction in frequency)--assumed cocaine use of 100 mg/day, three days a week.

When the weekly mean was used to represent each week's BE level, qualitative urinalysis utilizing a cut-off level of 300 ng/ml failed to detect a statistically significant difference between a reduction in dose or frequency with the control group while quantitative urinalysis was capable of statistically detecting a reduction in cocaine use (in dose or frequency). Qualitative urinalysis utilizing a cut-off level of 5000 ng/ml however was as capable of statistically detecting a reduction in cocaine use (dose and frequency) as a quantitative analysis. Additional model development is planned to generate simulated data matching that of an actual clinical database in order to optimize clinically useful cut-off levels of BE.

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QUANTITATIVE MEASUREMENT OF URINE BENZOYLECGONINE: IS IT A USEFUL MEASURE OF COCAINE ABUSE?

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OBJECTIVE: To determine the utility of quantitative urine benzoylecgonine (BE) concentrations as an indicator of the amount of cocaine use in outpatient clinical trials.

METHOD: We utilized gas chromatography/mass spectroscopy to measure quantitative urine BE as the primary outcome in two controlled studies of fluoxetine in the treatment of cocaine abuse. Of 84 subjects (52 secondary and 32 primary cocaine abusers) complete data sets existed for 76 subjects. Using only intake data, we examined multivariate relationships between quantitative BE concentrations and interview-derived self-reports of cocaine use in the previous week as well as reports of mood: Hamilton Depression, Hamilton Anxiety, and Beck Hopelessness scales. Due to observed extreme skew, the base 10 logarithm of the adjusted BE was used in these analyses.

RESULTS: Urine BE at intake was significantly and positively related to self-reported measures of cocaine use in the week prior to study intake: days of cocaine use ($r = 55$, $p = .0001$), dollars' worth used ($r = .43$, $p = .0001$), and times used ($r = .40$, $p = .0002$). BE levels correlated less robustly with psychological measures: HAM-A ($r = -.06$, $p = .6023$), HAM-D ($r = .06$, $p = .5678$), and hopelessness ($r = .09$, $p = .4091$); or with self-reports of subjective aspects of cocaine use: craving ($r = -.02$, $p = .8473$) and lack of control ($r = .12$, $p = .2929$). Quality of high related significantly and negatively to BE ($r = -.25$, $p = .0245$). A principal components analysis using a varimax rotation of all intake self-report measures indicates three latent factors: 1) amount of cocaine use, 2) psychological state, and 3) subjective aspects of use.

CONCLUSION: Quantitative urine BE at study intake is: 1.) a valid measure of cocaine use, 2) psychometrically distinct from psychological state, 3) psychometrically distinct from subjective aspects of use, and 4) a useful tool in the study of cocaine treatment.

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QUANTITATIVE MEASUREMENT OF BENZOYLECGONINE AS A MARKER FOR RELAPSE TO COCAINE ABUSE

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Cocaine abuse is a major addictive disease problem that is being addressed in many treatment clinics and by many research groups. Currently, the most common method for identification of cocaine use is qualitative urine analysis for the presence of benzoylecgonine (BE), a metabolite of cocaine. However, qualitative analysis has several shortcomings: cocaine use is usually detectable for only a few days, changes in the amount of cocaine a patient uses on different occasions cannot be identified, multiple days of use within a relapse period cannot be identified, and slow elimination of the metabolite may be mistaken for reuse. We undertook this study in order to evaluate the use of a simple urine analysis method that would allow for more accurate assessment of cocaine relapse for research purposes. In this study, we analyzed 24 hour urine specimens collected from eleven cocaine-addicted subjects in the Rockefeller University Hospital during cocaine abstinence. Six of the eleven were in methadone maintenance treatment. At admission, eight subjects had urinary BE concentration levels above 0.30 μg/ml. the standard cutoff for positive identification of cocaine use. Three subjects relapsed during their hospital stay. In total, 64 day passes were authorized and subjects used cocaine on nine (14%) of these days. Following cocaine use, urinary BE levels declined rapidly. In the eight subjects who tested "positive" at admission, urinary BE concentration remained above 0.30 μg/ml for 4.8 ± 0.5 (sem) days. Using BE normalized to creatinine (C) levels, cocaine use could be identified for 4.8 ± 0.5 days using a cutoff of 0.30 μgBE/mgC, for 6.9 ± 1.0 days using a cutoff of 0.10 μgBE/mgC, for 8.6 ± 1.3 days using a cutoff of 0.05 μgBE/mgC, and for 10.5 ± 1.5 days using a cutoff of 0.03 μgBE/mgC, the lower limit of accuracy calculated from BE concentration measurements at the 95% confidence level of 0.03 μg/ml. The half-life of BE during the initial elimination phase was 0.38 ± 0.08 days (n = 8) as calculated with Prophet computer program using normalized BE levels. Using the total BE measured in 24 hour urine collection, the half-life of BE was 0.46 ± 0.08 days as calculated with Prophet and 0.47 ± 0.08 days as calculated with SigmaPlot computer program.

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COCAINE AND METHAMPHETAMINE ADDICTS RELAPSE WHEN URINE METABOLITE CONCENTRATIONS DROP BELOW A CRITICAL LEVEL

D. Moll and F. Tennant

The majority of ambulatory, cocaine and methamphetamine addicts who demonstrate drug metabolites in body fluids and enter detoxification relapse and/or drop out in the first month of treatment. To help determine etiologic factors for the high drop out and relapse rates, we sequentially monitored, by Polarization Fluorescence Immunoassay (PFI), urine metabolite concentrations of 24 methamphetamine and 24 cocaine addicts who were consecutively admitted to ambulatory medical detoxification. Criteria for subjects to be included in this study were DSM-III-R for stimulant dependence, the presence of cocaine or methamphetamine metabolites in urine, and retention in treatment for seven or more days after admission. Treatment was with antidepressants or dopaminergic agonists. Urine concentrations were determined every 48 hours, and a total of 371 determinations were done. The 48 subjects submitted 371 urine specimens for urinalysis. Ten (41.7%) cocaine and 12 (50.0%) methamphetamine addicts achieved temporary detoxification by submitting at least one negative urine. Among the 12 methamphetamine addicts who achieved temporary detoxification, the first negative urine occurred in four (33.3%) during the first week, five (41.7%) during the second week, and three (25.0%) during the third week of treatment. Five (50.0%) of the 10 cocaine addicts who temporarily detoxified did so in the first week of treatment, two (20.0%) in the second, and three (30.0%) in the third or fourth weeks. There were 46 documented relapses in both groups. Nineteen (19) of 46 (41.3%) relapses occurred within 48 hours after submitting a negative urine. Ten (21.7%) subjects relapsed when their urine concentration dropped below 500 ng/ml, and 17 (37.0%) occurred when the urine concentration dropped to below 4300 ng/ml but above 500 ng/ml. All relapses in the latter two groups resulted in a raise of urine metabolite concentration to the admission baseline level, and all subjects relapsed within 48 hours after their urine concentration had initially dropped below the admission baseline level. Only 13 of the 48 (27.1%) subjects left treatment with a negative urine. Eight (8) of these 13 (61.5%) had at least one documented relapse before leaving treatment. Twelve (12) subjects never lowered their baseline, admission urine concentration during treatment despite submitting 62 urine specimens. Cocaine addicts remained in treatment longer than methamphetamine addicts. (26.2 ± 30.3 versus 21.5 ± 12.4 mean days; $t = 13.95$, $P < .0001$). Both the cocaine and methamphetamine groups significantly lowered their mean urine metabolite concentration between admission and discharge. This data suggests that methamphetamine and cocaine metabolites support dependence, and successful detoxification will require pharmacologic support to prevent relapse when metabolite concentrations drop below a critical level. Although the critical level may be variable, urine concentrations that drop below 1000ng/ml from a high level suggest that a relapse is likely.

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GENDER DIFFERENCES IN CEREBRAL PERFUSION IN COCAINE ABUSE: TC-99M HMPAO SPECT STUDY OF DRUG ABUSING WOMEN

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Cocaine abuse is associated with a variety of chronic and acute medical and neurological sequellae. Previous studies have demonstrated abnormalities in cerebral perfusion (Volkow *et. al.,* 1988; Holman *et. al.,* 1991) in chronic cocaine abusers, and after acute administration of cocaine. However, few studies have included women, and none has compared cerebral perfusion in women to men. We studied the cerebral perfusion of 13 cocaine dependent women, four of whom were also heroin dependent, with ^{99m}Tc- HMPAO SPECT. We compared these women to 13 cocaine dependent men, as well as to 26 healthy control subjects. Structural brain lesions and neurological abnormalities were excluded by MRI and neurological evaluation. Perfusion studies were interpreted in a standardized fashion by reviewers blinded to clinical information. We found that cocaine dependent women were much less likely to have abnormal studies than either cocaine dependent men ($p=0.003$) and were indistinguishable from normal women ($p=1.0$). However, women who concurrently used heroin plus cocaine were all abnormal, as were men, although women showed a trend toward fewer total abnormalities (areas of at least 40% reduced flow) than men ($p=0.08$). Perfusion abnormalities tended to be located in anterior brain structures, such as frontal and temporal cortex, as well as basal ganglia. These data suggest that cocaine dependent women have fewer abnormalities in cerebral perfusion than cocaine dependent men, and that concurrent abuse of heroin plus cocaine is associated with more perfusion abnormalities in both sexes. To our knowledge, this is the first evidence of gender-based differences in cerebral perfusion in any patient group.

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APPLICATION OF ABBOTT ADX/TDX-BASED PROCEDURES TO YIELD SEMIQUANTITATIVE URINE RESULTS IN A NIDA PHARMACOLOGIC TRIAL

J. Wilkins, D. Setoda, S.-H. Li, and P. Bridge

Semiquantitative urines, expressed as ng/ml or ng/mg of excreted creatinine, are being employed as an outcome measure in pharmacotherapy trials of substance abuse. The Abbott ADX and TDX analytical units are commonly used to determine substance abuse analyte levels. This abstract outlines two methodologies for determining urine levels of benzoylecgonine (BE) and other substance abuse analytes above the ADX and TDX assay limit of 5,000 ng/ml. Each method is based on the quantity of polarized light transmitted through the fluorescent antigen-antibody complex of the sample (the Net P value). The first method is a one step dilution protocol for samples found to exceed the ADX/TDX assay limit of 5,000 ng/ml on their first run. The table below specifies the recommended amount of sample dilution based on the Net P value. Sample dilution beyond 30 fold, in the absence of specially prepared diluted standards, is not recommended.

Dilution Protocol Table

1st run Net P	Dilution	Sample Volume	Diluent Volume
75-80	1:03	100 µl	200 µl
70-75	1:05	100 µl	400 µl
60-70	1:10	100 µl	900 µl
50-60	1:20	100 µl of 1:10	100 µl
40-50	1:30	100 µl of 1:10	200 µl

The second method categorizes urine BE results that exceed the 5,000 ng/ml assay limit but for which the dilution step is not feasible. The formula and estimation equation for Net P values ≥ 55 are as follows (P = the Net P).

Formula	Estimation Equation
$BE = 10^{[\beta_0+\beta_1 P+\beta_2 P^2+\beta_3 P^3]}$	$BE = 10^{[9.446-.1526P+.00128P^2-.000003P^3]}$

Results and Summary: Both methodologies were employed in a NIDA-funded multicenter trial of buproption (Wellbutrin, Burroughs Wellcome) for treatment of cocaine abuse/dependence in methadone-maintained patients. The dilution protocol was applied to 1.676 samples. Only one dilution step was required in over 90% of the diluted samples. The estimation equation was applied to samples with Net P value ≥ 55 from a pool of 1,098 samples previously defined only as >5,000 ng/ml. The equation produced an $R^2 = 0.64$ and met the statistical criteria for the Goodness of Fit Test. We are currently developing additional procedures to address Net P values <55.

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ONE YEAR FOLLOW-UP TO COCAINE TREATMENT RESEARCH PROTOCOLS

J. M. Hess, N. A. Kreiter, L. Covi, and K. L. Preston

One hundred thirty-five cocaine-dependent subjects were consented to two 12 week pharmacological treatment research protocols for cocaine dependence between 3/88 and 3/90. Eighty per cent (108) of this population participated in follow-up interviews one year from anticipated treatment completion (15 months from intake). Subjects who participated had more education (12.5±.19 vs 11.2±.32) and more years of regular cocaine use (3.4±.26 vs 2.26±.32) than those who did not participate in follow-up interviews. There was no significant difference between medication and placebo groups at follow-up or in protocol assignment. Significant improvement over time was found in several problem areas related to the subjects' substance abuse.

Multiple regression models were constructed to predict long- and short-term cocaine use at follow-up. Weeks of negative urines in treatment was the strongest single predictor of both number of months of regular cocaine use since intake and number of days of cocaine use in the thirty days preceding follow-up. Subjects with the most weeks of negative urines during treatment reported the fewest months of regular cocaine use and the fewest days of using cocaine during the thirty days prior to follow-up. Four other variables also significantly influenced the outcome models. Subject self-ratings of severity of family problems in the previous thirty days from intake (derived from the ASI) were negatively associated with both outcome variables; the highest ratings of problems were associated with the least reported cocaine use. Significant negative correlations were found between the number of weeks retained in treatment and the months of regular cocaine use at follow-up and between the number of drug treatment programs entered prior to the treatment attempt at NIDA/IRP and the months of regular cocaine use. Neither weeks in treatment nor the number of previous drug treatments were correlated with thirty day cocaine use at follow-up. Days of cocaine use in the thirty days prior to intake was positively associated with days of cocaine use in the thirty prior to follow-up, but months of regular use were not.

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GENDER DIFFERENCES AND SIMILARITIES IN AFRICAN-AMERICAN CRACK COCAINE ABUSERS

A. Lundy, E. Gottheil, R. D. Serota, S. P. Weinstein, and R. C. Sterling

Gender differences among cocaine abusers have been studied mainly in small samples of white, middle-class inpatients. We compared 652 male to 595 female African-American crack abusers in outpatient treatment in an inner-city clinic.

Demographics: Males were slightly older (1.4 years) and better educated (0.4 years) than females. These differences are probably of no practical importance, but are significant ($p < .001$) due to our large N. Similarities (*e.g.,* marital status) and differences (e.g., more males employed) were like those reported previously.

Drug use, treatment and legal histories: Others have found that cocaine-abusing females had more severe use problems than males, unlike opioid and alcohol abusers. In our clinic, males had a somewhat higher rate of cocaine-positive urines (56% vs. 47%). but there was no difference on the ASI Drug Composite score, and gender accounted for only 2% of variance on Alcohol. Slightly more women had had prior treatment, but many fewer had had legal difficulties.

Psychiatric symptoms and personality: Female substance abusers are generally thought to show more psychopathology, especially depression, than males. In our clinic, most test results were similar for men and women. On depression, males were higher ($p < .001$) on the SCL-90R while the BDI showed no difference. Of 149 patients tested on extraversion, neuroticism, locus of control, success expectancy, intelligence, and self-esteem, genders differed only on S-E.

Treatment participation and retention: It has been suggested that gender may be useful in matching patients to treatments. In our clinic, in-treatment performance (length of treatment, ratings of participation in treatment and status at discharge) were almost identical for men and women.

Conclusions: Males and females were very similar at intake and during treatment. Except for psychiatric symptoms, the similarities and differences we found were like those seen in very different cocaine abusing populations.

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STRESS, COPING AND SOCIAL SUPPORT AMONG AFRICAN-AMERICAN WOMEN IN TREATMENT FOR "CRACK" COCAINE ADDICTION

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Objective: This qualitative study identified stressors, coping methods, and social support among crack addicted African-American women in substance abuse treatment.
Method: Two audio taped 90 minute structured focus group interviews were conducted with seven African-American women 22-42 years old. The first group consisted of four women in treatment less than six weeks; the second group of three women were in treatment more than 12 weeks. The discussion guide for the focus group covered the following topics: self identity, self esteem, stressors, social support, and coping. Tapes were transcribed and analyzed using content analysis to rank the themes based upon frequency of responses.
Results: All the women indicated that "idle time", problems with male relationships, and family members as the most common stressful themes for both groups of women; furthermore, women less than five weeks also talked about depression. Relationships with children (primarily infants). friends who tended to use drugs, and family members were the main source of social support for women less than five weeks. They also utilized more negative coping strategies such as drugs, masking feelings, and suicidal ideation. Women more than 12 weeks utilized the treatment program and church as their main source of social support. In addition, more positive coping strategies such as seeking broad-based support to talk out their feelings, using tools learned in their programs, and drawing upon their desire to be strong, responsible, and independent women were utilized to cope with stress.
Conclusion: Programs need to identify the clients' stressors and help develop positive coping strategies for women to utilize more effectively with stressors. Women need support in developing and maintaining positive social support networks to help remain abstinent. Programs need to provide full-day structured programs or drop-in centers for social activities to help eliminate the "idle time" syndrome. Mental health needs must be assessed and included in treatment plans to identify women who have psychological problems. The motivation to remain in treatment must be assessed weekly and reflected in treatment plans. For example, women earlier in treatment were more motivated by legal requirements compared to women later in treatment.

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Multicultural Research Institute of the Bayview-Hunter's Point Foundation and the University of California San Francisco

ANTISOCIAL PERSONALITY DISORDER IN WOMEN: PROBLEMS AND ISSUES

M. J. Rutherford, J. S. Cacciola, and A. I. Alterman

There has been a great deal of work done recently in the assessment of antisocial personality disorder (APD) and in determining the relationship of APD to treatment outcome of substance abusers (SAs). The majority of these studies, however, focused primarily on men and have seldom explored issues of assessment and treatment outcome in relation to APD separately in women SAs. Rates of APD are typically much lower in samples of women SAs compared with men (6.5-30% vs. 40-50+%) depending on the diagnostic system employed. The low rates of APD in women often result in difficulty acquiring a large enough sample of APD women to warrant separate data analyses. What might account for the lower rates of APD in women? Is this a true gender difference or is this an artifact of the criteria used to assess APD?

The diagnostic rates, reliability, short term stability, and internal consistency of the APD diagnoses were compared in a sample of 57 women and 37 men methadone patients for DSM-III-R, III, and RDC. In all diagnostic systems the rates, reliability, stability, and internal consistency were considerably lower in women than men. DSM-III yielded the highest diagnostic rates (23.4%), internal consistency (alpha = .68 full scale, .67 child items, .60 adult items) and stability of APD for women (kappa =.63). The correlations between adult and childhood items were also lower in women compared with men in the three systems (DSM-III-R men=.46, women=.08; DSM-III men=.43, women=.21; RDC men=.37, women=-.08). When the frequency of endorsement of specific APD criteria was examined, women reported significantly lower rates on most criteria compared with men. Half of the childhood items in DSM-III-R were not endorsed at all by women or at a rate below 10%. Although the least reliable and internally consistent, the RDC identified the most significant differences on the ASI composite scores and interviewer severity ratings for both men and women. These results suggest that the lower rates of APD in women, may in part be, a factor of the criteria, especially childhood criteria, used to assess APD in the various diagnostic systems.

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SMOKED COCAINE SELF-ADMINISTRATION IN FEMALES

S. Dudish and D. Hatsukami

GOAL: To examine the self-administration patterns of female smoked-cocaine users and compare these data to our previously collected data on males.

METHOD: Female (n=6) and male (n=6) smoked-cocaine users participated in a six-day, within-subjects design on a clinical research unit. In females, phase of menstrual cycle was determined by hormonal levels on admission. During the morning of each of three sessions, subjects could earn up to five tokens, worth $5 each, by doing simple arithmetic problems. Tokens could be exchanged later that evening for deliveries of cocaine, or kept at face value. Three dose sizes of smoked cocaine (5 mg, 0.2 mg/kg, 0.4 mg/kg) were varied across, but not within, the experimental sessions. At the beginning of the evening self-administration session, subjects were given a free "sample" delivery of the dose size available that evening. The number of cocaine deliveries, as well as subjective and physiological measures, were recorded.

RESULTS: A significant dose effect was found in mean number of cocaine deliveries for females. No significant differences in the pattern of self-administration were observed between males and females. Females reported greater subjective effects of "cocaine high" from the 0.4 mg/kg dose than the other two doses, while males reported greater effects from both the 0.4 and 0.2 mg/kg doses than the 5 mg dose. A dose-by-gender interaction was found for "effect of dose," with males reporting greater effects from the 0.4 and 0.2 mg/kg doses than females. Females also reported greater heart rate effects from the 0.2 mg/kg dose, while males reported greater effects from 0.4 mg/kg, compared to the other doses.

CONCLUSIONS: Females and males appear to have similar dose-dependent behavioral responses to smoked cocaine. However, there may be differential subjective effects. Females report less effect from cocaine than do males. Plasma cocaine levels remain to be analyzed, and may yield some answers. These findings are worthy of further exploration.

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ASSESSMENT OF THE FREQUENCY AND ENJOYABILITY OF PLEASANT EVENTS IN COCAINE-DEPENDENT PATIENTS

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Drugs of abuse serve as potent reinforcers across many species, illustrating the biological normality of drug reinforcement. However, not everyone who experiences drug reinforcement becomes a drug abuser. A behavioral approach to drug abuse posits that vulnerability to abuse drugs is influenced by the density of alternative. non-drug reinforcers available. Support for this position comes from both laboratory and clinical studies demonstrating that drug use decreases as availability of non-drug reinforcers increases. What has not been addressed is whether drug abusers indeed experience a lower denstty of reinforcement that non-abusers in their natural environment.

The present study was conducted to approximate a measurement of reinforcement in cocaine-dependent patients by measuring the frequency and enjoyability of a variety of "pleasant events" using the Pleasant Events Schedule (PES). The PES is a self-reported, standardized behavioral inventory used previously to measure reinforcement density in depression research. Frequency and enjoyability ratings for 320 activities are reported on three-point scales over the past month and ten empirically derived scales are used to summarize scores across various types of activities (e.g. social activities, sexual activities, etc.). Fifty individuals seeking treatment for cocaine dependence completed the PES. Cocaine-dependent patients scored significantly below norms in their frequency of engaging in pleasant events on nearly all PES scales ($p<.01$). Interestingly, cocaine-dependent patients scored significantly above the norms on enjoyability ratings. This suggests that although these patients report a low density of alternative non-drug reinforcement, they enjoy such activities if/when they engage in them. This study provides preliminary support for a behavioral understanding of factors involved in vulnerability to cocaine dependence and also suggests important clinical implications.

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TEMPORAL PATTERNS OF COCAINE USE

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Does cocaine abuse vary as a function of short-term temporal cycles or is it determined solely by exposure to stimuli that elicit usage?

METHOD: Forty males enrolled in clinical treatment for cocaine use while receiving methadone maintenance completed Cocaine Questionnaires 3x a week for six weeks. Items consisted of daily records of cocaine use, degree of cocaine craving and resistance, and exposure to stimuli leading to cocaine use. The basic experimental design consisted of clinical treatment (two levels), week in study (six levels) and day of week (Monday through Sunday).

RESULTS: Twenty-four subjects had complete data which was used in a repeated measures ANOVA with cocaine use coded ("yes" or "no"). Two factors were statistically significant: day of the week and week in treatment. Cocaine use was lowest on Sunday (21%) while Saturday had highest use (57%). Weekday usage ranged from 37% (Wednesday) to 46% (Monday). Weekly cocaine use dropped over the course of treatment: highest usage during pre-treatment week (50%) and lowest usage at the fourth week of treatment (34%). A stepwise logistic regression analysis using day as the unit of analysis was performed on the design variables analyzed in the ANOVA and included variables on craving and exposure to stimuli-to-use. Day of week and week in treatment again were significant predictors as were the craving measures (*i.e.,* peak, average craving; and resistance) and three stimuli-to-use measures (seeing cocaine paraphernalia, being offered cocaine, and receiving money). The final model had an excellent fit to the data, with a 91% correct prediction rate (94% correct for abstinence and 87% correct for use). The most influential variables, as represented by odds ratios (OR), were: seeing cocaine or paraphernalia (OR = 8.9), Saturday (OR = 8.8). being offered cocaine (OR = 4.7), Monday (OR = 4.7), Wednesday (OR = 3.4). and having received money (OR = 3.1).

CONCLUSIONS: Strong day of the week effects were obtained. Whether this represents a direct factor, such as a circadian rhythm, or an indirect factor representing other variables that elicit cocaine use but vary in exposure on a daily basis, will be addressed in future analyses. In addition, internal stimuli, such as craving, and external stimuli also are involved in cocaine use.

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THE CONTEXT FOR TAKING COCAINE VERSUS FOR OVERCOMING THE URGE TO TAKE COCAINE

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The purpose of this study was to learn more- about the conditions that set off an episode of cocaine use versus an episode in which craving is stimulated but then controlled. To do this, we developed a Cocaine-Using and Cocaine-Refusing Interview which elicits five narratives about an interaction between the patient and another person, three narratives about situations in which the patient used cocaine and three narratives in which the patient was tempted to use cocaine yet remained abstinent. From pilot interviews we constructed a Cocaine-using and Cocaine-Refusing Questionnaire which asked subjects to rate factors contributing to their use and control by their importance. Interviews and questionnaires were administered to 35 adult volunteers with primary cocaine dependence, seeking addiction treatment. Responses to the interview were content analyzed to yield a set of 23 factors about drug taking and 19 factors about resisting a desire to take drugs. The frequency at which each factor was mentioned in the narratives and the percentage of patients who referred to each factor were tabulated: Results from the interview and the questionnaire were fairly consistent in identifying the factors perceived by patients to play an important role in drug taking and control. We found that patients attributed cocaine use primarily to external conditions: most frequently having enough money to buy drugs and being around people using drugs, although, patients also endorsed the internal conditions of wish to end physical/emotional pain and wish or decision to use. Patients attributed abstaining from cocaine use to the following factors: most importantly to arranging conditions to be non-stimulating but also to recognition of bad consequences and wish/decision not to use. These findings are consistent with treatment strategies that focus on minimizing the exposure to external cues, but they also imply that patients' wish or decision is an important factor in using or resisting the urge to use cocaine.

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FACTORS ASSOCIATED WITH SUCCESSFUL FOLLOW-UP CONTACT OF CRACK COCAINE USERS

R. C. Sterling, E. Gottheil, S. P. Weinstein, A. Lundy, and R. D. Serota

While substance abuse treatment is best evaluated by assessing patient functioning at some point following treatment, substance users are often lost to follow-up. This study examined A) if predisposing factors contributed to the probability of completing follow-up, and B) whether post-treatment functioning related to ease of contact.

Subjects were 450 former patients of a 12 week cocaine treatment program. All subjects consented to telephone follow-up nine months following admission. Subjects' functioning was assessed by the Addiction Severity Index (ASI), Beck Depression Inventory (BDI), and SCL-90R. Of the 450, 392 completed the follow-up interview.

Cocaine use decreased significantly from admission to follow-up. Demographics, intake measures (ASI, SCL, BDI), time in treatment, final in-treatment urine results, and discharge status did not relate to our ability to make contact.

Greater difficulty in conducting follow-up (i.e., time to contact) was associated with number of DSM-III-R criteria for cocaine dependence and retention in treatment. Poorer follow-up functioning, but no other measure, was also related.

A respectable proportion (87%) of cases were located for follow-up. While we were surprised that admission and in-treatment factors did not relate to ability to make follow-up contact, it wasn't surprising that longer retention and fewer DSM criteria were associated with less time to complete follow-up. Poorer post-treatment functioning was related to greater difficulty in making contact, but this owed more to the statistical power of a large sample than to any meaningful relationships.

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COCAINE AND SEXUALITY QUESTIONNAIRE: PRELIMINARY FINDINGS

D. W. Mayo, J. A. Hoffman, J. J. Koman III, and B. D. Caudill

In an effort to understand and reduce high-risk sexual behaviors associated with the spread of HIV/AIDS, researchers have begun to examine the substance abuse and sexual histories of addicts. As part of a larger cocaine abuse treatment study in Washington, D.C., which investigated the therapeutic effectiveness of several group and individual therapies, 131 African-American clients (41 females and 90 males) completed an intake assessment, the Millon Clinical Multiaxial Inventory II (MCMI-II), and the Cocaine and Sexuality Questionnaire (CSQ). Based on the literature and our experience counseling cocaine addicts, the CSQ was devised to examine the relationship between cocaine use and sexual behavior. Three constructs were envisioned when the CSQ was developed: sexual enhancement (SE), negative sexual consequences (NS), and sexual compulsion (SC). A factor analysis (FA) for each gender using varimax rotation was utilized to determine whether these constructs were valid. The FA confirmed that many of the questions did belong in those original constructs. Cronbach alphas ranged from .63 to .77. Overall, participants did not exhibit elevated scores on the MCMI-II or the three CSQ scales.

The factor showing the most promise in providing a profile of the cocaine abusers responding to the CSQ was SC. A number of personality profiles on the MCMI-II correlated significantly with this factor. These correlations suggest the existence of a behavioral pattern of sexual compulsivity that may have some enduring features. When first starting to use cocaine, about half felt that it did make sex more enjoyable, and for some, more exciting. This sexually enhancing quality did not continue with chronic use of cocaine, and sex became less enjoyable for a large percentage of respondents. Reports of difficulty achieving erection (males) and orgasm (both males and females) were common.

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SCREENING TREATMENT-SEEKING COCAINE ADDICTS FOR PTSD

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The co-occurrence of posttraumatic stress disorder (PTSD) and substance use disorders is common. Little is known about the rate of comorbidity among ambulatory treatment-seeking addicts, or about the course of the comorbidity with treatment. In this study, consecutive admissions to an inner-city cocaine treatment clinic were given the Mississippi Scale for Civilian PTSD. Score ranges are 39-86 = normal to mild distress; 87-106 = generalized psychiatric distress; 107-195 = PTSD. Chart review was undertaken for information regarding substance use indices and ASI severity scores. Data collection is on-going. Preliminary results in this sample of 107, show the sample was 38% female, 52% African-American. 47% probation referred. Mean age was 30.5±6.7 years. Mean duration of cocaine use was 9.1±5.1 years; median cocaine used per episode $40; 68% used crack. Mean Mississippi Scale score was 94±20. Forty-six percent of respondents had been exposed to trauma. There was a trend for more women than men to score in the generalized distress range ($x2 = 5.80$, $p = .055$), but there was no gender difference in trauma exposure. Mississippi Scale scores were negatively correlated with age of first use of cocaine ($r = -0.24$, $p .05$), alcohol ($r = -0.29$, $p .005$), and marijuana ($r = -0.31$, $p .01$), and with amount of alcohol typically used ($F = 5.01$, $p .01$). Traumatic exposure was associated with duration of alcohol use ($t = 2.00$, $p .05$) and marijuana use ($x2 = 4.35$, $p .05$). Based on these preliminary findings, the Mississippi Scale is a feasible means for screening patients. The associations, of Mississippi Scale scores with age of first use of substances, and traumatic exposure with duration suggest that an influence of early life disruptions on Mississippi Scale responses. There is a continuing need for further diagnostic and treatment research in this area. Further results from this study will be forthcoming.

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COGNITIVE-BEHAVIORAL COCAINE TREATMENT WITH AND WITHOUT CONTINGENCY MANAGEMENT

K. C. Kirby, D. B. Marlowe, R. J. Lamb, S. D. Husband, and J. J. Platt

We investigated use of contingency management techniques combined with cognitive-behavioral counseling to initiate and maintain cocaine abstinence and improve social functioning. Contingency management has been demonstrated to be effective in changing target behaviors of addicted individuals in general (e.g., Miller 1972; Stitzer et al., 1977; Stitzer and Iguchi 1989; Stitzer *et al.,* 1979). and of cocaine abuses in particular (*e.g.,* Crowley 1986; Higgins *et al.,* 1991). The primary questions to be addressed in this study were whether non-drug consumables would be effective in reinforcing abstinence from stimulant use, if there was a significant therapeutic advantage during treatment to using a contingency management program, and if so. whether these effects would endure beyond the period that the contingency management program was in effect.

We used a two-group design with random assignment and a no contingency control to address these questions. Subjects were 95 cocaine-dependent individuals who were seeking treatment for their cocaine use. The subjects mean age was 32 years; about two-thirds were male and 80% were black. Most were economically disadvantaged and resided in inner-city Camden, New Jersey. All subjects were assigned to receive 26 sessions of individual cognitive-behavioral counseling and ten sessions of interpersonal problem-solving. Half of the subject additionally received vouchers for providing cocaine-negative urine samples. Vouchers had associated dollar values and were awarded on a schedule that began with a $5 payment for one to two cocaine-free urines during the week and increased to $40 for 12 consecutive cocaine-free samples. Vouchers were exchanged for goods and services that promoted prosocial behaviors. All subjects were scheduled to provide urine samples three times weekly. The Addition Severity Index (ASI) was administered at intake, and at 3, 6, 9, and 12 months after treatment entry. Follow-up data collection was ongoing at the time of this report and less than 50% of the 12-month data was available. Thus, this preliminary analysis included results to nine months post treatment.

The data suggest there were no differences between the groups in treatment attendance or in cocaine use during treatment. ASI reports suggested a trend toward reduced cocaine use and drug spending after treatment for the group receiving vouchers, and increased employment for the group that did not receive vouchers. While time of follow-up appeared significant as a main effect, the interactions with voucher group were not significant in this preliminary analysis. These trends will be more thoroughly explored in the completed sample. Since the voucher system encouraged prosocial behavior, it could function to stimulate a natural community of reinforcement that supports reduced drug use after treatment. Apparent differences in employment may suggest that providing vouchers inhibits employment seeking, however the No Voucher group reported more problems related to employment at intake and may have been more motivated for work than the subjects in the Voucher group.

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FAMILY HISTORY OF SUBSTANCE ABUSE IN COCAINE ABUSERS

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The risk of alcoholism has been shown to have a strong familial predisposition even among illicit substance abusers where the risk might be expected to be less elevated. Previous work has considered the risk of alcoholism among relatives of in-treatment illicit substance abusers, mostly among white males, and previous work has not considered the family history of polydrug abusers. The present study evaluates data from a project which targeted predominantly African American persons for referral to substance abuse treatment. Although only 55% entered treatment, the refusers were also included in the study so both in- and out-of-treatment respondents participated in interviews. Among the 343 non-adopted index subjects with a lifetime history of DSM-III-R cocaine abuse or dependence, 66% (n=225) had a history of DSM-III-R alcohol abuse or dependence (alcoholism) and 40% (n=136) had a history of opiate use. Among those subjects with both cocaine and alcohol diagnoses, 40% had a family history of alcohol problems, compared to 28% in those with cocaine diagnoses only (p<03). Using multiple logistic regression modeling to correct for possible confounding by gender, race, age, and antisocial personality disorder in the proband, family history of alcohol problems remained associated with the respondent's alcoholism (OR 1.6, 95% CI 1.0-2.7). In contrast, for probands with history of opiate use in addition to cocaine (i.e. polydrug users), family history of drug problems was positive in 35% compared to 31% in respondents without additional opiate use (p=NS). When the age-corrected specific morbidity risk for drug and alcohol problems in first degree relatives was calculated, female relatives were found to have much lower rates than males (*i.e.* mothers lower than fathers and sisters lower than brothers). Opiate use in the index subject was associated with increased rates of drug problems in both brothers and sisters, but neither parent. Similarly, history of alcoholism in the index subject was associated with increased rates of alcohol problems in siblings but not parents. Although these findings must be considered preliminary and tentative due to the limitations of the family history methodology, several findings stand out: 1) Family history of alcohol problems is consistently associated with proband's alcoholism; 2) female relatives had lower rates of substance problems than males; and 3) both drug and alcohol problems are more similar between siblings than across generations.

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CORRELATES OF COCAINE USE REDUCTION

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The identification of variables associated with increased control over cocaine use is of particular importance for understanding factors affecting maintenance of the addiction and the design of interventions. This study investigated pre-to post-treatment changes in level of consumption using an empirical, descriptive approach. The variable *cocaine use reduction,* amenable to definition and measurement, was constructed and used as the outcome variable. Four cocaine use levels were defined: level zero (no use), level one (1-40 days of use/year), level two (41-140 days) and level three (more than 140 days). The level of use during the year before and after treatment were compared. The *cocaine use reduction* variable had four possible values: no change in level of use and one, two or three levels down. The, association of pre-treatment variables such as severity and frequency of cocaine use on level of reduction following treatment in a 21 day residential treatment program was studied, as were the roles of sociodemographic and social adjustment variables. Two hundred-sixty -three male subjects participated in the study. Measures at intake included sociodemographic indices and the Natural History Schedule, which was updated at two follow-up points (at one and two years). Urinanalysis tests for cocaine metabolites assessed the validity of self reports. Patients were classified according to the type of change in the number of cocaine use days from pre-to post-treatment, *i.e. stability, reduction or increase.* Twenty-one percent of the sample did not change their level of use from the 12 months pre-to 12 months post-treatment (group 0); 35% reduced their use by one level (group 1); 30% by two levels (group 2) and 30% by three (group 3). Discriminant analysis generated one discriminant function that accounted for 70% of the between group variance ($p<0.0001$), canonical $r=0.37$. This function mostly separated group 3 from groups 1 and 0 (group means: -0.26 for group 0, -0.36 for 1, 0.26 for 2 and 0.7 for 3). The items that loaded positively, therefore predicting cocaine use reduction, were: total number of grams of cocaine used during the cocaine use career, grams used during the 12 months before treatment and mean percent time dealing during the 12 months pre-treatment period. Inversely related were: number of cocaine use level changes from first cocaine use to treatment entry, mean percent of time involved in crime during the cocaine career, mean percent of time using marijuana daily from first severe use to treatment entry and the length of time between last severe use period and treatment entry. The demographic characteristics of the subjects did not predict post-treatment changes in levels of cocaine use.

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THE PROCESS OF DEVELOPMENT OF A COUNSELING MANUAL FOR CONTROLLED TREATMENT STUDIES OF COCAINE ABUSE

N. A. Kreiter, L. Covi, J. M. Hess, and M. Arias

Key to the development and implementation of outcome studies of psychosocial treatment in substance abuse is the treatment manual, specifically formulated for the population to be treated. In the process of development of treatment manuals for individual and group counseling for cocaine abuse, we identified four stages. In stage 1, clinical experience and the contributions of other authors (Beck *et al.,* 1979. Marlatt and Gordon 1985, Rounsaville *et al.,* 1985), were formulated into a draft of a manual consisting of 18 techniques. In stage 2, 32 subjects were treated once or twice a week for 12 weeks by six experienced counselors and from this pilot a further 21 component techniques were reformulated into the second draft. In stage 3, 100 cocaine abusers were randomly assigned to three "dosages" of counseling, *i.e.,* twice a week, once a week or once every other week. At the end of each 50-minute individual session, the counselor completed a technique utilization checklist which was analyzed for frequency of techniques utilization. The techniques use pattern was similar across the three "dose" assignments. Comparison of the initial sessions (1 or 2) with the later sessions showed them to have a different pattern of techniques use as compared to the later sessions as prescribed by the manual. Six techniques had low utilization. In stage 4 of this process, a group manual is being formulated with adaptation of most of the individual therapy techniques and introduction of a few new ones. An inventory of techniques. rated by an observer has become key to review of quality and direction of therapy in this stage.

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RELAPSE PREVENTION TREATMENT IN RECENTLY HOSPITALIZED COCAINE DEPENDENT PATIENTS

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For the majority of hospitalized drug abusers, inpatient treatment is not sufficient for long-term abstinence. To address this problem, we have developed and implemented a Relapse Prevention (RP) outpatient treatment program for cocaine abusers who have recently completed a 14-day inpatient treatment program. A main objective of this study is to determine the relative effectiveness of individual-based or group-based RP treatment format. The experimental design is pre-treatment, post-treatment, and follow-up assessment of therapeutic effectiveness employing objective, behavioral, and self-report outcome measures. Upon hospital discharge patients are randomly assigned to either individual or group RP format, consisting of 12 treatment sessions over a two month period. Outcome is assessed at treatment termination, followed by repeated follow-up assessments over a two year period (in progress). In this report we present short-term outcome based on three month follow-up data. Twenty-nine of the 41 patients enrolled in RP treatment have completed, suggesting a very low treatment attrition rate (29%). Urinalysis data indicate that the proportion of cocaine free urine screens during RP treatment for the total group is high, ranging from 68-98%. Subjects receiving group RP format show a trend ($p=.07$) toward less cocaine use during treatment compared to subjects receiving individual RP. At three month follow-up the average proportion of cocaine-free urine screens is 40%. indicating a clinically significant increase in cocaine use following treatment. However, non-abstinent subjects report using significantly less cocaine at three month follow-up than at the time of intake. Comparison of ASI severity scores at intake and three month follow-up show a significant reduction in alcohol, drug, and employment problems, suggesting an overall favorable effect of RP treatment. In summary, these findings support the application of RP treatment interventions following inpatient drug treatment. Although very few patients display continuous cocaine abstinence over follow-up, those who lapse or relapse after RP treatment report a pattern of cocaine use that appears to be less problematic than at treatment onset.

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TREATMENT INTENSITY AND OUTCOME WITH HOMELESS COCAINE ABUSERS

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Homeless substance abusers (N=176) were randomly assigned to an enhanced day treatment program (EC, n=89) or usual care (UC, n=87) and assessed on three outcomes (cocaine use, homelessness, and employment) at baseline and at 2-, 6-, and 12-months. The sample was primarily male (79.4%). African-American (96.2%). young adult (mean age=35.8 years), high school educated (mean education=12.2 years), cocaine abusers (71.8%). EC Ss were ofered work and housing and more frequent and varied psychoeducational counseling than UC. Treatment outcome results showed EC Ss had fewer positive urines for cocaine (p=0.003). fewer days homeless in the last 60 (p=0.026), than UC Ss across time. It was hypothesized, for this study, that treatment intensity would positively relate to outcome. Ss who completed some treatment (74.4%. n=131) were categorized into three treatment intensity groups: Low (< .5 contacts/wk), Moderate (.5 to < 2 contacts/wk), and High (2 to 6.25 contacts/wk). The distribution was: L (43.5%, n=57), M (26.0%, n=34), and H (30.5%, n= 40). There were more UC (73.7%, n=42) than EC Ss (26.3%, n=15) in the L group and more EC (92.5%, n=37) than UC (7.5%, n=3) clients L the H group. Wei-Lachin longitudinal between groups analyses across all time points showed the H group had fewer positive urines for cocaine than the M (p=0.034) and L (p<0.001) groups and the M group had fewer than the L group (p=0.086). The H group had fewer days homeless in the last 60 days than the M group (p=0.042) and the L group (p=0.002). The H group were employed more days in the last 30 than the L group (p=.083). The findings are consistent with a dose effect of psychosocial treatment for substance abuse. Since this study was retrospective, future research needs to be conducted to validate these results and replicate treatment intensity ranges.

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EFFECT OF DRUG OF CHOICE, FAMILY INVOLVEMENT, AND EMPLOYER INVOLVEMENT ON TREATMENT COMPLETION RATES OF SUBSTANCE ABUSERS

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In an effort to evaluate the hypothesis that cocaine abusers complete treatment less frequently than alcohol abusers, and to evaluate variables that may increase the effectiveness of treatment, a sample of 102 primary alcohol abusers and 98 primary cocaine abusers were followed during the course of intensive outpatient treatment. Sixty-one percent of the alcohol abusing group completed treatment whereas 39% of the cocaine abusing group completed treatment. Chi-square analysis revealed the groups differed significantly regarding treatment completion $X2$ (2, $N=200$) $p<.01$.

The relationship between family and employer involvement on treatment completion was assessed using a Gamma statistic. Analysis revealed a significant relationship between family involvement and treatment completion ($g=.58$, $z=2.8$, $p<.01$ for alcohol abusers, and $g=.44$, $z=2.11$, $p<.05$ for cocaine abusers). The impact of employer involvement on treatment completion was significant for the alcohol abusing group ($g=.37$, $z=1.66$, $p<.05$), however significant differences were not found with the cocaine abusing group ($g=.335$, $z=1.31$, $p=.09$).

Multiple Stepwise Logistic Regression was performed evaluating the effects of these variables (drug of choice, family involvement, and employer involvement) as well as additional descriptive variables (gender, race, and prior treatment) on treatment completion. Drug of choice and family involvement significantly increased the likelihood that the subject would complete treatment ($p<.001$). Employer involvement enhanced the likelihood that the subject would complete treatment ($p=.02$). Gender, race, and prior treatments did not have a significant impact on treatment completion.

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SOCIAL SUPPORT AND TREATMENT OUTCOMES AMONG CRACK USERS

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Social support satisfaction has often been linked in empirical research with improved levels of social, psychological and even physiological functioning. Recent research has also suggested that social support is linked to a longer tenure in substance abuse treatment and a lower likelihood of relapse. Research on the applicability of these findings to crack abuse treatment outcome, however, is sparse. The current investigation examines the relationships of three measures of clients' social functioning upon admission to crack abuse treatment outcomes. In a recent study with crack abusers, the investigators reported that lower levels of social support satisfaction (SSS) was linked to psychological distress, behavioral problems, and more alcohol use; lower levels of support for a positive lifestyle (SPL) was linked to behavioral problems and an earlier onset of drug and alcohol use; and drug and heavy alcohol use in the social network (DAU) was linked to heavier drug use, more behavioral problems, and current psychopathology. For this investigation, the relationship between these same social support factors and measures of cocaine abuse treatment outcomes was examined with 102 clients. Contrary to expectations, clients with low levels of social support satisfaction (SSS) remained in treatment for significantly longer and attended more sessions than did high SSS clients. Low SSS clients also showed a tendency to exhibit and maintain more treatment gains a year after treatment termination, especially regarding illegal activities. Findings also showed that regular users of alcohol at admission were more likely to remain regular users of alcohol a year after treatment termination if they were high on the DAU factor at intake. In general, it is suggested that, with this population of crack smokers, the social support that was attained by participating in treatment may actually have served to maintain low SSS clients in treatment for longer and to have increased their participation rates. It also appears that in spite of entering treatment with more social and behavioral deficits, low SSS crack smokers were still able to exhibit significant levels of treatment gain - perhaps due to their increased levels of treatment retention and exposure. Findings suggest that low SSS crack smokers may benefit significantly from participating in an intensive outpatient treatment program that emphasizes social, coping, and relapse prevention skills training.

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COMMUNITY OUTCOMES FOLLOWING RESEARCH EXPOSURE TO COCAINE OR OPIOIDS

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Problem: Clinical pharmacology research with drugs of abuse is an important scientific approach to advancing drug abuse knowledge and to developing and evaluating potential new drug abuse treatments. However, administering drugs of abuse to human volunteers raises both safety and ethical questions that must be addressed by investigators and by Institutional Review Boards. One such question is whether research exposure alters participants' subsequent community functioning and drug use. Despite much anecdotal experience, few systematic data have been available.

Method: This study used the Addiction Severity Index (ASI) to evaluate the psychosocial functioning and drug use patterns of 25 experienced drug abusers who were volunteer participants in residential laboratory studies of cocaine and/or opioids. Sixteen were exposed to opioids only, four to cocaine only, and five to both. The details of drug exposure varied across individuals, but included multiple exposures over several weeks of research participation. Doses were sufficient to produce subjective drug intoxication. ASI interviews were conducted at intake and at one-month post-research follow-up to characterize and to compare drug use and social functioning during the month prior to, versus the month following research participation.

Results: There were no significant pre-post changes in number of days of reported drug use or in amount reported spent for various drug classes, or in any of the composite severity scores for the seven ASI domains. The only statistically significant effects were that clinician ratings of problem severity showed significant improvement on three of seven ASI domains (employment, alcohol use, drug use) following research participation.

Conclusion: These data indicate that human laboratory studies of drugs with significant abuse potential may be conducted without apparent adverse effect on the behavioral and psychosocial outcomes of participants.

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THE DISCOVERY OF A NOVEL TROPANE ANALOG WHICH BINDS POTENTLY AND SELECTIVELY TO THE DOPAMINE TRANSPORTER

P. C. Meltzer, A. Y. Liang, and B. K. Madras

Cocaine is a reinforcer and stimulant that binds to monoamine transporters. Its mechanism of action has been ascribed to inhibition of the dopamine transporter. The natural isomer, (1*R*)-(-)-cocaine is considerably more potent than the unnatural isomer, (1*S*)-(+)-cocaine. Among the more potent of the cocaine congeners at [^{3}H]cocaine binding sites in striatum are WIN 35,428, O-401, RTI 55 and RTI 121. The currently accepted molecular requirements for binding of cocaine and analogs include: the *R*-configuration of the tropane, a 2ß-substituent, and an aromatic ring at C_3, preferably in the 3ß-orientation.

We prepared a series of topologically different benztropine analogs. Benztropine has an IC_{50} for inhibition of [^{3}H]WIN 35,428 binding of 0.312nM. We attributed this weak binding to the absence of the 2ß-carbomethoxy group. We report that (*S*)-(+)-2ß-carbomethoxy-3 α-[bis(4-fluorophenyl)methoxy]tropane [Difluoropine™] binds potently and selectively to the dopamine transporter and is considerably more potent than the *R*-enantiomers in this series.

2-Carbomethoxy-3-(diphenylmethoxy)-1αH,5αH-tropane exists in eight stereoisomeric forms. We synthesized these compounds as follows. Tropin-3-one was reacted with dimethyl carbonate to provide (±)-2-carbomethoxy-3-tropinone. Resolution was effected by crystallization of the bitartrates from D- and L-tartaric acid to obtain (*S*)-(-)-2-, and (*R*)-(+)-2-carbomethoxy-3-tropinone. respectively [ee > 99% by HPLC (Chiralcel OC)]. Reduction provided six 2-carbomethoxy-3-hydroxy tropanes. Epimerization at C-2 provided the ß-carbomethoxy epimers. The tropanols were reacted with difluorobenzhydrol to obtain eight 2-carbomethoxy benztropine analogs. Each of the four enantiomeric pairs had identical spectra and equal but opposite optical rotations. Chiral HPLC showed ee >99% for Difluoropine.

Only Difluoropine of the eight isomers showed significant binding (IC_{50}= 10.9 nM) and selectivity (324) for the dopamine transporter. We conclude that either the benztropines and the tropane analogs bind differently to this receptor, or bind at different sites, or the tropanes and benztropines bind at the same general site on the dopamine transporter but differ in how they fit that site. An hypothesis of how Difluoropine may fit the site is offered.

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IN CONTRAST TO R-COCAINE/R-COCAINE CONGENERS, NOVEL BENZTROPINE ANALOGS OF COCAINE ARE ACTIVE IN THE S-FORM: IMPLICATIONS FOR COCAINE BINDING

B. K. Madras, A. Y. Liang, and P. C. Meltzer

The dopamine transporter is a principal target of cocaine in the brain. Compounds targeted to the dopamine transporter also have been proposed as cocaine substitutes and as drug therapies for other indications. Detailed structure-activity'studies with cocaine isomers and phenyltropane analogs of cocaine such as WIN 35,428, have generated principles regarding the binding domain for cocaine and cocaine congeners on the dopamine transporter. High affinity binding is thought to be conferred by 2ß and 3ß substituents on the tropane ring and the R isomeric form. In order to develop compounds with improved binding properties and to expand the structure-activity framework, a novel series of benztropine analogs were prepared. In contrast to cocaine and WIN 45,428, benztropine has no substituent on the 2ß-position and its 3-substituent is in the 3α position. In further contrast, although benztropine has moderate affinity for the dopamine transporter, it has relatively high selectivity. The benztropine analogs were prepared (Meltzer *et. al.,* J. Med. Chem., 1994) and their affinities determined at the dopamine and serotonin transporter in cynomolgus monkey striatum. In marked contrast to R-cocaine or to R-WIN 35,428, S-difluoropine (2ß-carbomethoxy-3α-methoxydifluorophenyltropane) was the active form. It bound the dopamine transporter with high affinity (IC_{50}: 10.9 nM), stereoselectivity (200-fold, S-over the R-form) and DA/5HT selectivity (324-fold). This compound challenges recent views of the binding domain of cocaine/cocaine congeners on the dopamine transporter. In further contrast, I or CI substituents were less potent than F substituents. The unique structures and binding properties of this series of compounds offer novel routes to clarifying the mechanisms of action of cocaine.

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PET IMAGING OF COCAINE BINDING SITES ON THE DOPAMINE TRANSPORTER: AN APPLICATION FOR MEDICATIONS DEVELOPMENT

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Cocaine blocks dopamine transport in brain, a process strongly implicated in the effects of the drug. Dopamine transport inhibitors with long onset times and sustained transporter occupancy may have reduced abuse liability and lower risk for acquiring AIDS by frequent intravenous injections. One approach for identifying long-acting agents is to determine transporter occupancy of a candidate by *in vivo* PET (positron emission tomography) imaging of the transporter (Madras *et. al.,* NIDA Research Monograph, Vol. 138, 57-69, 1994). We recently introduced [^{11}C]WIN 35,428 ([^{11}C]CFT) as a PET imaging agent to label the transporter *in vivo*. In the present study we labeled the dopamine transporter in cynomolgus monkey brain with [^{11}C]WIN 35,428 ([^{11}C]CFT) and monitored occupancy by indantraline (Lu 19-005), a potent dopamine transport inhibitor. Baseline values for [^{11}C]WIN 35,428 accumulation by the transporter were determined. Subsequently, indantraline was administered i.m. (0.2 mg/kg or 1.0 mg/kg) to three cynomolgus monkeys and 24 hours later the transporter was imaged again by PET. [^{11}C]WIN 35,428 accumulation was reduced by over 60% compared with untreated controls, suggesting that indantraline occupies the dopamine transporter for at least 24 hours. These findings are consistent with the prolonged behavioral effects of this drug. PET imaging with [^{11}C]WIN 35,428 is a rapid and efficient method for determining dopamine transporter occupancy by drugs *in vivo*. This report demonstrates the feasibility of identifying potentially useful long-acting cocaine substitutes by PET imaging.

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MODULATION OF COCAINE-INDUCED INCREASES IN NUCLEUS ACCUMBENS DOPAMINE LEVELS BY KAPPA OPIOID LIGANDS

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Recent studies have shown that kappa agonists and antagonists modulate dopamine (DA) release in the nucleus accumbens (NAC) (Spanagel *et. al.,* 1990); kappa agonists have also been reported to attenuate the rewarding effects of cocaine (Suzuki *et al.,* 1992). Because an increase in extracellular levels of DA in the NAC has been associated with the reinforcing effects of several addictive drugs, and in view of a critical need for developing a pharmacological treatment for cocaine addiction, we investigated whether kappa agonist and antagonist drugs would alter cocaine-induced increases in NAC DA. Sprague-Dawley rats were implanted with guide cannulae over the shell of the NAC. Four days after recovery from surgery, *in vivo* microdialysis was conducted while rats were awake and freely moving. U50,488 (10 mg/kg i.p.), a kappa agonist, significantly decreased extracellular DA levels in the NAC ($P < 0.00001$). This effect was significant from 20 to 80 minutes after cocaine administration. Pretreatment (40 minutes beforehand) with norbinaltorphimine (10 mg/kg s.c.) produced no change in the effect of cocaine on DA levels. The data demonstrate that activation of kappa receptors inhibits cocaine's effects on mesolimbic dopaminergic neurons and indicate a potential role for kappa agonists in the pharmacological management of cocaine addiction.

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PRELIMINARY CHARACTERIZATION OF MULTIPLE NON-SEROTONERGIC [^{125}I]RTI-55 BINDING SITES IN MEMBRANES PREPARED FROM WHOLE RAT BRAIN MINUS CAUDATE

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Previous studies have shown that the cocaine analog [^{125}I]RTI-55 labels DA and 5-HT biogenic amine transporters (BAT) with high affinity. Here we characterized [^{125}I]RTI-55 binding to membranes prepared from whole rat brain minus the caudate nuclei. Paroxetine (50 nM) was used to block [^{125}I]RTI-55 binding to 5-HT transporter sites. Initial experiments identified drugs which displaced [^{125}I]RTI-55 binding with low slope factors. Binding surface analysis of the interaction of RTI-113 and RTI-122 with [^{125}I]RTI-55 binding sites readily resolved two binding sites for [^{125}I]RTI-55 with Kd values of 0.44 nM and 17 nM and Bmax values of 31 and 245 fmol/mg protein. Selective 5-HT and NE uptake inhibitors had low affinity for both sites. Whereas cocaine, CFT and WIN35,065-2 were 7-, 30- and 23-fold selective for the first site, benztropine, PCP and the novel pyrrole, RTI-14, were moderately selective for the second site: 2.0-fold, 14.9-fold and 9.2-fold, respectively. Intracerebroventricular (i.c.v.) administration of the neurotoxin 5,7-DHT decreased [^{125}I]RTI-55 binding to site one more than to site two. Viewed collectively, these data indicate that [^{125}I]RTI-55 labels a non-classical binding site with high affinity for transporter ligands in membranes prepared from whole rat brain minus caudate.

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A COMPARATIVE STUDY OF [^{125}I]RTI-55 BINDING TO THE DA TRANSPORTERS OF RAT-, MONKEY-, AND HUMAN-CAUDATE MEMBRANES AND THE CLONED RAT AND HUMAN DA TRANSPORTERS EXPRESSED IN COS AND CHO CELLS

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The cocaine analog [^{125}I]RTI-55 labels DA and 5-HT biogenic amine transporters (BAT) with high affinity. Here we characterized [^{125}I]RTI-55 binding to membranes prepared from rat-, monkey- and human-caudate as well as COS cells expressing the cloned rat and human DA transporter. Paroxetine (50 nM) was used in all experiments to block [^{125}I]RTI-55 binding to 5-HT transporter sites. Ketanserin inhibited [^{3}H]DA uptake by rat brain synaptosomes in a biphasic manner. Binding surface analysis was thus used to examine the interaction of cocaine and ketanserin with DA transporters labeled with [^{125}I]RTI-55. The results demonstrated that [^{125}I]RTI-55 labeled a single binding site in membranes prepared from rat caudate and in COS cells transiently expressing the cDNA for the rat DA transporter. In contrast, [^{125}I]RTI-55 labeled two sites in membranes prepared from monkey and human caudate. Interestingly, [^{125}I]RTI-55 labeled a single binding site in membranes prepared from CHO cells stablely expressing the cDNA for the human DA transporter. In cases where a two site model best fit the data, the Kd values of [^{125}I]RTI-55 for the two sites were so similar that [^{125}I]RTI-55 binding was well described by a linear Scatchard plot. Further experiments are indicated to clarify the factors underlying the occurrence of two site models for [^{125}I]RTI-55 binding to the DA transporter.

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FURTHER INVESTIGATION OF STRUCTURE-ACTIVITY RELATIONSHIP OF NEW GBR12935 AND GBR12909 ANALOGS AS POTENT DOPAMINE REUPTAKE INHIBITORS

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Cocaine is a medically useful, potent local anesthetic with vasoconstrictor properties which is widely abused as a stimulant. In the brain, cocaine acts primarily on the dopamine (DA) reuptake system, which is the main mechanism responsible for euphoric and reinforcing properties of this drug. Diphenylmethoxyethyl piperazines GBR12935 and GBR12909 were the first agents described which had high affinity and selectivity for the DA transporter. Some other properties (*e.g.* slow dissociation from the DA transporter or long duration of action) also suggest that these compounds may be potential medications for cocaine abuse.

Our previous structure-activity relationship studies (SAR) towards developing novel probes for the DA transporter related to GBR12909, showed that replacement of the piperazine ring with other diamine moieties increased the affinity and selectivity of new ligands for the [^{3}H]GBR12935 binding site as well as for inhibition of [^{3}H]DA reuptake. We have recently evaluated affinity of a number of "GBR" derivatives, mono- and symmetrically disubstituted piperazines and *trans*-2,5-dimethylpiperazines. In accordance to our previous findings, these results showed that it is possible to maintain the biological activity for the DA reuptake site with "GBR partial structures" containing only the diphenyl- or *bis*(p-fluorophenyl)methoxyethyl fragment. Other congeners monosubstituted with phenylpropyl moiety were considerably less potent at this site. We observed the same relations for other piperazines or *trans*-2,5-dimethylpiperazines symmetrically disubstituted with diphenylmethoxyethyl, *bis*(p-fluorophenyl)methoxyethyl or phenylpropyl substituents. Since the *bis*(p-fluorophenyl)methoxyethyl moiety appeared to be the important pharmacophore for effective binding to the DA transporter and possibly to [^{3}H]cocaine binding site, we utilized another route for SAR expansion and introduced simple heterocyclic systems instead of the benzene ring in the phenylpropyl chain of GBR12909 molecule. These new ligands containing pyridine, furan or thiophene ring revealed nanomolar affinity for DA transporter labeled with [^{125}I]RTI-55. The most potent ligand for [^{3}H]DA reuptake inhibition was thiophene derivative with IC_{50} of 6.10 nM. The substitution with the pyridine ring resulted in significantly increased selectivity (175.3 versus 61.4 for GBR12909) for binding to the DA (relative to the 5HT) transporter . These findings will be helpful to continue SAR studies involving the substitution of the phenyl ring in "right-hand" fragment of GBR structure in order to increase the potency of new ligands at the DA transporter binding site as well as to improve their bioavailability.

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RELATIONSHIP BETWEEN COCAINE-INDUCED CHANGES IN DOPAMINE CLEARANCE AND STRIATAL *IN VIVO* ELECTROCHEMICAL ELECTRODE LOCALIZATION

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Acute systemic cocaine injection inhibits dopamine (DA) transport and thereby produces dose-dependent changes in DA clearance in the brain. This measure reflects the activity of the DA transporter. Understanding the nature of this inhibition is important because it is related to cocaine's abuse potential. There is a differential effect of cocaine on DA clearance in dorsal striatum and nucleus accumbens. Previous studies have suggested that this difference is due to fewer transporter sites in nucleus accumbens. Other studies have demonstrated heterogeneity in DA transporters within the dorsal striatum. It is therefore possible that even within the dorsal striatum, the effect of cocaine may be heterogeneous. Understanding the interaction of cocaine with the DA transporter in striatum may provide further clarification of the role of this region in the effects of cocaine.

We used in vivo electrochemical recording to examine the effect of i.p. cocaine on DA clearance in medial (med) and lateral (lat) dorsal striatum, with respect to both DA transporter binding sites ([^{3}H]mazindol), and electrode localization to striosomes or matrix ([^{3}H]naloxone). After baseline DA signals were reproduceable, we recorded from the med or lat dorsal striatum of anesthetized rats following i.p. saline and cocaine.

The amplitude and duration of the DA signal in med striatum decreased over time following saline injection. In contrast, these same parameters were relatively stable in lat striatum. Relative to saline injection, 15mg/kg cocaine increased both the amplitude and duration of the DA signal (decreased clearance) in med striatum. All five of these electrodes were localized to striatal matrix. 20mg/kg cocaine caused a more pronounced increase in both parameters. Five out of six of these electrodes were also localized to matrix. In contrast, the only significant cocaine-induced change observed in lat striatum was a decrease in DA signal amplitude following injection of 15mg/kg cocaine. The majority (8/13) of these electrodes were localized to striosomes. Consistent with previous reports, [^{3}H]mazindol binding was higher in lateral, as compared with medial, dorsal striatum and was not in register with striosome or matrix subcompartments.

These results show a differential effect of cocaine on exogenous DA clearance. Cocaine significantly decreased DA clearance medially. This is as would be expected because there are fewer DA transporters there. This area is also primarily matrix, but this is probably not the most significant factor in this diffemtial effect because DA transporter distribution didn't correspond to matrix. However, a greater effect of cocaine on DA clearance medially is consistent with the innervation of this area by VTA and other limbic projections and the greater apparent sensitivity of these pathways in the behavioral effects of cocaine.

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[^{3}H]-7-OH-DPAT BINDS DOPAMINE D_3 AND SIGMA$_1$ RECEPTORS IN THE RAT NUCLEUS ACCUMBENS

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Administration of 7-OH-DPAT blocks cocaine self-administration without exhibiting reinforcing effects; the proposed mechanism for 7-OH-DPAT is via the D_3 receptors of the nucleus accumbens (Caine and Koob 1993). We have examined the specificity of [^{3}H]-OH-DPAT binding in the nucleus accumbens (Acb) region of the rat with respect to potential D_3-sigma$_1$ receptor interactions. Whole brains from adult male Sprague-Dawley rats (N = 5) were cryostat-cut (20 μm) and adjacent sections collected at five rostral-caudal levels throughout the entire Acb. Quantitative autoradiography with redirected sampling against Nissl- and AChE-stained sections was used to accurately define the rostral cone, core and shell subregions of Acb. Carbetapenatane, a sigma$_1$-selective ligand, resulted in 20-50% displacement of [^{3}H]-(±)-7-OH-DPAT (2nM) binding in the striatum, nucleus accumbens and olfactory tubercle. The striatum exhibited the lowest displacement, whereas the medial shell subregion of the nucleus accumbens had the highest displacement (50%). The rostral cone region exhibited the highest levels of [^{3}H]-7-OH-DPAT total binding (11.4±2.2 fmol/mg). These results suggest that 7-OH-DPAT binds D_3 receptors with high affinity; however, a significant proportion of 7-OH-DPAT binding is to sigma$_1$ receptors, most prominently in the shell subregion of the nucleus accumbens. These findings suggest that D_3 and sigma$_1$ receptors may exhibit comparable binding characteristics. Thus, studies in which 7-OH-DPAT is used must be cautiously interpreted as its effects may be mediated by both D_3 and sigma receptors. Such D_3-sigma$_1$ receptor interactions may have an important role in the mechanism of action of psychostimulants, such as cocaine.

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LOCALIZATION OF DOPAMINE RECEPTOR SUBTYPES OCCUPIED BY INTRA-ACCUMBENS ANTAGONISTS THAT REVERSE COCAINE-INDUCED LOCOMOTION

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The role of DA receptor subtypes in the nucleus accumbens (NAc) in cocaine-induced locomotion was investigated. Locomotor activity was measured for one hour following an injection of saline on one day and cocaine (15 mg/kg, IP) on a different day separated by a three to four day interval (counterbalanced order). Fifteen minutes prior to these injections, the rats (N=8-13 per group) received bilateral intra-accumbens injections (0.5 µl) of either saline, SCH 23390 (0.1, 0.3, 0.5, 1.0, or 3.0 µg/side), or sulpiride (0.05, 0.1, 0.3, 0.5 or 1.0 µg/side). After completing all behavioral tests, a new technique was employed to visualize and quantify receptors occupied by the drugs administered intracranially. Rats received intra-accumbens injections of their respective dose of antagonist. Fifteen minutes later, they were injected systemically with the nonselective irreversible antagonist, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ; 10 mg/kg, IP), and 90 minutes later they were sacrificed. D1 or D2/D3 receptors were then labeled with ^{3}H-SCH 23390 or ^{3}H-sulpiride, respectively, in sections containing the NAc. The radioligands bound to the receptors protected from EEDQ by the antagonist given *in vivo,* such that binding on the autoradiograms represented receptors that had been occupied by the antagonist.

Only the 3 µg dose of intra-accumbens SCH-23390 blocked cocaine-induced locomotor activity. The 0.5 µg dose of SCH-23390 did not alter cocaine-induced locomotor activity despite occupying the same amount of ^{3}H-SCH 23390 binding sites in the NAc as the 3 µg dose. Therefore, blockade of cocaine-induced locomotion by the 3 µg dose is likely due to blockade of D1 receptors in a region(s) other than the NAc. Intra-accumbens sulpiride produced a U-shaped dose-dependent blockade of cocaine-induced locomotion. Intermediate doses of 0.1 and 0.3 µg decreased cocaine-induced locomotion, whereas doses of 0.5 and 1.0 µg did not alter the response. These findings are consistent with the binding data since, paradoxically, the higher dose of 0.5 µg occupied fewer ^{3}H-sulpiride binding sites in the NAc relative to the lower dose of 0.3 µg. The results suggest that D_2 receptors in the NAc are involved in cocaine-induced locomotion. Furthermore, this study illustrates the importance of quantifying receptor binding sites occupied by drugs administered intracranially.

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ROLE OF CORTICOSTERONE IN THE MODULATION OF DA AND NE OVERFLOW IN THE AWAKE, FREELY MOVING RAT: IMPLICATIONS FOR THE MECHANISM OF ACTION OF COCAINE

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The hypothalamic-pituitary adrenal axis (HPA) plays an important role in the adaptive response to stress and also may be involved in the addictive process. For example, rats exposed to uncontrollable electric footshock show an increased vulnerability to self-administer cocaine (Goeders *et al.,* CPDD, 1992). This response can be eliminated by adrenalectomy, suggesting a role for HPA in the reinforcing effects of cocaine. Recent studies (Goeders et al., Soc. Neurosci., 1993) have implicated corticosterone (CORT) in the reinforcing properties of cocaine, since pretreatment with metyrapone attenuated cocaine self-administration. The mechanism by which CORT may exert such actions appears to be unclear. Since catecholamines are involved in mediating many of the pharmacological actions of cocaine, we investigated the actions of CORT and cocaine on the dopaminergic and noradrenergic systems in the awake, freely moving rat.

Male Sprague Dawley rats were implanted with guide cannulae aimed at either the nucleus accumbens (NAc) or the frontal cortex (FCx). The animals were then allowed to recover from the surgery for seven days prior to introducing a dialysis probe into the region of interest. Rats were either acutely dialyzed or chronically treated as follows; CORT (10mg/kg/day; 10 days), cocaine (30mg/kg/day; 7 days) or respective vehicle. Chronically treated animals were dialyzed 24 hours following the last drug dose. Following stabilization of the basal dopamine (DA) and norepinephrine (NE) a challenge dose of CORT (5mg/kg) was administered. Extracellular levels of DA and NE were followed for a further two hours. Acute CORT produced a significant decrease in extracellular DA in the NAc (46%) and FCx (45%), while NE was increased in the FCx (40%). Following chronic CORT the response to a CORT challenge was attenuated in the NAc and FCx for DA and NE respectively. In contrast, a CORT challenge following chronic cocaine produced increases in NAc DA (38%) and a concomitant decrease in NE in the FCx (20%).

Meso-accumbens and meso-cortical DA were found to be decreased following acute injections of CORT. Since the reinforcing properties of cocaine are mediated predominantly through increases in DA function, it is unlikely that CORT is involved in the acute actions of cocaine. Interestingly, following chronic cocaine DA overflow in the NAc increased in response to an acute CORT challenge. These data suggest that repeated cocaine may sensitize the HPA axis and hence increase the vulnerability to further self-administration in response to stressors. Such alterations in the response to CORT following chronic cocaine may have relevance for understanding the enhanced actions of cocaine on catecholamine function.

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SELF-ADMINISTRATION OF DOPAMINE AGONISTS: COMPARISON WITH COCAINE

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There is a growing awareness that activation of more than one subtype of dopamine receptor may be involved in the self-administration of abused drugs such as cocaine. Recent studies have identified multiple subtypes of dopamine receptors, which can be broadly classified into two families: D_1-type (D_1, D_5) and D_2-type (D_2, D_3, D_4) receptors. In the present experiments the D_1-type agonist SKF 82958 (0.003-0.30 mg/kg/injection) and the D_2-type agonists (+)-PHNO (0.0003-0.056 mg/kg/injection) and quinpirole (0.003-0.30 mg/kg/injection) were compared with cocaine for their capacity to maintain i.v. self-administration in squirrel monkeys under a second-order fixed-interval schedule of reinforcement. Cocaine and all three dopamine agonists were found to maintain i.v. self-administration, and dose-response curves generally took the form of an inverted "U". Maximum rates of responding maintained by SKF 82958, (+)-PHNO and quinpirole, however, typically were lower than those maintained by cocaine, suggesting that activation of neither the D_1- nor D_2-type receptors alone is sufficient to duplicate the full range of cocaine's effects. The results show that both D_1- and D_2-type agonists can maintain self-administration behavior and are consistent with the view that multiple dopamine receptors contribute to cocaine's reinforcing effects.

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CHARACTERIZATION OF THE BEHAVIORAL EFFECTS OF (±)-7-HYDROXY-DIPROPYLAMINOTETRALIN (7-OH-DPAT)

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The identification of ligands selective for subtypes of dopamine receptors presents the opportunity for defining the roles of those receptor subtypes in the control of dopamine-mediated behaviors. Given that the dopamine system has been implicated in the abuse of a number of drugs, characterization of behavioral effects associated with specific dopamine subtypes is critical to a complete understanding of the mechanism of action of drugs of abuse (*e.g.,* the direct-acting agonist cocaine). Selective D_1 and D_2 dopamine agonists produce behavioral effects that are generally distinct from those of indirect-acting dopamine agonists and one another. In attempts to characterize behaviors that may be uniquely transduced via D3 receptors, the effects of the D3/D2 agonists 7-OH-DPAT and quinpirole were compared with those of D1, D2 and non-selective D1/D2 dopamine agonists in a variety of dopaminergically-mediated behaviors. 7-OH-DPAT that quinpirole produced dose dependent increases in scratching similar to that produced by D2 agonists in squirrel monkeys. In rats trained to discriminate cocaine or methamphetamine from saline, 7-OH-DPAT substituted completely for cocaine and partially for methamphetamine. However, both degrees of substitution were only evident at doses of 7-OH-DPAT that markedly reduced response rates. Incidences of climbing, immobility, nose-poking, switching sides and gnawing were observed in mice. Generally, 7-OH-DPAT- and quinpirole-treated mice behaved similarly to those treated with bromocriptine. Finally, patterns of horizontal locomotor activity in mice following 7-OH-DPAT and quinpirole were similar to that produced by apomorphine. With minimal exceptions, 7-OH-DPAT shared similar behavioral effects with other compounds having varying degrees of affinity for D2 and D3 receptor subtypes across a range of behaviors and several species. The development of more selective dopamine agonists and antagonists is critical to elucidating the roles of these receptor subtypes in mediating specific behaviors and in their contribution to drug abuse.

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THE REINFORCING EFFECTS OF THE PUTATIVE DOPAMINE D-3 AGONIST 7-OH-DPAT IN RHESUS MONKEYS

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There is a large database linking the reinforcing effects of cocaine to the dopaminergic system (*e.g.,* Ritz *et al.,* 1987). The D-3 agonist 7-hydroxy-*N,N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) has been shown to function as a reinforcer in rats trained to self-administer cocaine (Caine and Koob 1993). The purpose of the present study was to 1) extend these results to monkeys; 2) directly compare the reinforcing potency of 7-OH-DPAT to cocaine; and 3) examine whether the reinforcing effects of 7-OH-DPAT were influenced by prior experience with cocaine. Three adult male rhesus monkeys, with extensive (>2 years) histories of i.v. cocaine self-administration, responded under a fixed-interval five minute schedule of cocaine (0.03 mg/kg/inj) presentation during daily four hour sessions. When responding was stable, saline or different doses of cocaine (0.01-0.3 mg/kg/inj) or 7-OH-DPAT (0.001-0.03 mg/kg/inj) were substituted for 0.03 mg/kg/inj cocaine, for at least five consecutive sessions. Both drugs maintained responding, with rates varying as a function of dose in an inverted-U shaped manner. 7-OH-DPAT was 0.5-log units more potent than cocaine in two animals with peak rates occurring at 0.003-0.01 mg/kg/inj, while it was equipotent with cocaine in the third animal. Acquisition of 7-OH-DPAT self-administration was examined in two experimentally-naive monkeys. Self-administration of 7-OH-DPAT (0.003-0.01 mg/kg/inj) could not be maintained in either monkey over a 10-12 day training period. When 0.03 mg/kg/inj cocaine was made available to these subjects, self-administration occurred at high rates within one to three sessions. These results suggest that a history of cocaine self-administration may be necessary for 7-OH-DPAT to function as a reinforcer.

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EFFECTS OF DOPAMINE REUPTAKE INHIBITORS ON FR RESPONDING MAINTAINED BY COCAINE AND FOOD

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The effects of several dopamine reuptake blockers on responding maintained under mult FR 30-response schedules of food delivery and intravenous cocaine injections were compared using rhesus monkeys. When relatively low doses (5.6-10 mg/kg/inj) of cocaine and 1 g banana pellets were used to maintain responding, rates of responding and numbers of reinforcers taken during a session were generally comparable for both events. Under these conditions, GBR12909 and GBR12935 decrease cocaine-seeking behavior (up to 100%) at doses that have little or no effect on food-seeking behavior. These effects are further explored by, 1) altering the maintenance dose of cocaine while assessing the effects of GBR 12909; 2) comparing these effects to other related agents having high affinity for the DA re-uptake site, including LR-1111, DM-69, DM-58, and DM-77; and 3) comparing these effects to other non-chemically related agents having affinity for the DA re-uptake site, including d-amphetamine, CFT and mazindol. The results are presented in terms of both rate of responding and numbers of each type of reinforcer produced. Emphasis is placed on developing measures which characterize the difference in effect of these agents on both behaviors. The results show that drug-seeking behavior can be selectively attenuated by high-affinity dopamine reuptake inhibitors, suggesting that such agents may be useful in treating cocaine abuse. However, the results also suggest that other factors (*e.g.* lipophilicity, bioavailability, etc.) may be important in determining the behavioral effects of these agents.

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EFFECTS OF MONOAMINE UPTAKE INHIBITORS ON COCAINE SELF-ADMINISTRATION IN RATS

S. R. Tella

It has been reported that acute pretreatment with both norepinephrine- and serotonin-selective reuptake inhibitors markedly potentiate the discriminative stimulus effects of cocaine and this potentiation is nearly equal to that produced by a dopamine-selective reuptake inhibitor, GBR 12909 (Cunningham and Callahan 1991). However, it is not known whether this potentiation is due to an enhancement of a specific interoceptive stimulus related to the rewarding property of cocaine or due to an enhancement of some other interoceptive stimuli unrelated to the rewarding property of cocaine.

The objective of this study was to investigate the effects of acute enhancement of monoaminergic function by pretreatment with various monoamine selective reuptake inhibitors on cocaine self-administration in rats. Pretreatment with GBR 12909 (1-5.6 mg/kg, IV), a dopamine-selective reuptake inhibitor, produced a dose-dependent and large reduction in the self-administration of cocaine (1 mg/kg/infusion). The 3 and 5.6 mg/kg doses of GBR 12909 produced downward shifts in the dose-response curves for cocaine (0.3-3 mg/kg/infusion) self-administration. Unlike GBR 12909, the norepinephrine-selective reuptake inhibitors, desipramine and nisoxetine, at 10 mg/kg dose produced small, but significant, reductions in the self-administration of cocaine (1 mg/kg/infusion). The 10 mg/kg dose of fluoxetine, a serotonin-selective reuptake inhibitor, produced a small, but not significant, reduction in the self-administration of cocaine (1 mg/kg/infusion). The 10 mg/kg dose of desipramine. nisoxetine or fluoxetine produced brief respiratory distress and motor abnormalities immediately following IV injections thereby suggesting that this dose is close to the toxic range for all three drugs. Desipramine, nisoxetine or fluoxetine at non-toxic doses of 1 and 3 mg/kg had no significant effects on cocaine self-administration (1 mg/kg/infusion). These data indicate that the acute enhancement of endogenous dopaminerigc activity by pretreatment with dopamine reuptake inhibitor reduces the total intake of cocaine thus supporting the hypothesis that the dopamine is critically involved in the reinforcing properties of cocaine. The data also suggest that the acute enhancements in the endogenous norepinephrine or serotonin systems by nontoxic doses of norepinephrine- or serotonin-selective reuptake inhibitors do not appear to alter the reinforcing properties of cocaine.

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STUDIES ON THE REINFORCING EFFECTS OF GBR 12909 IN RHESUS MONKEYS

F. H. E. Wojnicki, D. Matecka, K. C. Rice, R. B. Rothman, and J. R. Glowa

Previously we reported that under a mult FR 30 schedule of food and i.v. drug delivery schedule, doses of up to 30 mg/kg/inj of GBR 12909 failed to maintain responding in drug-naive monkeys. Subsequent exposure to the reinforcing effects of cocaine (5.6-10 mg/kg/inj) was sufficient to maintain responding with 30 mg/kg/inj GBR. Two additional studies extended these observations. In one, drug-naive monkeys were initially trained to respond under an FR 30 schedule of food delivery, and then exposed to a multiple schedule with GBR delivery in one of the components. Under these conditions, 56 mg/kg/inj GBR failed to maintain responding, but responding could be maintained by 100 mg/kg/inj. When the GBR dose was then decreased to 30 mg/kg/inj responding was still well-maintained. In a second study responding was first established in another group of monkeys under a multiple FR 30 schedule of food and cocaine (10 mg/kg/inj) delivery and GBR was then substituted for cocaine. Under these conditions, 30 mg/kg/inj of GBR maintained moderate rates of responding in half the animals and 56 mg/kg/inj of GBR maintained moderate rates of responding in the others. These results suggest that drug-seeking behavior can he maintained by the high-affinity dopamine reuptake inhibitor GBR 12909, supporting the results of previous studies. In addition, these results suggest that prior exposure to the reinforcing effects of cocaine or GBR 12909 enhances the ability of low doses of GBR to support drug-seeking behavior, possibly indicating a sensitization-like phenomenon.

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A NOVEL PROGRESSIVE-RATIO PROCEDURE FOR STUDYING DRUGS AS REINFORCERS: COMPARISON BETWEEN COCAINE AND PROCAINE IN RHESUS MONKEYS

W. L. Woolverton and M. Layng

Progressive-ratio procedures typically provide all-or-none results for self-administration of a drug at a particular response requirement. The present experiment was designed to develop a procedure to provide graded drug intake and a variety of response requirements and to compare two drugs, cocaine and procaine, known to differ in their relative reinforcing efficacies.

Five male rhesus monkeys were prepared with chronic intravenous catheters and trained to lever press under a novel progressive-ratio (PR) schedule of drug injection. The PR schedule consisted of five components, each made up of four trials (*i.e.,* 20 trials total). Each trial within a component had the same response requirement. The response requirement in the first component was 120/trial and doubled in successive components to a maximum of 1920 in the fifth. A trial ended with an injection or the expiration of a limited hold (LH). The inter-trial interval (ITI) was 15 or 30 minutes. Following an injection or expiration of the LH (12 or 24 minutes, respectively), all stimulus lights were extinguished and responding had no consequence for the remainder of the trial. A session ended when the response requirement was not met within the LH for two consecutive trials. When responding maintained by cocaine was stable (± 10% variation in number of injections/session for five consecutive sessions), saline was substituted for cocaine until responding declined to low levels. Cocaine-maintained behavior was re-established and various doses of cocaine or procaine were made available in an irregular order until responding was stable.

For both drugs, injections/session, responses/session and breakpoint (response requirement for the last injection taken) increased as a function of dose over a 4- to 8-fold dose range at both ITI values. Maximum values for these measures were higher with the 30 than with the 15 minute ITI. Cocaine maintained higher maximum values than for procaine for all measures and was approximately 10-fold more potent. These findings are consistent with previous PR data demonstrating that the breakpoint of a drug increased with dose. In addition, they are consistent with previous choice studies demonstrating that a high dose of a drug was chosen more often than a low dose and that cocaine was preferred to procaine. Thus, the present PR procedure can be used to measure reinforcing efficacy both within and between drugs. Its major advantages over other PR procedures are relatively rapid determination of reinforcing efficacy and graded as opposed to quantal measures of responding at each response requirement.

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CROSS-TOLERANCE BETWEEN COCAINE AND CNS STIMULANTS UNDER A PROGRESSIVE RATIO PARADIGM

D.-H. Li and M. W. Emmett-Oglesby

The purpose of this experiment was to determine whether chronic administration of cl-amphetamine or methamphetamine would result in cross-tolerance to cocaine under a progressive ratio (PR) schedule of reinforcement. Rats were implanted with indwelling jugular catheters and were trained to self-administer cocaine, 0.25 mg/infusion, under a PR schedule. Under the PR schedule, an increasing number of responses was required to obtain each subsequent cocaine infusion. The required ratio needed to be completed within one hour, and the last cocaine injection that was received was termed the breaking point. When the breaking point for each subject was stable, a cocaine dose-response curve was determined. The subjects were then randomly assigned to two groups. One group received injections of d-amphetamine (3.2 mg/kg, s.c.) or saline three times a day for seven days, while the other group received injections of methamphetamine (3.2 mg/kg, s.c.) or saline twice a day for seven days. This was a random block design and each rat received all doses of each treatment. During this chronic regimen, the rats were not allowed to self-administer cocaine. Twenty-four hours following the last chronic injection, cocaine dose-effect data were redetermined in both treatment groups. Both the *d*-amphetamine and the methamphetamine group showed a significant shift to the right of the post-chronic dose response curves of breaking points for cocaine self-administration. These data support the hypothesis that chronic treatment with a CNS stimulant of the amphetamine type will produce cross-tolerance to the reinforcing efficacy of cocaine.

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AMPEROZIDE DECREASES COCAINE SELF-ADMINISTRATION BY RATS

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Amperozide (APZ) is an atypical neuroleptic which affects oral intake of alcohol and cocaine in rodents. The effects of APZ pretreatment were examined on IV cocaine' self-administration' reinforced on a fixed ratio (FR) and a progressive ratio (PR) schedule of reinforcement as well as a discrete trials paradigm. Rats were implanted with a chronically indwelling IV cannula and were trained to self-administer cocaine on an FR 1 schedule. Following stable baseline rates of responding animals were tested in one of three procedures. APZ, (2.5 mg/kg, SC) had no effect on rate of cocaine intake on an FR 1 schedule. However, APZ pretreatment significantly reduced breaking points across a unit injection dose of cocaine (0.18, 0.37, 0.75, and 1.5 mg/kg/inj) in a dose dependent manner on a PR schedule. Another group of rats was tested using a discrete trials procedure whereby the rats' access to cocaine was limited to two 10 minute trials every half hour continually over a number of days. This procedure yields a circadian pattern of drug intake restricted to a 6-10 hour period of the dark/active phase of the cycle. During each trial, animals could receive a single injection of cocaine (1.5 mg/kg/inj) on an FR 1 or an FR 5 schedule. APZ (0.625, 1.25, 2.5 mg/kg, SC) pretreatment produced a dose dependent reduction in drug intake. An additional group of cocaine naive rats was trained to respond for food reinforcement (45 mg Noyes food pellet) on a PR schedule. APZ pretreatment produced a slight but significant dose dependent decrease in overall food intake. APZ's effect is unlikely to be due to a motor impairment or sedation since it has lesser effects on food reinforced responding and reduces cocaine intake even when response requirements are minimal *(i.e.* discrete trials procedure). These data suggest that APZ has potential therapeutic properties in the treatment of cocaine addiction.

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MAINTENANCE OF SELF-INJECTION BY HISTAMINE H_1 ANTAGONISTS IN BABOONS

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Histamine H_1 antagonists are commonly used for treating symptoms of allergies, the common cold and motion sickness. Although the histamine antagonists tripelennamine (TRP), diphenhydramine (DPH), and chlorpheniramine (CHL) have complex mechanisms of action, previous studies have shown that they share discriminative stimulus effects with psychomotor stimulants such as cocaine (COC) or amphetamine. The ability of TRP, DPH. CHL, and promethazine (PRM) to maintain self-injection was examined in seven baboons using a standard i.v. substitution procedure. Responding was maintained under a fixed-ratio schedule of i.v. COC delivery (0.32 mg/kg/inj). Each drug inj produced a three hour time-out allowing a maximum of 8 inj/day per day. Vehicle or a drug dose was substituted for COC for a period of 15 or more days. TRP (0.32 mg/kg/inj) and DPH (1.0 mg/kg/inj) maintained moderate to high rates of self-injection in three baboons. CHL maintained low to moderate rates of self-injection. PRM did not reliably maintain self-injection, but did suppress responding relative to control in two of three baboons. High doses of TRP, DPH, and CHL produced signs of behavioral toxicity, including agitation and sometimes seizures. These data suggest that H_1 antagonists can serve as reinforcers and can produce behavioral toxicity in the baboon.

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THE EFFECTS OF COCAINE, ALCOHOL AND COCAINE/ALCOHOL COMBINATIONS ON SCHEDULE-CONTROLLED RESPONDING IN THE RAT

B.-F. X. Sobel and A. L. Riley

Within a number of physiological preparations the effects of alcohol and cocaine in combination are reported to be greater than the effects of either drug given alone. Little has been reported, however, on the behavioral effects of the interaction. The present study addressed this issue. Specifically, six experimentally naive, female Long-Evans hooded rats were trained to respond on an FR20 schedule for a water reinforcer. Sessions were five minutes in duration with four sessions occurring daily, each session being separated by a nine minute time-out period. Subjects were then injected with cumulative doses of cocaine or alcohol. Following this, subjects were injected with ineffective doses of cocaine prior to further dose-response assessments with alcohol and with ineffective doses of alcohol prior to further dose-response assessments with cocaine. Individually, cocaine and alcohol produced dose-related decreases in responding. Furthermore, the dose-response function for cocaine was shifted to the left by alcohol and the dose-response function for alcohol was shifted to the left by cocaine. Finally, in a preliminary assessment of the mechanism underlying the interaction, cocaethylene (the unique cocaine metabolite produced when cocaine and alcohol are co-administered) was tested for its effects on responding. Like cocaine and alcohol, cocaethylene decreased responding in a dose-dependent manner. Similar to prior work on more physiological indices, the present data indicate a synergistic interaction between cocaine and alcohol on schedule-controlled responding. This synergistic interaction may be in part due to the added effects of cocaine, alcohol and cocaethylene.

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EFFECTS OF FOOD DEPRIVATION IN A MODEL OF COCAINE RELAPSE IN RATS

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The purpose of the present study was to evaluate the effects of priming injections of cocaine (0.32, 1.0 and 3.2 mg/kg i.v.) administered during the extinction period in rats self-administering either 0.2, 0.4 or 1.0 mg/kg/injection cocaine when they were maintained under three different feeding conditions (8 g food, 20 g food, and food satiation). The variables were also compared when the rats were fed either before or after the daily seven hour session to examine the difference between acute and chronic food deprivation/satiation. Rats trained to self-administer either 0.2, 0.4, or 1.0 mg/kg cocaine i.v. were maintained under an FR 1 schedule for the first two hour during daily seven hour sessions and were fed either before or after the session. At the beginning of hour three, saline replaced cocaine in the infusion pumps. At the beginning of hour four, a priming injection of either saline or cocaine (0.32, 1.0, or 3.2 mg/kg i.v.) was administered. In the first experiment, the effects of cocaine maintenance dose on both extinction and relapse responding was assessed. During hour three (extinction responding), rats typically self-administered several infusions of saline, which gradually decreased to near-zero levels through the seventh hour. Extinction responding during hour three was positively related to the maintenance dose of cocaine during hour one and two, and was greater when feeding occurred after, compared to before the session across all cocaine maintenance doses. During hour four (relapse responding), cocaine priming injections reinstated responding in all of the groups tested in a dose-related manner. Although the magnitude of relapse responding was similar across cocaine maintenance doses, it was always greater when rats were fed after, compared to before, the session.

In the second experiment, the effects of food deprivation level (8 g, 20 g, ad libitum food) and time of feeding (before versus after the session) were assessed in rats maintained on 0.4 mg/kg cocaine. During hour three, rats in the 8 g food group self-administered more infusions than rats in the 20 g or ad libitum food groups when feeding occurred after the session. During hour four, reinstatement of responding was greatest in rats in the 8 g food group and increased when rats were fed after the session. Relapse responding did not differ as a function of time of feeding in rats maintained at either 20 g or ad libitum food. In both Experiment one and two, self-administration during hour one and two did not differ as a function of food deprivation level or time of feeding. However, in Experiment one, the number of cocaine infusions self-administered during hour one and two was inversely related to maintenance dose. Results from Experiment one and two indicate that both extinction behavior and relapse behavior increase under food deprivation conditions, and that extinction, but not relapse, behavior increases more at higher maintenance doses of cocaine.

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ACQUISITION OF COCAINE SELF-ADMINISTRATION IN RATS: CORRELATION OF ACQUISITION WITH SHORT INTER-REINFORCEMENT TIMES

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Six, male, Long-Evans rats were implanted with chronic, indwelling venous catheters and allowed to recover for one week. They were then placed in an operant chamber for two hours each day, where a nose-poke served as the response. There were two holes into which the rats could respond. One hole was active and each nose-poke was followed by an injection of 0.06 mg of cocaine. Each cocaine injection was followed by a 20-second timeout. The other hole was inactive and responses had no scheduled consequence. After any day, except the first, in which 30 responses were made, the number of responses required to receive cocaine was increased by one, up to a fixed-ratio of three. To determine if inter-reinforcement interval (IRI) might be important in acquisition, IRIs (exclusive of the timeout) were tabulated over the first ten responses of the day for all days prior to the first day on which the 30 response criterion was met and compared to the first ten responses on the day that the rats met the 30 response criterion. Day one was excluded as response rates tended to be high on this day due to exploratory activity. Not all days had at least ten responses. An average IRI of less than 220 seconds would be sufficient to meet the 30 response criterion. On the days prior to the rats meeting criterion, approximately 3% of the IRIs were less than 25 seconds, while over 58% were greater than 300 seconds. In contrast, on the day the rats appeared to acquire the response, approximately 38% of the first ten IRIs were less than 25 seconds while only 13% were greater than 300 seconds. There was no relationship between day one IRIs or day one responses ($r = 0.012$ for day 1 IRI and $r = -.396$ for day 1 responses) and days to criterion, suggesting that inherent activity was not an important factor in acquisition. In addition, these short IRIs do not appear to reflect the spacing of injections following acquisition, as the average day ten IRI was 107.5 seconds, not including the timeout. While these data are preliminary, they do suggest that acquisition of drug self-administration may not occur unless a number of short IRIs are observed early in the session. Whether these short IRIs occur due to chance or prior conditioning is unclear. The role of genetics in the current finding is also unclear. As an outbred strain of rats was used, it is possible that the tendency to emit short IRIs is under genetic control, although it seems unlikely that this is the case as one would expect to see a broader distribution of IRIs on the day at which criterion were met if IRIs were under genetic control. Nevertheless, these data do suggest that the patterning of IRIs may be a useful metric for the study of acquisition of drug self-administration.

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REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF ß-CIT IN RHESUS MONKEYS

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ß-CIT (also designated RTI-55) is one of a series of 2ß-carbomethoxy-3ß-phenyltropane cocaine analogs that have recently been synthesized for characterizing the dopamine (DA) transporter and its function. The present study was designed to examine the behavioral effects of ß-CIT in rhesus monkeys. Two monkeys were allowed to self-administer cocaine (0.01 or 0.03 mg/kg/inj, i.v., fixed-ratio 10, 1 hour/day) in baseline sessions. When behavior was stable, ß-CIT (0.0007 to 0.003 mg/kg/inj, i.v.) was made available for self-administration for several consecutive sessions. ß-CIT maintained responding above saline levels in both monkeys. Two other monkeys were trained to discriminate cocaine (0.2 or 0.4 mg/kg, i.m.) from saline in a two-lever, food-reinforced drug discrimination paradigm. ß-CIT (0.012-0.025 mg/kg, i.v.) fully substituted for cocaine as a discriminative stimulus. In both preparations, ß-CIT was at least 8-fold more potent than cocaine and had a longer duration of action. Thus, ß-CIT has cocaine-like behavioral effects indicative of a functional interaction with the DA transporter.

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EFFECTS OF SIGMA LIGANDS ON THE COCAINE DISCRIMINATIVE STIMULUS IN RATS

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Several compounds with affinity for s sites have been shown to reduce the stimulation of locomotor activity induced by amphetamine, cocaine or morphine in rodents (Menkel *et al.,* Eur J Pharmacol 201:251-252, 1991; Clissold *et al.,* J Pharmacol Exp Ther 265:876-886, 1993; Poncelet *et al.,* Neuropharmacology 32:605-615, 1993). To evaluate further the role of σ ligands in the pharmacological activities of psychostimulants, several drugs with affinity for σ sites: haloperidol, BMY 14802, rimcazole, 1,3-di-o-tolylguanidine (DTG), ifenprodil and eliprodil were studied for their potential to block or to increase the discriminative stimulus effects of cocaine.

Male Sprague-Dawley rats were trained to discriminate a dose of 6 mg/kg (ip) of cocaine from saline.

Haloperidol (0.25 mg/kg) exerted a partial antagonism of the discriminative stimulus effects of cocaine; this antagonism may be related to its antidopaminergic activity. Testing of higher doses was not possible because of the marked response rate decrease induced by the drug association. DTG (5 mg/kg), ifenprodil (10 mg/kg) and eliprodil (10 mg/kg) did not affect the discriminative stimulus effects of cocaine, whereas rimcazole (10 mg/kg) and to a lesser extend BMY 14802 (10 mg/kg) appeared to potentiate the cocaine cue.

The present results suggest that whereas the locomotor stimulant effects of cocaine may be blocked by several ligands of σ sites, the discriminative stimulus effects of the drug are not. Rimcazole is a selective σ ligand and its potentiation of the cocaine discriminative stimulus effects needs further investigation.

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NORADRENERGIC MECHANISMS IN THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE: INFLUENCE OF TRAINING DOSE

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The role of noradrenergic mechanisms in the discriminative stimulus (DS) effects of cocaine was investigated in squirrel monkeys using a two-lever drug discrimination procedure. Monkeys initially were trained to discriminate a relatively high dose of cocaine (1.0 mg/kg) from saline and subsequently retrained to discriminate a 3.3- or 5.6-fold lower dose of cocaine (0.30 or 0.18 mg/kg). In drug substitution experiments, the selective norepinephrine uptake inhibitors talsupram, tomoxetine and nisoxetine mimicked the DS effects of cocaine in the majority of subjects under the low-dose training condition and the dopamine uptake inhibitor GBR 12909 mimicked the DS effects of cocaine under both training conditions. Representative a_1 (ST 587 and SDZ NVI 08.5), a_2 (UK 14,304 and clonidine) and ß (clenbuterol) adrenoceptor agonists did not consistently mimic the DS effects of cocaine under either training condition. In antagonism experiments, the al adrenoceptor blocker prazosin attenuated the DS effects of cocaine as well as the cocaine-like effects of talsupram and tomoxetine under the low-dose training condition. The a_2 adrenoceptor blocker efaroxan and the ß adrenoceptor blocker propranolol did not consistently attenuate the DS effects of cocaine under either training condition. In additional studies, talsupram, at doses that did not mimic the DS effects of cocaine when tested alone, enhanced the cocaine-like effects of GBR 12909 under both training conditions. The results suggest that: 1) norepinephrine uptake inhibition contributes to the DS effects of cocaine in squirrel monkeys; 2) the contribution of this mechanism becomes more prominent as the training dose of cocaine is reduced; and 3) although direct stimulation of adrenoceptors is insufficient to reproduce the DS effects of cocaine, blockade of al adrcnoceptors can attenuate these effects.

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EVALUATION OF COCAINE ANALOGS MORE SELECTIVE FOR DOPAMINE UPTAKE IN RATS AND SQUIRREL MONKEYS TRAINED TO DISCRIMINATE COCAINE FROM SALINE

P. M. Beardsley and R. L. Balster

Recent reports have indicated that the phenyltropane analogs of cocaine, RTI-113 {3ß-(4-chlorophenyl)tropan-2ß-carboxylic acid phenyl ester hydrochloride} and RTI-120 {3ß-(4-methylphenyl)tropan-2ß-carboxylic acid phenyl ester hydrochloride} are amongst the most selective dopamine transporter inhibitors available (Boja *et al.,* 1992). Inhibition of dopamine uptake is one possible event mediating the discriminative stimulus properties of cocaine. In these studies we evaluated the ability of RTI-113 and RTI-120 to produce the discriminative stimulus effects of cocaine in rats and in squirrel monkeys *(Saimiri sciureus).* The rats and monkeys were trained to discriminate cocaine (10 mg/kg i.p. or 0.3 mg/kg i.m., respectively) from saline during 0.5-hr experimental sessions during which food pellets were delivered for every 32 consecutive lever presses on one lever following saline injection and on the other lever following cocaine injection. Following discrimination training, dose-response curves for cocaine, RTI-113, and RTI-120 were obtained under test conditions in which 32 consecutive presses of either lever resulted in food delivery. All three compounds produced dose-responsive increases in cocaine lever responding such that at least one dose of each compound produced near-100% levels of cocaine-lever responding. The order of potency to produce ≥ 80% cocaine-lever responding was RTI-113≈RTI-120≈cocaine (rats) and RTI-113>>cocaine>RTI-120 (squirrel monkeys). Cocaine's discriminative stimulus effects dissipated (≤50% DBR) 30-60 min (rats) and 60-80 min (monkeys) following injection, while RTI-113's cocaine-like effects persisted about >10x and >3x longer than cocaine's in the rat and monkey, respectively. RTI-113's effects also appeared to develop slowly requiring about 60 min to maximally develop in the monkey or about 6x longer than cocaine's. These studies demonstrate that RTI-113 and RTI-120 generalize from the cocaine discriminative stimulus and RTI-113 has a much longer duration of activity than cocaine.

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ANALYSIS OF THE EFFECTS OF DIVERSE ANTIDEPRESSANTS ON THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE

P. M. Callahan and K. A. Cunningham

Antidepressants are being used as pharmacotherapeutic interventions for the treatment of cocaine abuse, however, their success appears to vary among patient populations. Drug discrimination procedures have been used to model the "subjective" effects of cocaine in animals. While DA systems primarily mediate the stimulus effects of cocaine, we have reported that the reuptake inhibitors for DA (GBR 12909), 5-HT (fluoxetine) and NE (desipraminc) *enhunce* the "subjective" state induced by low doses of cocaine (Cunningham and Callahan 1991), however, this effect is not common to all drugs known to inhibit monoamine reuptake (Callahan and Cunningham 1992; Spcalman 1993). To further delineate these issues, rats were trained to discriminate cocaine (5 or 10 mg/kg) from saline using a drug discrimination task. While none of the antidepressants mimicked the cocaine cue, fluoxetine (4 mg/kg) and sertraline (4 and 8 mg/kg) dose-dependently *enhanced* the cocaine dose-response curve (0.625-5 mg/kg). On the other hand, fluvoxamine and the tricyclic antidepressant clomipramine (4 and 16 mg/kg) were not as efficacious in this regard. The rank order of potencies for these compounds to inhibit 5-HT reuptake *in vivo* (Koe *et. al.,* 1983; Scatton *et. al.,* 1988) appears to correlate with their ability to produce a leftward shift in the cocaine dose-response curve (fluoxetine $\approx$ sertraline > > fluvoxamine > clomipramine). Trazodone and nefazodone are non-tricyclic antidepressants with very similar 5-HT reuptake and 5-$HT_{2A/2C}$ receptor binding properties, however, unlike trazodone, nefazodone lacks binding affinity at at-adrenoreceptors (Eison *et. al.,* 1987). Thus, the ability of trazodone, but not nefazodone (2.5-20 mg/kg), to antagonize the cocaine cue may reflect its action at α_1-adrenoreceptors. While the partial 5-HT_{1A} agonists buspirone and gepirone possess similar pharmacological profiles, gepirone lacks binding affinity at dopumine receptors (Eison *et. al.,* 1987). Thus, the ability of buspirone, but not gepirone (2.5-20 mg/kg), to block the cocaine cue may reflect its action as a dopamine antagonist. Taken together, these results suggest that the "subjective" properties of cocaine in humans (euphoria, anxiety?) might be potentiated or blocked following acute administration of antidepressants depending upon the predominant neurochemical action of the specific compound.

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EFFECTS OF EXTEROCEPTIVE STIMULUS CONDITIONS ON COCAINE (COC) DISCRIMINATION IN DISCRIMINATED TASTE CONDITIONING (DTC)

B. L. Slifer and S. L. Serdikoff

The purpose of this study was to characterize the discriminative effects of the psychomotor stimulant Cocaine HCl (COC) using discriminated taste conditioning (DTC) methodology. Fourteen naive Sprague-Dawley rats were randomly assigned to two groups; the Experimental group (n=8) and the Control group (n=6). Training sessions consisted of a pre-session injection, fixed-duration access to 40 ml of a saccharin solution (SAC, 0.15% w/v), and a post-session injection. During drug training sessions for the Experimental group, there was a pre-session injection of COC (10 mg/kg, i.p.) and a post-session injection of LiCl (1.8 mEq/kg, 0.15 M, i.p.). Control training sessions for the Experimental group and all training sessions for the Control group consisted of pre-session and post-session saline injections. Once reliable selective suppression of fluid intake following COC administration was evident in the Experimental group, testing began. Test sessions for both groups were conducted in the same manner as training sessions except there was no post-session injection. Generalization tests in both groups were conducted by providing access to 0.15% SAC following pre-session administration of the following compounds:

Cocaine HCl - (V, 0.1, 0.3, 1.0, 3.0, 10, and 17.5 mg/kg)
Chlorpheniramine HCl - (V, 1.0, 3.0, 10.0, and 20.0 mg/kg)
Diphenhydramine HCl - (V, 1.0, 3.0, 10.0, and 20.0 mg/kg)
Promethazine HCl - (V, 1.0, 3.0, 10.0, and 20.0 mg/kg)
Pentobarbital Sodium - (V, 1.0, 3.0, 10.0, and 20.0 mg/kg)

Fluid intake during access to graded concentrations of SAC (H_2O, 0.05%, 0.10%, and 0.15%) following pre-session administration 10 mg/kg COC was also tested. Responding during COC test sessions was characterized by a dose-related decrease in fluid intake as COC test doses approached and exceeded the training dose of 10 mg/kg for animals in the Experimental group. In contrast, doses of COC had little effect on the fluid intake of the Control group animals. Similarly, during SAC test sessions responding of the animals in the Experimental but, not Control group, was characterized by a concentration-related decrease in fluid intake as SAC concentrations approached the training concentration of 0.15%. Like COC, both chlorpheniramine and diphenhydramine resulted in dose-related decreases in the fluid intake of rats in the Experimental group but no reliable effects on the fluid intake of the Control group. Promethazine also resulted in dose-related decreases in the fluid intake of rats in the Experimental group. Unlike the other compounds, however, promethazine also decreased the fluid intake of animals in the Control group but, only al the highest dose tested. Failure of response suppression to generalize following pentobarbital was evidenced by the lack of a differential fluid intake of rats in the two groups. The dose-effect function for COC clearly indicates stimulus control over fluid intake by COC for animals in the Experimental group. Furthermore, these data indicate that although SAC concentration was not differentially associated with the unconditioned stimulus (LiCl), the SAC stimulus also acquired discriminative control over behavior. The data demonstrate the development of multiple sources of discriminative control in drug discrimination. Moreover, the test data indicate that response patterns developed under the control of COC in this training paradigm generalized to other compounds and is consistent with data from investigations of COC's discriminative stimulus effects that have used other methodologies where multiple sources of control typically have not been examined.

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BEHAVIORAL SENSITIZATION: ROLE OF THE CYCLIC AMP SYSTEM IN NUCLEUS ACCUMBENS

M. J. D. Miserendino and E. J. Nestler

The phenomenon of behavioral sensitization, in which animals show enhanced behavioral responsivity to stimulants or opiates after repeated drug exposure, provides a useful behavioral assay for evaluating the neurobiological mechanisms underlying the chronic actions of drugs of abuse on the mesolimbic dopamine system. Prior work in our laboratories has suggested that the cyclic AMP system at the level of the nucleus accumbens (NAc) may be critically involved in behavioral sensitization. Specifically, we have observed that chronic cocaine or morphine administration produced increased levels of adenylate cyclase and cyclic AMP-dependent protein kinase (PKA) in the NAc. We now report the results of preliminary work directly examining cyclic AMP system alterations in the NAc in behavioral sensitization. In this work, rats were implanted with chronic bilateral cannulae aimed at the NAc and were pretreated on three consecutive days with cocaine (10 mg/kg, ip) concurrent with local intra-accumbens infusion of either saline vehicle, 8-bromo cyclic AMP (2 µg/.5 µl/side), a membrane permeant analog of cyclic AMP which activates PKA, or RP-CPT-cAMP (20 nmoles/.5 µl/side), which inhibits PKA. Control animals received local infusion of 8-bromo cyclic AMP or saline concurrent with ip saline in the same regimen. All animals were then tested for locomotor activity in response to an acute cocaine challenge. During the three pretreatment days, animals given intra-accumbens 8-bromo cyclic AMP showed greater cocaine-induced locomotor activity, ($F[1,24] = 7.163$, $p < .02$); further, there was an interesting trend toward decreased activity in those animals given intra-accumbens RP-CPT-cAMP compared to saline-infused controls. When subsequently challenged with cocaine, animals which had previously received 8-bromo cyclic AMP showed greater locomotor activity during the last 30 minutes of the 60 minute test session than did animals pretreated with saline, ($F[1,24] = 7.53$, $p < .02$). Thus, prior administration of 8-bromo cyclic AMP into the NAc during cocaine exposure produced a protracted enhancement of locomotor activity to subsequent cocaine. No differences in locomotor activity were evident between the two control groups during either the pretreatment days or in response to subsequent cocaine challenge. This suggests that local application of exogenous cyclic AMP system activating agents at the level of NAc does not in itself produce increased locomotor activity, but rather may have a permissive role with respect to stimulant-induced activity.

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INTRA-A10 ADMINISTRATION OF THE PROTEIN KINASE C INHIBITOR H7 BLOCKS THE DEVELOPMENT OF SENSITIZATION TO COCAINE

J. D. Steketee

The augmented motor-stimulant response which occurs with repeated cocaine administration is termed behavioral sensitization. Previous studies have suggested that sensitization results in part from an enhanced response of the mesolimbic dopamine system to cocaine (Kalivas and Stewart 1992). In particular, it has been reported that daily injections of cocaine produces a transient decrease in G protein-mediated tonic inhibition of dopamine neurons located in the A10 region, which is the origin of the mesolimbic system (Steketee and Kalivas 1991; Nestler *et. al.,* 1990; Striplin and Kalivas 1992; Ackerman and White 1992). The mechanisms involved in the development of this transient decrease in the tonic inhibition of dopamine neurons remain to be determined. In addition, since sensitization is a long-lasting phenomenon, mechanisms involved in the maintenance of sensitization need to be determined. A recent study has shown that injection of the protein kinase inhibitor H7 into the A10 region blocked the acute motor-stimulant response to cocaine in a dose-dependent manner (Steketee 1993). Thus, in this study the effects of intra-A10 injection of H7 on cocaine-induced sensitization was examined. Animals received bilateral stereotaxic implants of cannulae 1 mm above the A10 region one week before the start of an experiment. Animals were adapted to the injection procedure and motor activity boxes 24 hours before the experiment began. Animals received intra-A10 injections of saline (0.5 µl/side/min) or H7 (10 nmol/side) five minutes before receiving injections of saline (1 ml/kg, ip) or cocaine (15 mg/kg). Motor activity was monitored for two hours following injections. Animals then received the same injection regimen for three consecutive days in their home cages and 24 hours later all animals received a challenge injection of cocaine, without intracranial pretreatment, and motor activity was monitored. Total crossovers (mean ± SEM), a measure of locomotor activity, were as follows: Day 1, Saline = 26.9 ± 11.5: H7 = 87.6 ± 45.7, Cocaine = 315.3 ± 67.7 and H7 + Cocaine = 231.9 ± 63.5 and Day 5, Saline = 362.2 ± 100.7; H7 = 481.4 ± 97.1; Cocaine = 602.9 ± 72.1 and H7 + Cocaine = 454.7 ± 64.9. Statistical analysis revealed that daily cocaine injections produced a sensitized motor stimulant response and that H7 attenuated the development of the sensitized response. Examiniation of the time course of motor activity (data not shown) revealed that H7 blocked the acute motor stimulant response between 15 and 30 minutes after cocaine injection. In addition, H7 pretreatment blocked the sensitized response to cocaine during the first 30 minutes after injection. These data suggest that inhibition of protein kinase activity in the A10 dopamine region may block the development of cocaine-induced behavioral sensitization. H7 is a nonspecific protein kinase inhibitor, therefore, which protein kinase(s) is (are) important in the development of sensitization remains to be determined. However, studies of other forms of sensitization in the nervous system, including long-term potentiation and kindling, have demonstrated that increased protein kinase C activity plays an important role (Colley and Routtenberg 1993; Kohira *et. al.,* 1992).

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A SINGLE INJECTION OF A SELECTIVE D-1 AGONIST INTO THE NUCLEUS ACCUMBENS PRODUCES SENSITIZATION TO THE LOCOMOTOR ACTIVATING EFFECTS OF COCAINE

T. J. De Vries and T. S. Shippenberg

The repeated and intermittent administration of either direct (apomorphine) or indirect (cocaine, amphetamine and opioids) dopamine (DA) agonists is known to cause an augmentation of their locomotor stimulating and reinforcing effects. This phenomenon, called behavioural sensitization, is thought to play a critical role in the acquisition and maintenance of drug abuse. Although the integrity of the mesolimbic DA system appears to be essential for initiation and expression of behavioural sensitization, the neurochemical changes and anatomical sites mediating such are still poorly understood. Studies with morphine and amphetamine have indicated that the A10/A9 DA cell body region might be an anatomical site of initiation. However, most adaptive neurochemical changes that have been associated with the development and expression of behavioural sensitization seem to occur in the terminal regions of the dopaminergic projections, especially the nucleus accumbens. These changes include an enhanced release of DA and supersensitivity of postsynaptic DA D-1 receptors. Although activation of D-1 receptors within the ventral temental area is thought to play a critical role in the initiation of sensitization, the role of D-1 receptors within the nucleus accumbens has not been examined. To address this issue, Sprague-Dawley rats were equipped with bilateral guide cannulae aimed at the nucleus accumbens. After a five day period of recovery, rats received the following injections. On day one, rats were injected with the selective D-1 agonist SKF 82958 (1 μg) or its vehicle and on day two and three, rats received cocaine (10 μg) in the home cage. On day four and five, rats were challenged with an intra-accumbens injection of sterile water and cocaine (10 μg), respectively, and on day six and seven with systemic injections of saline and cocaine 20 mg/kg, respectively. Immediately following these injections, locomotor activity was measured in photocell equipped test chambers for 100 min. In rats pretreated with vehicle on day one, intra-accumbens cocaine produced an increase in locomotor activity that lasted for ca. 70 minutes. Rats pretreated with the D-1 agonist, however, showed an even greater augmentation of activity during the first 40 minutes. A systemic injection of cocaine also resulted in a augmented and prolonged stimulation of locomotor activity in rats primed with the D-1 agonist compared to the control rats. Similar results were obtained with the more selective, but less potent, D-1 agonist SK&F 38393, suggesting a selective effect on DA D-l receptors. Thus, a single bilateral infusion of a selective D-1 receptor agonist into the nucleus accumbens caused hyperactivity to subsequent intra-accumbens and systemic injections of cocaine. These data give further support to the idea that activation of D-1 receptors is critical for the development of sensitization and show that the nucleus accumbens may, in fact, be an anatomical locus of initiation of behavioural sensitization.

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SENSITIZATION AND CONDITIONING WITH INTRASTRIATAL ADMINISTRATION OF DOPAMINE AGONISTS

P. B. Silverman

Rats with a unilateral 6-hydroxydopamine lesion of substantia nigra were injected intrastriatally via an indwelling cannula ipsilateral to the lesion. Their circling behavior was quantified by use of a video camera and motion analyzer. Intrastriatal administration of dopamine resulted in contralaterally directed circling. Repeated (daily) administration of dopamine resulted increased response (sensitization). Intrastriatal administration of the D2 selective dopamine agonist, PHNO, also induced contralateral rotation and, with repeated administration, sensitization. When placed, undrugged, into the rotation environment weeks after their last drug session, rats that had previously been administered dopamine briefly circled rapidly contralaterally. This conditioned rotation was entirely absent in rats that had previously been administered PHNO. Thus the results show sensitization and conditioning with intrastriatal dopamine, and sensitization but not conditioning with intrastriatal PHNO. The results are consistent with those obtained with systemic administration of dopamine agonists in showing that D1, D2 and D1/D2 agonists induce sensitization, but D1 dopaminergic stimulation is required for conditioning rotation (Silverman, 1991, 1993).

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SENSITIZATION TO THE CONDITIONED REWARDING EFFECTS OF COCAINE

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Increasing evidence suggests that the repeated administration of cocaine can lead to an enhancement of its positive reinforcing effects. Fundamental questions, however, exist as to whether sensitization also develops to the conditioned rewarding effects of this agent. The pharmacological and temporal characteristics of this effect are also unclear. Accordingly, the present study employed an unbiased place preference conditioning procedure to address this issue in the rat.

Male Sprague-Dawley rats (200-250 g) received once daily injections of cocaine (10.0 mg/kg; ip), morphine (MOR: 5.0 mg/kg; sc) or saline for five days in a colony room. Place conditioning in response to cocaine (1.0-10.0 mg/kg) or MOR (1.0-5.0 mg/kg) was assessed 1-14 days after cessation of drug pre-exposure. In saline pretreated rats, a minimum of six conditioning sessions (three drug; three saline) was required for the establishment of cocaine or MOR-induced conditioned place preferences (CPP). The minimum doses producing this effect were 10.0 and 3.0 mg/kg, respectively. In cocaine-pre-exposed rats, CPP occurred after only four conditioning sessions. Cocaine in doses of 5.0 mg/kg and greater resulted in significant CPP. This enhancement of responding was apparent when conditioning commenced either three, seven, or ten days after the cessation of the repeated drug treatment. It was no longer apparent 14 days later. Cross-sensitization between cocaine and MOR was also apparent. No such enhancement of drug-induced CPP was observed in animals which had received the dopamine receptor antagonists SCH23390 (0.01-0.05 mg/kg) or raclopride (0.1-0.5 mg/kg). Administration of the D-1 receptor antagonist, SCH23390, however, in combination with the repeated cocaine treatment prevented the enhancement of cocaine-induced place conditioning. In contrast, the D-2 antagonist, raclopride, was without effect.

These data demonstrate that the repeated administration of either cocaine or MOR results in a long-lasting enhancement of their conditioned rewarding effects (e.g., sensitization). Such treatment also results in cross-sensitization. The effectiveness of a D-l dopamine receptor antagonist in preventing sensitization to cocaine suggests that the activity of this dopamine receptor type is necessary for the development of these phenomenon.

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CHRONIC COCAINE ADMINISTRATION DOES NOT PRODUCE SENSITIZATION TO THE LOCOMOTOR EFFECTS OF GBR12909

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INTRODUCTION: Repeated administration of cocaine to rodents will sensitize the locomotor response to a range of psychomotor stimulants when they are substituted for cocaine on the test day. The purpose of the current experiment was to investigate the ability of cocaine to sensitize the locomotor response and stereotypic effects of several dopamine uptake blockers with unique pharmacological profiles; Mazindol (Maz), GBR12909(GBR), RTI-55 (RTI) and Cocaine (Coc).

METHODS: Full dose-response curves were obtained in male Sprague Dawley rats for Coc, Maz, RTI and GBR with either cocaine or saline given on the previous pretreatment day. All subjects received two injections on the pretreatment day; the first injection (saline or 40 mg/kg Coc) was given immediately prior to being placed in the activity monitor for 60 minutes, the second saline injection was given two hours later in the home colony. Dose-effect curves for each drug were determined on day two.

RESULTS: There was a significant effect of cocaine pretreatment on locomotor stimulant dose-response curves for each drug. Cocaine pretreatment shifted the Coc, Maz and RTI dose-effect curves to the left while decreasing the maximal stimulant effect and dose-effect function of GBR to the right (all $p < .0001$). Cocaine pretreatment did not alter the time course of Coc-, Maz-, or RTI-induced locomotor activity. Cocaine pretreatment altered drug-induced stereotypy time to a greater extent than locomotor activity. Cocaine pretreatment increased the amount of stereotypy time and shifted the Coc, Maz, and RTI dose-effect curves to the left (all $p < .0001$) but did not affect the GBR dose-response curve.

DISCUSSION: The ability of cocaine to sensitize the locomotor effects of other psychomotor stimulants provides information relevant to the pharmacology of the investigated drugs and the mechanisms underlying the sensitization process. Despite the similarity of Coc, Maz and RTI and GBR to inhibit dopamine uptake, previous cocaine administration did not sensitize the locomotor effects of GBR. In this respect, the pharmacological properties of GBR12909 impart resistance to cross-sensitization from cocaine and warrant further investigation. The results of this study further demonstrate the unique pharmacology of GBR and support the further study of this compound in the sensitization process and as a potential treatment medication for cocaine abuse.

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METHOD FOR ANALYSIS OF IBOGAINE IN PLASMA

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Ibogaine (IBG) is a psychotropic indole alkaloid currently being studied for its ability to prevent drug craving. IBG has a terminal plasma half-life in rats of ca. 2.7 hours and is excreted both unchanged and as a series of metabolites. After a single intravenous dose of 5 mg/kg of tritiated IBG average plasma levels of IBG fell from concentrations of ca. 300 ng/g (females) and 240 ng/g (males) at 7.5 minutes after dosing to 0.2 - 0.3 ng/g at 24 hours. Because of its reported long duration of pharmacological activity and the difficulty of studying radiolabeled chemicals in humans, a method to measure very low quantities of IBG in human plasma is needed. HPLC assays with UV detection generally have limits of quantitation considerably higher than 1 ng/g and/or rely on fairly large quantities of plasma. In contrast we have developed a very sensitive capillary GC/MS assay for IBG using plasma samples of 1mL. A stable isotope derivative of IBG is used as the internal standard. IBG was isolated from plasma using a Cl 8 solid phase extraction column and acidified methanol as the eluting solvent. Aliquots of the isolated IBG were quantitated on a 30 m capillary DB-1 gas chromatography column coupled to a quadrapole mass spectrometer operating in the methane chemical ionization mode with selective monitoring of the protonated molecular ions. Plasma samples spiked with IBG at concentrations ranging from 0.1 ng/g to 33,000 ng/g were analyzed by this method. The limit of quantitation was ca. 0.5 ng/g. At 3, 30 and 300 ng/g, the intra- and inter-assay variability for each calculated concentration was <25%.

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EVIDENCE THAT IBOGAINE MODULATES DOPAMINE RELEASE VIA A KAPPA RECEPTOR MECHANISM

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Ibogaine, a proposed pharmacotherapeutic for stimulant and opiate addiction, has been studied extensively for its effects on mesolimbic dopamine. The findings, however, have been less than conclusive since some have found that it reduces while others have found that it enhances stimulant induced doparnine release in the nucleus accumbens. Furthermore, there is little evidence to suggest that it has any effects on nucleus accumbens dopamine release when administered alone. Therefore, in the present study we have looked at the dopamine effects of several doses of locally administered ibogaine, using *in vivo* microdialysis in the nucleus accumbens and striatum of freely moving rats. In addition, the effects of the kappa antagonist norbinaltorphimine (norBNI), alone and in combination with ibogaine, were also studied. Ibogaine (10^{-6}-10^{-3} M), in both nucleus accumbens and striatum, produced a biphasic dose-response effect on dopamine release. Lower concentrations of ibogaine (10^{-6}-10^{-4} M) reduced, while higher concentrations of ibogaine ($5x10^{-4}$-10^{-3} M) stimulated dopamine levels. These findings demonstrate the importance of dosage in studies on ibogaine and may perhaps help clarify discrepancies in previous studies on ibogaine and dopamine release. Co-administration of of norBNI (10^{-5}M and 10^{-6}M; no effects on dopamine when given alone) with an inhibitory concentration of ibogaine (10^{-4} M) blocked the decrease in dopamine levels produced by ibogaine alone, and in some cases actually enhanced the levels of dopamine. The finding that NorBNI potently blocks the inhibitory effect of ibogaine indicates that low doses of ibogaine inhibit dopamine release via kappa receptors. This is consistent with the ability of kappaergic agonists to reduce basal and cocaine stimulated dopamine release (Maisonneuve and Glick 1994-CPDD). Thus, it may be suggested that the therapeutic effects of ibogaine in addiction treatment are mediated via kappa receptors. The increase in dopamine levels seen when NorBNI and ibogaine were co-perfused might reflect the stimulatory effects of ibogaine, as seen with higher concentrations of local ibogaine ($5x10^{-4}$-10^{-3} M), that are unmasked by the blockade of kappa receptors.

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IBOGAINE, THE PUTATIVE ANTI-ADDICTIVE DRUG IS A COMPETITIVE INHIBITOR OF [^{3}H]MK-801 BINDING TO THE NMDA RECEPTOR COMPLEX

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Ibogaine, an indole alkaloid originally isolated from *Tabernanthe iboga,* has been claimed to decrease dependence and withdrawal symptoms to opiates, stimulants, nicotine and ethanol. The molecular mechanisms responsible for these putative anti-addictive properties are unknown. Converging lines of evidence have implicated the N-methyl-*D*-aspartate (NMDA) subtype of glutamate receptor in tolerance and dependence phenomena. The similarity between the ability of MK-801 (a non-competitive antagonist of the NMDA receptor) to attenuate phenomena associated with tolerance and dependence in animals and the therapeutic claims which have been made for ibogaine prompted us to determine if MK-801 and ibogaine share a common neurochemical action at NMDA receptors.

[^{3}H]MK-801 and [^{3}H]TCP {1-[1-(2-thienyl)-cyclohexyl]piperidine} binding were assayed in extensively washed rat forebrain membranes supplemented with glycine and glutamate (30 μM each). Membranes were incubated for two hours (25°C) with either 0.1-25 nM (to generate saturation isotherms) or (to generate competition curves) 4 nM [^{3}H]MK-801 or [^{3}H]TCP. Nonspecific binding was defined with 100 μM TCP hydrochloride or MK-801 maleate, respectively.

Ibogaine inhibited [^{3}H]MK-801 binding with a K_i of 1.01±0.1 μM. This inhibition was effected through a concentration dependent reduction in the apparent affinity of [^{3}H]MK-801 with no concomitant change in the maximum number of binding sites (B_{max}). The K_D of [^{3}H]MK-801 increased from 1.72±0.25 nM in control membranes to 7.78±0.45 and 14.31±1.72 nM in the presence of 5 and 10 μM ibogaine, respectively. No statistically significant effects of ibogaine were observed on the corresponding B_{max} values: 3.5 ± 0.1, 3.4 ± 0.2 and 3.3 ± 0.3 pmols/mg protein, respectively. Ibogaine also inhibited [^{3}H]TCP binding with Ki of 1.08±0.1 μM. Ibogaine (at concentrations of up to 100 μM) did not affect ligand binding to kainate, AMPA or mctabotropic glutamate receptors.

Based on these findings, it is hypothesized that ibogaine can act as a use-dependent blocker of NMDA coupled cation channels. Since both non-competitive and competitive NMDA antagonists can attenuate the development of tolerance to morphine and alcohol as well as sensitization to stimulants in preclinical studies, the reported ability of ibogaine to modify drug-seeking behavior in man may be attributable to a blockade of NMDA receptor coupled cation channels.

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ACUTE IBOGAINE AND COCAINE: ACTIONS AND INTERACTIONS IN RHESUS MONKEYS

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Ibogaine, an alkaloid from the shrub Tabernanthe iboga, is said to be useful in the pharmacotherapy of stimulant abuse (H. Lotsof, patent #4,587,243). It was tested in a cocaine hyperarousal model (Rausch) designed to investigate a stage of dependence most likely associated with compulsive abuse and other psychopathological changes (Aceto and Bowman, Arzniemittel-Forschung 43, 1993). Three or four monkeys (M. mulatta) per treatment regimen were pretreated s.c. with ibogaine (2 or 8 mg/kg) or vehicle (veh) and 20 min later received sterile saline (Sal) or cocaine (1 mg/kg) i.v. Each animal was individually tested and observed by a trained "blind" evaluator who scored each monkey for the following signs: checking, escape attempts, restlessness, tremors and oral dyskinesias (chewing and tongue movements). The high-dose ibogaine-Sal-treated monkeys displayed significantly more total signs than veh-sal treated monkeys and significantly fewer signs than the veh-cocaine group. When ibogaine and cocaine were given together, an increased incidence of tremors occurred. In addition, two monkeys receiving the high-dose ibogaine-cocaine dose regimen convulsed. It is concluded that ibogaine did not attenuate cocaine-induced hyperarousal; instead, it increased the incident of tremors and convulsions and perhaps stereotyped behavior in combination with cocaine. The results suggest that treatment of compulsive cocaine abusers with ibogaine (acutely) may have adverse consequences.

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HALOPERIDOL PREVENTS COCAINE-INDUCED RAUSCH IN RHESUS MONKEYS

E. R. Bowman, Z. Ji, and M. D. Aceto

The cocaine (COC) hyperarousal or rausch model in rhesus monkeys was developed to investigate stages of COC dependence most likely associated with compulsive abuse. Studies in many animal models have shown that dopamine antagonists such as haloperidol (HALO) block or attenuate COC's reinforcing psychomotor and other effects (*e.g.,* Woolverton, Pharmacology Biochemistry Behavior 24: 531, 1986). Accordingly, this study was designed to establish whether HALO was effective in the rausch model. Four groups (3/group) of rhesus monkeys (M. mulatta) were randomly selected to receive either water (VEH) (1 ml/kg) or HALO (0.02 or 0.1 mg/kg) s.c. followed by i.v. administration of COC (1 mg/kg) or sterile saline (SAL) 20 minutes later. After treatment, each animal was scored once every 3 min during a 15 min observation period for the signs designated, escape attempts, checking, feinting, searching, tremors, restlessness, wide-eyed, standing, crouching, and chewing. All signs associated with COC hyperarousal were blocked by HALO at both doses. It is noteworthy that the doses of HALO tested are approximately equivalent to those used clinically. Furthermore, it seems obvious that lower doses also might have been effective. In addition, none of the control monkeys (VEH-SAL) showed any hyperarousal signs and the VEH-COC-treated monkeys elicited a pronounced hyperarousal syndrome. Thus, the dopaminergic system appears to play an important role in the expression of the COC rausch.

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COCAINE ABSTINENCE PHENOMENON: DIFFERENTIATION OF WITHDRAWAL PHASES' IN RODENTS

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Cessation of cocaine use in humans results in abstinence symptoms with distinct phases of crash, withdrawal, and extinction. These phases are defined by the appearance of specific symptoms at specific times after the last intake of cocaine (Gawin 1991).

In this study we tested the hypothesis that cocaine induced abnormalities in glutamatergic and dopaminergic systems in mice are reflected in behavioral measures that dissociate the dopamine agonist and a glutamatergic NMDA antagonist induced behaviors in mice. We studied the delayed effects of cocaine, by monitoring the apomorphine (APO) and MK-801 induced behaviors as a function of time following cocaine withdrawal. Mice were treated with either cocaine (10mg/kg/2xday) or saline for seven days. At withdrawal weeks 0,1,2,3,4,5,6, the cocaine and saline treated mice were challenged with one of the following: nothing, APO (1mg/kg), MK-801 (1mg/kg) and saline; locomotor behaviors were monitored in a Digiscan activity monitor. While exerting no effect on saline stimulated behaviors, cocaine enhanced the APO induced locomotion at weeks one through six by 50%. The cocaine treated mice, challenged with MK-801 showed a significant time delay in the onset of cocaine's effect [$F(1,6)=2.9$, $p<0.01$); a 41% reduction was present only at weeks four through six.

The delayed and persistent changes in MK-801 and APO stimulated behaviors seen after prolonged withdrawal from cocaine is consistent with the findings of Carrol and Lack (1987) and with our biochemical data (Hitri and Wyatt 1994) suggesting that long-term exposure to cocaine in rodents mimics the protracted anhedonia in cocaine addicts by dampening of reward systems in the brain.

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ANALYSIS OF 5HT 1A AUTORECEPTOR FUNCTION AFTER CHRONIC COCAINE EXPOSURE IN RATS

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Repeated cocaine injections are reported to cause alterations in the sensitivity of 5HT 1A autoreceptors regulating 5HT cell firing. Discrepancies exist between the *in vivo* and *in vitro* findings, however, and the precise nature of cocaine-induced changes in 5HT 1A receptor function are still unresolved. In the present study, we used the selective 5HT 1A agonist 8OH-DPAT (±-8-hydroxy-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene hyydrobromide) as a probe to assess 5HT 1A receptor responsiveness in rats previously exposed to cocaine or saline. Rats were treated with cocaine (15 mg/kg, ip, bid) or saline for seven days. After a 20 hour withdrawal period, rats were challenged with low doses of 8OH-DPAT (0-300 µg/kg, sc) and various endpoints were measured including inhibition of 5HT biosynthesis in the brain and stimulation of feeding. These particular 8OH-DPAT-induced responses are presumably mediated via activation of 5HT 1A somatodendritic autoreceptors in raphe nuclei. Cocaine treatment did not change the basal rate of 5HT synthesis in cortex or brainstem. Moreover, 8OH-DPAT induced inhibition of 5HT synthesis was similar in cocaine-treated and saline-treated rats. Cocaine exposure markedly increased the control feeding response in our paradigm, but the hyperphagia elicited by 8OH-DPAT was comparable in both groups. In summary, we found no evidence for changes in the sensitivity of 5HT 1A autoreceptors after chronic cocaine administration.

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DIFFERENTIAL EFFECTS OF (+)-HA960, A GLYCINE-SITE PARTIAL AGONIST ON COCAINE-INDUCED LOCOMOTOR ACTIVATION

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Studies with competitive and non-competitive antagonists of the N-methyl-D-aspartate (NMDA) receptor suggests glutamate is critical in the development and expression of the behavioral effects of cocaine (Karler *et. al.,* 1989; Karler and Calder 1992). However, these antagonists produce phencyclidine-like effects, responses that are undesirable for developing agents for the treatment of psychomotor stimulant dependence and toxicity. In this present study, we report on the effects of the glycine-site partial agonist (+)-HA966, a compound modulating the NMDA receptor, on cocaine-induced locomotor activity in rats. Under surgical anaesthesia, male Sprague-Dawley rats were implanted with a unilateral guide cannula aiming to penetrate the lateral ventricle. Following recovery, rats were treated daily with (+)-HA966 (30, 100, 200 µg, icv) or sterile water (2 µl) followed five minutes later with cocaine (20 mg/kg i.p.) or saline (1 ml/kg). After three days of chronic treatment, rats were tested for locomotor activity immediately after saline (on day four) and cocaine (day five) injections (20 mg/kg i.p.) administration. (+)-HA966 blocked the sensitisation that developed to locomotor activating effects of cocaine, and activity following saline injection remained unaffected. Three days of chronic (+)-HA966 (30, 100 and 200 µg) treatment alone failed to affect cocaine-induced locomotor activation. In contrast, 30 µg of (+)-HA966 when tested acutely, significantly potentiated the hyperlocomotive effects of cocaine without affecting activity after saline injection. Larger doses of (+)-HA966 were without effect. The present data demonstrate that glycine-site modulatory compounds can modify behavioral effects of cocaine. (+)-HA966 is different from other NMDA antagonists, since as well as preventing development of sensitisation. this partial agonist potentiates the acute effects of cocaine. These findings suggest that NMDA-modulated systems provide another approach to modify behavioral effects of cocaine, and thus represents one class of drug that may be effective in managing psychomotor stimulant dependence.

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CHROMOSOMAL MAPPING OF LOCI INFLUENCING COCAINE SENSITIVITY IN BXD RECOMBINANT INBRED MICE

L. L. Miner and R. J. Marley

Among inbred mice, genetic factors mediate differences in cocaine response, including the development of sensitization and convulsant effects. However, the gene(s) underlying cocaine's effects have not yet been identified. To help elucidate the gene(s) responsible for cocaine response, we used Recombinant Inbred-Quantitative Trait Loci (RI-QTL) analyses to identify chromosomal loci associated with cocaine-related phenotypes. RI-QTL analyses seek to identify associations between a quantitative measure of a particular phenotype and one or more previously mapped marker genes across a panel of RI strains. This association is determined by correlating a quantitative measure such as locomoter activity or seizure sensitivity, for each RI strain with a series of marker loci for which the two progenitor strains are polymorphic. The marker loci in each RI strain are scored as zero if they are contributed by C57BL/6J strains or one if they are derived from the DBA/2J strain. For the following analyses a panel of 655 chromosomal markers was utilized.

In the present study we examined five cocaine-related phenotypes. Sensitivity to the convulsant effects of cocaine was assessed for 26 BXD RI strains after the administration of 60 mg/kg cocaine HCl. In a separate experiment, the psychomotor stimulant properties of cocaine were assessed for 11 BXD RI strains. Differences among the strains in basal activity was assessed in Columbus Instruments Opto-Varimax activity monitors. After 30 minutes of basal testing, the mice were administered 10 mg/kg cocaine and monitored for another 30 minutes. For development of habituation/conditioned sensitization and cocaine sensitization, the mice were tested in the exact same manner on the following day. Habituation/conditioned sensitization is the change in baseline activity on day two compared to day one. Sensitization is the change in cocaine sensitivity on day two compared to day one. The results of the RI-QTL analysis for cocaine seizure susceptibility revealed a number of significant correlations clustered in two regions on chromosomes 12 and 6. The results of the RI-QTL analyses on the psychomotor stimulant properties of cocaine identified a number of chromosomal loci which may influence cocaine response. Habituation/conditioned sensitization yielded significant associations with loci on chromosomes 4 and 14 with the highest association being with the Glud locus for glutamate dehydrogenase. Cocaine sensitization mapped to loci on chromosomes 3, 12, 13 and 14. Acute cocaine sensitivity mapped to loci on chromosomes 2, 4, 5, 9, 13 and 16 and basal activity levels was associated with loci on chromosomes 1, 4, 5, 9, 11, 13, 16, 17 and 19. Among the phenotypes, basal activity level and acute cocaine sensitivity was significantly correlated indicating at least some common genetic mechanisms influencing both phenotypes. While these mappings are provisional, this is the first identification of chromosomal loci associated with a cocaine-related phenotype.

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DETECTION AND CHROMOSOME MAPPING OF QUANTITATIVE TRAIT LOCI ASSOCIATED WITH COCAINE RESPONSES IN INBRED MICE

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The present study investigated the effects of acute and repeated administration of cocaine on locomotor activity and stereotypy in 16 BXD recombinant inbred (RI) strains and in the DBA/2J and C57BL/6J progenitor strains from which the RI strains are derived. Quantitative trait loci (QTL) analysis was used to provisionally detect and map minor gene loci which are associated with cocaine responsiveness. Upon acute administration of 32 and 56 mg/kg cocaine, DBA/2J mice were stimulated to a much greater extent than C57BL/6J mice. In DBA/2J mice, a decline to control levels in the locomotor stimulant effect of cocaine was accompanied by sensitization to stereotypy with repeated daily injections of 32 mg/kg cocaine. In C57BL/6J mice, locomotor stimulation remained consistent and no sensitization to stereotypy developed with repeated cocaine. BXD RI strain means for acute locomotor, long-term locomotor, and stereotypy responses were correlated with strain distribution patterns of allelic variation at 670 marker loci covering over 90% of the genome. This QTL analysis indicated significant associations of differences in cocaine responsiveness with marker loci on several chromosomes in the BXD RI series. Regions of five chromosomes, including clustered markers on chromosomes nine and 17, were associated with the acute locomotor response. Those marker loci associated with the acute cocaine response were in most cases different from those markers associated with long term responses. The current results demonstrate that genotype-dependent variation exists in behavioral responsiveness to cocaine in mice and suggest that the acute and long-term responses to cocaine may be under the control of separate sets of genes. The implicated map sites will be tested in an F2 cross using PCR genotyping to verify these results.

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THE EXPRESSION OF PROTEIN KINASE C ISOFORMS IN PC-12 CELLS ARE DIFFERENTIALLY MODULATED BY ALCOHOL AND COCAINE

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Pheochromocytoma (PC- 12) cells express neuronal function and can synthesize and store monoamine neurotransmitters like dopamine and norepinephrine. These cells possess the necessary requirements to study signal transduction mechanisms involved in generating biological responses. Protein Kinase C (PKC) is a ubiquitous family of kinascs involved in a number of diverse and critical cellular functions. PKC is a major mediator of transducing signals to the interior of the cell, and is activated *in vivo* by Ca^{2+} and diacylglycerol. Ten different PKC isoforms have been identified in different species, tissues and cell lines. Alcohol and abused drugs like cocaine induce changes in neuronal Ca^{2+} channels that are associated with withdrawal anxiogenesis. The objective of this study was to determine the changes in the expression and translocation of PKC isoforms in the neural PC-12 cell line exposed to alcohol and cocaine.

PC-12 cells were grown in nutrient medium containing 10% fetal bovine strum until confluent. The cells were incubated with 50-100 mM alcohol and 1-2.5 mg/ml cocaine from four hours - six days. Cells were rinsed in PBS buffer and homogenized. The homogenate was centrifuged at 4°C for one hour at 100, 000 X g and the supernatent used as the cytosol while the pellet was prepared as the membrane fraction. The activity and the expression of PKC isoforms, $\alpha, \beta, \gamma, \delta, \varepsilon$ and ζ in the cytosol and membrane were assessed. The levels of Ca^{2+} were also measured using fura 2, after exposure of the cells to alcohol and cocaine. Monoclonals against α, β and γ and polyclonals against δ, ε and ζ were used for western blotting analysis. The results indicate that PKC activity was enhanced by the incubation of the PC-12 cells with alcohol and cocaine in the cytosol and membrane fractions. The marked increase of PKC activity was associated with the translocation of the PKC isoforms to the membrane fraction when compared to the untreated cells. Western blot analysis using antibodies to the isoforms indicated a dose dependent increase and decrease in the expression of these isozymes by alcohol and cocaine respectively. However, both alcohol and cocaine caused an increase in PKC mediated phosphorylation and Ca^{2+} levels. It has previously been demonstrated that alcohol increases the expression of PKC δ and ε. We extend this observation to PKC α, β, γ and ζ and also demonstrate for the first time, the inhibition of the expression of the six isoforms after incubation with cocaine.

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EVIDENCE FOR NORADRENERGIC MECHANISMS IN COCAINE-INDUCED SUPPRESSION OF RENIN SECRETION

L. D. Van de Kar, K. **Kunimoto, Q. Li, A. D. Levy, and J. M. Yracheta.**

The renin-angiotensin system controls blood pressure and is vital for survival during cardiovascular emergencies that can occur after cocaine abuse. Cocaine reduces the secretion of renin in conscious rats. The present study investigated: 1) whether cocaine acts centrally or peripherally, and 2) whelher noradrenergic mechanisms mediate the effect of cocaine on renin secretion. A central site of action was suggested by the fact that cocaine was more potent in reducing plasma renin concentration when injected intracerebroventricularly (ICV) (0.05 mg/kg) than when injected ip (5 mg/kg). Since cocaine is a local anesthetic drug, we tested whether the local anesthetic drug procaine (500 µg/kg ICV) also would produce these effects. Procaine did not reduce renin secretion. In addition, its hypertensive effect was similar to that of cocaine at the same ICV dose, suggesting that the hypertensive effects of cocaine are not likely the mechanism responsible for the reduction of the release of renin (Van de Kar *et al.,* 1992). Since previous studies indicate that central noradrenergic mechanisms reduce renin secretion (Van de Kar *et al.,* 1994), we investigated whether noradrenergic mechanisms mediate cocaine's effect on renin secretion. Cocaine can block norepinephrine uptake, which could increase its concentration in the synapse, producing an inhibitory stimulus to the kidneys to reduce renin secretion. Thus, sustained blockade of the norepinephrine uptake sites would preclude cocaine from binding to this uptake site and thus prevent it from producing any additional suppression of renin secretion. To test this hypothesis, rats received an injection of saline or the norepinephrine uptake blocker desipramine (10 mg/kg ip), one hour and fifteen minutes prior to the injection of saline or cocaine (7.5 mg/kg ip) and were sacrificed 15 minutes after the latter injection. Pretreatment with desipramine alone reduced plasma renin concentration. In addition, desipramine also completely blocked the suppressive effects of cocaine on renin secretion. However, the a_2 antagonist yohimbine (1 mg/kg sc) did not alter the effect of cocaine on renin secretion. Together, our data suggest that cocaine acts centrally on noradrenergic pathways to decrease renin secretion by activating an as yet unidentified noradrenergic receptor.

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BEHAVIORAL AND HISTOPATHOLOGICAL EFFECTS OF CHRONIC COCAINE ADMINISTRATION

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Chronic cocaine use has two manifestations. The first is changes in sensitivity to the acute effects of repeated cocaine administration. Behavioral sensitization or tolerance may be observed depending on the experimental conditions. The second is the cumulative toxic effects of the repeated drug administration on many physiological systems. Cardiac alterations include myocardial infarction, arrhythmias, accelerated therosclerosis and hypertension. Hepatotoxicity following cocaine administration has also been reported. However, these effects appear to be species specific. The present studies were undertaken to determine the behavioral and histopathological consequences of long term cocaine treatment. Male Wistar rats were administered single daily injections of saline or cocaine (20 mg/kg, ip) for 368 days. Locomotor activity was monitored monthly. Twenty-four hours after the last injection, animals were sacrificed and heart, liver and kidneys were removed for histopathological examination. Cocaine produced significant increases in locomotor activity on all days tested. The degree of stimulation varied, with no specific trend. The highest response was observed in month two. The lowest activity was recorded in month five. This activity was 45% of that observed in month two. Histopathological studies indicated that cocaine induced acute inflammation with hepatocellular damage. There was hyperplasia of Kupffer cells and focal eosinophilic degeneration of hepatocytes with intracytoplasmic red granular precipitates. Also small foci of coagulative necrosis were observed in the ventricles and protein casts were present in the distal tubules of the kidney. The present study has demonstrated cocaine-induced hepatotoxicity in the rat. The ability of cocaine to produce hepatic necrosis in mice is well documented. Cocaine has also been associated with clinical hepatotoxicities in humans. Every individual who uses cocaine does not experience liver toxicity. Genetics and exposure conditions may contribute to the differences in humans. Other animal models are therefore needed to fully understand the role of genetics in cocaine-induced hepatotoxicity. The rat can be used as such a model.

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EFFECTS OF PHENTERMINE AND FENFLURAMINE ON EXTRACELLULAR DOPAMINE AND SEROTONIN IN RAT NUCLEUS ACCUMBENS

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Preliminary evidence suggests that combined administration of the amphetamine derivatives, phentermine (PHEN) and fenfluramine (FEN), may be useful for treating cocaine and alcohol addiction. In open-label studies, some addicts report marked decreases in drug craving within hours of taking this medication. While these medicines are thought to modulate monoamine neurotransmission, the precise mechanism of action has not been characterized. In the present work, we used *in vivo* microdialysis methods to assess the neurochemical effects of PHEN, FEN, and PHEN/FEN combinations in rat nucleus accumbens. Microdialysis experiments were performed in awake rats, and dialysate samples were analyzed for dopamine (DA) and serotonin (5HT) using high pressure liquid chromatography followed by electrochemical detection. All drugs were dissolved in Ringers' perfusion fluid (148 mM NaCl, 4 mM KCl and 2 mM $CaCl_2$) and infused locally via the probe (0-100 μM). PHEN selectively increased DA at 1 μM, but at higher doses, both DA and 5HT levels were elevated. FEN selectively increased 5HT at all doses, and even at 100 μM, effects on DA were minimal. Infusion of the PHEN/FEN combination elevated extracellular DA and 5HT to a similar degree at all doses. Our data support the notion that PHEN/FEN treatment causes dual stimulation of DA and 5HT neurotransmission. Moreover, this action may underlie the ability of PHEN/FEN to reduce drug craving and alleviate withdrawal symptoms in abstinent addicts.

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IS PROTEIN KINASE C ACTIVATION A KEY STEP IN MDMA-INDUCED NEUROTOXICITY OF SEROTONERGIC NEURONS?

H. K. Kramer and E. C. Azmitia

3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy") is a ring-substituted amphetamine which produces a biphasic depletion of cortical serotonin levels and results in nerve terminal degeneration. MDMA also increases the uptake of Ca2+ into rat brain synaptosomes. Several agents have been found effective at reducing-MDMA-induced neuropathology including: specific 5-HT uptake inhibitors, calcium channel blockers and antagonists to the central 5-HT2 receptor. This receptor is also linked to the activation of protein kinase C (PKC), which has been implicated as an active intermediate in the development of calcium-mediated neuron death. These observations suggest that MDMA manifests its acute and neurotoxic effects via the release of 5-HT and the activation of calcium-dependent processes. This study investigated the ability of MDMA to induce a translocation of PKC to the cortical plasma membrane, and to examine the role of PKC on the development of MDMA-induced neuropathology.

TREATED LABORATORY RATS: Rats treated with MDMA (20 mg/kg x8) showed a significant increase in the density of membrane-bound PKC sites 1 (48.0%), 3 (54.5%), and 5 (41.6%) days after the cessation of treatment over saline controls (measured by 3H-phorbol ester binding). This response was abolished when the animals were pretreated with the 5-HT neurotoxin p-chloroamphetamine, and indicates that the *in vivo* translocation of PKC by MDMA requires viable nerve terminals and 5-HT release.

FETAL RAPHE NEURON CULTURES: Activation (24 hrs.) of PKC with phorbol 12 myristate-13 acetate (PMA; 100 nM) results in an increase of 3H-5HT uptake after 3 days *in vitro,* and is consistent with the maturation of astrocytes by PMA. PMA pretreatment (100 nM; 24 hrs.) also produced a dose-dependent potentiation of the neurotoxic effects of MDMA and a subsequent loss of uptake capacity. However, inhibiting PKC binding with the glycosphingolipids, sphingosine and ganglioside GM1 (IC50 = 1 mM), protected fetal 5-HT neurons from MDMA-induced cell death.

PRIMARY ASTROGLIAL CULTURES: Glycogen phosphorylase is an astroglial enzyme which regulates the liberation of glucose into the synapse. Both MDMA and 5-HT (EC50 = 5 mM and 1 mM, respectively) produced a dose-dependent activation of this critical PKC substrate. This response was attenuated by co-incubation with the 5-HT2 receptor antagonist, mianserin. In summary, MDMA may produce cytotoxicity by elevating synaptic 5-HT levels, and compromising the homeostatic energy state of serotonergic synapses through the activation of the 5-HT2 receptor and PKC.

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METHCATHINONE: A NEW AMPHETAMINE-LIKE DRUGOFABUSE

J. M. Tolliver

Over the past three years a new drug called methacathinone has appeared on the street. Chemically called alpha-N-methylaminopropiophenone, it has a chemical structure similar to that of methamphetamine. Animal studies indicate that it produces cential nervous system stimulation. Methcathinone is produced in clandestine laboratories via the oxidation of 1-ephedrine. The drug was first encountered by law enforcement officials in February 1991 in the Upper Peninsula of Michigan. The first laboratory was seized in Ann Arbor, Michigan in June 1991. Between November 1991 and June 1994, 33 additional laboratories making methcathinone were seized, all in the Upper Peninsula of Michigan. Between August 1992 and June 1994, methcathinone laboratories were seized in eight other states including Wisconsin (eight labs), Indiana (11 labs), Illinois (one lab)., Colorado (one lab), Virginia (one lab), Ohio (one lab), Washington (one lab), and Missouri (one lab). Methcathinone samples have also been found in Montana and Utah.

L-Methcathinone HCl is the form of methcathinone synthesized and distributed on the street. It is a white to off-white, chunky material that is water soluble and chemically stable. It is sold in quarter gram, gram, 3.5 grams (8-ball), and ounce quantities. It is distributed either as itself or as amphetamine or methamphetamine. Street names for I-methcathinone HCl include “Cat”, “Goob”, “Speed”, “Crank”, “Go Fast”, “Slick’s Superspeed”, “Cadillac Express”, “White”, and “Sniff”.

In order to obtain information on patterns of abuse and on the effects of methcathinone produced in humans, seven-page questionnaires were given to and filled out by 21 experienced methcathinone users living in the Upper Peninsula of Michigan. Within the group, methcathinone was administered primarily by snorting but also via intravenous injection, smoking and oral ingestion. Abuse was usually in binge episodes lasting two to seven days. The drug was administered at doses ranging from 1/32th to 1/4th of a gram at intervals of between 15 minutes and two hours. Reported desirable effects included a speeding of the mind, euphoria and a feeling of invincibility. Reported undesirable effects included paranoia, anxiety, hallucinations, tremors, sweating, heart pounding, hypertension, dehydration, and weight loss. The binge was followed by a “crash” characterized by irritability, prolonged sleep periods, excessive eating and a suhsequent craving for the drug.

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MECHANISMS INVOLVED IN METHAMPHETAMINE-INDUCED TOLERANCE

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A pretreatment consisting of incremental increases in methamphetamine (METH) doses causes tolerance to serotonin toxicity resulting from a challenge with multiple high doses of METH (10-15 mg/kg/dose). The brain concentration of METH following this challenge treatment was reduced in tolerant rats. Surprisingly, the plasma concentration of METH was elevated in these same animals (see Figure 1). One explanation is that tolerance is associated with a redistribution of METH. We examined the possibilities that the tolerance-inducing pretreatment either blocks the passage of METH into the brain or enhances its transport out of the brain following METH challenge. This was achieved by pretreating METH-exposed rats with the transport-blocking drug, probenecid. Under these conditions, METH-induced changes in the serotonergic system of the hippocampus were dramatically enhanced (see Figure 2) and METH concentrations in the brain were increased (data not shown). Based on these findings it is possible that METH is actively transported out of the brain by a probenecid-sensitive mechanism; thus, tolerance-inducing pretreatment may stimulate this transport mechanism resulting in reduced brain concentrations of METH after a challenge with this drug.

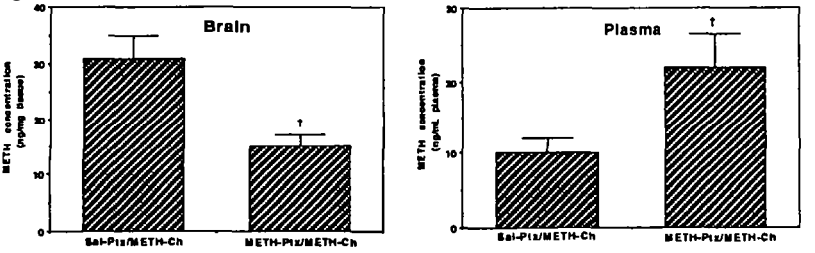

Fig. 1. Effects of METH or saline (Sal) pretreatment (Ptx) on METH concentrations in plasma and brain after a METH challenge (Ch). †P<0.05 vs. groups receiving saline.

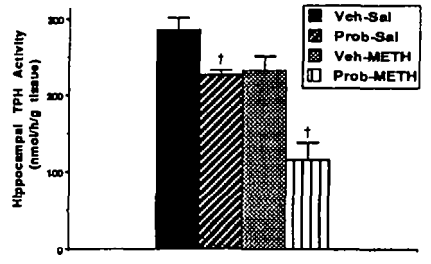

Fig. 2. Effects of probenecid (Prob) or vehicle (Veh) on TPH activity following a single low dose of METH. †P<0.05 vs. Veh-METH.

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METHYLENEDIOXYMETHAMPHETAMINE (MDMA) - INDUCED DOPAMINE AND SEROTONIN RELEASE *IN VIVO* ARE ATTENUATED BY RESERPINE PRETREATMENT

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Methylenedioxymethamphetamine (MDMA) is an analog of amphetamine (AMPH). AMPH-like compounds are thought to release dopamine (DA) and serotonin (5HT) from newly synthesized, cytosolic transmitter stores, rather than vesicular stores. Contrasting evidence suggests that DA and 5HT release induced by AMPH-like drugs relies, in part, on vesicular storage pools (see Seiden *et al.* 1993). In order to further evaluate this problem, we studied the effects of reserpine pretreatment on MDMA- and AMPH-induced 5HT and DA release *in vivo*. Rats were implanted with dialysis guide cannulae in the cortex above the striatum. Four to seven days later, dialysis probes were lowered into the guides; 16 hours later, baseline DA (and 5HT) measurements were taken from striatum, for a minimum of two hours. The rats then received MDMA or AMPH. Half the rats received reset-pine (10.0 mg/kg) pretreatment, 18 hours prior to testing. The table below shows extracellular DA and 5HT levels 30 minutes after MDMA or AMPH.

		DA (pg/10uL)	5HT (pg/10uL)	N
1.0 AMPH		92.4 + 16.4		8
1.0 AMPH	10.0 RES	53.9 + 11.6		8
10.0 AMPH		404.0 + 67.0		8
10.0 AMPH	10.0 RES	178.7 + 22.7		7
2.0 MDMA		15.0 + 03.9		4
2.0 MDMA	10.0 RES	2.1 + 01.4		4
5.0 MDMA		30.9 + 06.0		4
5.0 MDMA	10.0 RES	7.1 + 01.0		5
10.0 MDMA		125.8 + 28.9	30.0 + 4.7	8, 5
10.0 MDMA	10.0 RES	26.5 + 07.4	10.5 + 2.7	6, 5

This experiment shows that reserpine attenuated AMPH- and MDMA-induced DA and 5HT release, and suggests that AMPH and MDMA-induced transmitter release is dependent on vesicular stores. However, reserpine is known to lower body temperature (Larsson *et al.,* 1986). In addition, DA release induced by the AMPH analog methamphetamme, is temperature dependent (Bowyer et al., 1993). The attenuated release of DA induced by AMPH and MDMA after reserpine, may be due to a reduction in body temperature. In the rats receiving 5.0 mg/kg MDMA. body temperature was measured. Reserpine caused a reduction in body temperature which was not altered by 5.0 mg/kg MDMA treatment. From these results one can conclude that either: 1. MDMA and AMPH-induced DA release is dependent upon vesicular stores; or 2. MDMA and AMPH-induced DA release is attenuated by a reset-pine-induced reduction in body temperature. Such a reduction in temperature could reduce or slow down cellular mechanisms involved in carrier-dependent transmitter release.

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TRANSITIONS IN ROUTES OF ADMINISTRATION OF REGULAR AMPHETAMINE USERS

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Aims: To determine the extent of, and factors associated with, transitions between routes of administration of regular amphetamine users.

Procedure: Eight hundred and one regular (>monthly use) amphetamine users were administered a confidential structured interview regarding current drug use, amphetamine use history and transition between routes of amphetamine administration.

Analyses: Logistic regressions were used to determine factors associated with transitions to injecting. Analyses were conducted using SYSTAT.

Results: Sixty-seven percent of subjects had injected amphetamines in the preceding six months. Forty-one percent of injectors had shared a needle in the preceding month. A transition to regular amphetamine injection from other routes of administration was reported by 40% of subjects (median number of such transitions = 1), with males being twice as likely to report this transition. Having made a transition to injecting was associated with more years of amphetamine use, greater polydrug use, heavier dependence, poorer social functioning and more frequent use of amphetamines. The main reasons given by subjects for the transition to injecting were liking the "rush" from injecting being more economical and a healthier way to use 9% of subjects reported a transition away from injecting amphetamines (median = 1). The most common reason given for abandoning injecting was concern about vascular damage.

Conclusion: A transition to injecting was common, and was associated with heavier dependance and drug use. Interventions need to address the misconceptions that injecting is more economical and healthier, and to emphasize the vascular problems associated with injecting, rather than concentrating solely on HIV.

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METHCATHINONE - A POTENT NEW DRUG OF ABUSE

W. L. Pickard, D. E. Presti, D. Harlow, and G. Galloway

Methcathinone ("cat") is a novel psychomotor stimulant which appeared in the former Soviet Union in 1982 and rapidly spread. It is the drug of choice in the Russian "speed" culture, and is reportedly the most widely abused illicit drug in Russia except for heroin. Methcathinone is chemically related to methamphetamine (being the beta-carbonyl derivative) and cathinone from the khat plant (being the N-methyl derivative). It was apparently unknown as an illicit drug in United States prior to 1989, when it was synthesized in a clandestine laboratory in rural Michigan. More recently, methcathinone use has been associated with emergency room admissions in the midwestern United States and it has been classified as a Schedule I drug by the Drug Enforcement Administration. Subjective effects of methcathinone include increased alertness, euphoria, and increased libido. Heavy or repeated use may result in agitation and symptoms of psychosis. We performed an exhaustive electronic search of the text databases of all US newspapers over the last seven years and have found that news media accounts of the properties of methcathinone have varied considerably, with significant exaggeration of its properties. Nonetheless, this amphetamine analogue could potentially supplant methamphetamine and cocaine due to its extremely facile synthesis, the ready availability of chemical precursors, and reported subjective preference of drug users for methcathinone over methamphetamine and cocaine. Chemical syntheses are currently being discussed on worldwide electronic-mail networks. This is the first indication that synthetic data for a newly scheduled drug may be rapidly disseminated throughout the world in an uncontrolled manner, in contrast to the historically slower and more controlled routes of journal and book publications. Additionally, we note that the pharmaco-epidemiology of methcathinone in the US can be traced to a single individual and site. This situation provides an opportunity to study the mechanisms involved in the potential spread of other novel drugs of abuse which may occur in the future.

We are beginning a project to monitor new psychoactive compounds with potential addiction liability. We encourage concerned researchers and clinicians to contact our group with comments and suggestions for identifying unscheduled drugs which may achieve social use.

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THE EFFECTS OF ACUTE COCAINE ADMINISTRATION IN ANABOLIC-ANDROGENIC STEROID ABUSERS

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Both cocaine and anabolic-androgenic steroid (AAS) abuse are major drug problems in the United States. Durant *et al.,* (1993) reported that adolescents use AAS with marihuana, cocaine, smokeless tobacco, and alcohol. The purpose of the present study was to assess the effects of an acute dose (0.90 mg/kg, i.n.) of cocaine in subjects who were using high doses of AAS. Four healthy adult male volunteers, (ages 21-35) with no history of AAS use and four male body builders (ages 21-35) who were self-administering AAS, provided informed consent. On the study day, baseline parameters were obtained for 30 minutes before cocaine administration. Blood pressure, heart rate, and integrated plasma cocaine levels were monitored and subjects completed POMS, ARCI, and Visual Analog Scales throughout the two hour study. AAS subjects reported feeling less high and had fewer episodes of euphoria after cocaine. AAS users also experienced a significant delay in reporting the onset of cocaine effects (17.74 min vs 4.31 min. $p=0.03$), as well as a significant difference in the duration of cocaine effects (13.43 min vs 42.48 min, $p=.03$). Finally, excitement, MBG, anxiety, anger, depression, sedation, physical unpleasantness scales and heart rate changes were lower in the AAS group than the control group. These data demonstrate that AAS use may attenuate some of the behavioral and physiologic effects of cocaine.

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ABUSED ANABOLIC STEROIDS RAPIDLY INDUCE ANXIOLYTIC BEHAVIORAL CHANGES IN MICE

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Chronic administration of abused anabolic steroids (AAS) induces alterations in behavior. However few studies have examined behavioral effects of acute AAS administration. We have observed anxiolytic effects for acutely administered AAS as assessed in a novel murine behavioral assay (Toubas *et. al.,* 1990 Pharmacol. Biochem. Behav. 35:121) that is sensitive to the benzodiazepine and serotonin anxiolytics. The behaviors were assessed in 10 week old male BALB/cBK mice (n = 10/dose) 30 minutes after i.p. injection of the steroids. Large dose dependent reductions in aversive behavior were found as measured by decreased latency to enter, and increased total time spent, inside a mirrored chamber. These effects were behaviorally specific. No significant alterations in locomotor activity or aggressive behaviors occurred at these doses. The compounds examined for anxiolytic activity included four commonly abused AAS, testosterone (T) as the prototypic AAS, and the four primary metabolites of T. Nandrolone (N) and dehydrotestosterone (DEHT) were active with estimated ED_{50} values of 0.05 and 1.8 µg/kg respectively (0.18 and 6.3 nmoles/kg), with methandrostenolone and fluoxymesterone having no effect. The ED_{50} values for T and its metabolite, dihydrotestosterone. were 0.01 and 0.11 mg/kg respectively (35 and 379 nmoles/kg). Estradiol, the estrogenic T metabolite, had an ED_{50} value of 0.17 mg/kg (624 nmoles/kg). Androsterone and etiocholan-3alpha-ol-17-one, two primary metabolites of T that have no virilizing capacity, were inactive in the mirrored chamber assay. Structural comparisons of the commonly abused AAS tested reveal differences for the active compounds (N and DEHT) in the groups attached to the steroidal D ring to include a methyl group attached to carbon 13 and the absence of a methyl group attached to carbon 17. Rapidly induced behavioral changes by the AAS may be indicative of rewarding or reinforcing properties that could contribute to their chronic abuse.

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BEHAVIORAL EFFECTS OF ANABOLIC STEROIDS: ALTERATION OF THE MOTOR RESPONSES OF MICE TO EITHER PENTOBARBITAL OR COCAINE

D. R. Compton

Anecdotal data suggest adverse pharmacological effects of high dose anabolic steroid abuse by humans. Polydrug abuse is also common, so possible interactions between other drugs of abuse and steroids could pose significant health problems. Also, data in a mouse model indicated indirect effects of steroids could be observed upon cannabinoid-mediated catalepsy. Thus, indirect effects of steroids on motor responses induced by a stimulant and a depressant were evaluated. Male ICR mice were pretreated with a single dose of testosterone propionate (i.p.) or sesame oil one hour before administration of various doses of pentobarbitnl (i.p.) or cocaine (i.p.). Pentobarbital-treated mice were evaluated for the loss of righting reflex, and both "sleep time" (minutes) of mice affected as well as the percent induction (of total injected) were recorded. Cocaine-treated mice were acclimated to the locomotor activity chambers for 0.5 hours prior to cocaine administration, and motor responses recorded for 0.5 hours. To determine whether steroid effects were specific to locomotor stimulation, cocaine-induced hypothermia was also determined. Data indicate that pretreatment with testosterone enhances barbiturate-induced sedation. Also, testosterone diminishes cocaine-induced locomotor stimulation, but does not affect hypothermia. This suggests some specificity of action, and indicates that sesame oil 'trapping' of i.p. drug can be ruled out as a mechanism of action. It may be possible to use indirect measures of anabolic steroid activity as a model for further evaluation of the adverse effects of chronic high dose anabolic steroid abuse.

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RAVES, YOUTH AND DRUGS

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Background: In the past few years "raves" - huge all-night trance-dances with primarily youthful participants - have spread throughout the world. Fifteen fatalities in the United Kingdom from hyperthermia associated with the use of 3,4-methylenedioxymethamphetamine (MDMA) at raves, and reported binge use of MDMA, provide for concern. This exploratory study was conducted in late 1993 and 1994 in San Francisco and New York.

Methods: Participant observation of twelve raves, a convenience sample survey of ravegoers (N = 759), and semi-structured interviews with ravegoers. rave organizers, law enforcement, treatment personnel, disk jockeys and rave vendors.

Results: Ravegoers tend to be young (median age 18), and more diverse, ethnically and socioeconomically, than the traditional picture of psychedelic users. Use and initiation of LSD, MDMA, and other drugs were frequent. In a random sample (N = 385) of our survey, 79 percent reported initiating at least one illicit drug at a rave and 66 percent reported drug use at the last rave attended. LSD use was far more common in New York, while MDMA was more widely used in San Francisco. Some methamphetamine use was noted in San Francisco; small minorities of New York ravegoers used PCP, cocaine and heroin. Drug combinations and newer compounds (*e.g.,* 2C-B and GHB) were reported in both cities. Few acute adverse drug effects were observed or reported, but many ravegoers reported dysphoria in connection with what they believe to be adulterated MDMA. Alcohol use and aggression were much less prevalent than at other events with youthful audiences, and anti-alcohol sentiments were expressed by many ravegoers. Although music was loud enough to threaten significant hearing damage, nearly all ravegoers and rave organizers seemed unaware of this danger.

Discussion: Widespread ignorance and misinformation about drugs, combined with a great demand for accurate information, make rave attendees attractive targets for harm reduction efforts. The concentration of youthful drug use and initiation and the introduction of new drugs and drug combinations suggest the value of raves as research sites. In particular, whether or not the reported dysphoria among MDMA users results from neurochemical changes, rather than adulteration, deserves investigation.

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PHENCYCLIDINE PHARMACOKINETICS IN NEONATAL PIGLETS

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The residual motor and cardiovascular (CV) effects of developmental exposure to phencyclidine (PCP) are poorly understood. In order to determine the relationship between blood levels of PCP and acute behavioral and CV effects in neonates, a pharmacokinetic study was conducted in piglets to characterize the disposition of PCP. Six piglets, eight to nine days old, were instrumented with a jugular cannula for dosing and blood sampling. 1.5 mg/kg (iv) PCP-HCl was administered and 11 5.0 ml blood samples were drawn over 0-24 hrs. Plasma levels of PCP were determined using GC-MS methods. Average plasma concentrations of 0.8±0.3 mg/L and 0.06±0.03 mg/L were observed five minutes and eight hours post-dosing. Model-independent pharmacokinetic results were as follows: AUC=139±6 mg/L x min, systemic clearance (Cl_s) = 0.012±0.03 L/min/kg, volume of distribution (V_{ss}) = 3.07±1.9 L/kg, $t_{1/2\beta}$ = 222±42 min and MRT = 256±56 min. PCP followed two compartment model kinetics with distribution and elimination half-lives of 2.7±1.3 min, and 2.5±1.9 h, respectively. The results suggest that the large increases in BP observed after iv administration of PCP could be related to high blood levels during the distribution phase of PCP whereas prolonged locomotor increases may be associated with the elimination phase in this animal model.

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EFFECTS OF POSTNATAL PHENCYCLIDINE EXPOSURE ON NMDA RECEPTOR DISTRIBUTION PATTERN

R. Sircar and H.-J. He

N-methyl-D-aspartate (NMDA) receptor plays an important role in developmental plasticity - cell migration, synaptogenesis and in the establishment of neuronal circuitry. Phencyclidine (PCP) and PCP-like drugs (MK-801, ketamine) act as non-competitive antagonists at the NMDA receptor. We have earlier shown that postnatal PCP treatment produced long-term changes in seizure susceptibility in rats. Here we report the effects of chronic postnatal PCP treatment on NMDA receptor distribution pattern. Pups were treated with PCP (5 mg/kg/day) for 11 days from postnatal days 5 to 15, intraperitoneally. Control pups received saline (1 ml/100 g body-weight). On postnatal day 21. groups of saline- and PCP-treated rats were sacrificed, their brains removed and immediately frozen in crushed dry ice. Twenty μ brain sections were cut and thaw-mounted onto gelatin-coated slides. Sections were incubated with [^{3}H]MK-801 in the absence and presence of excess nonradiolabeled MK-801, washed, dried, and juxtaposed against tritium-sensitive film. Quantitative densitometric analyses of the autoradiographic films indicate that postnatal PCP administration produced age-specific alterations in the [^{3}H]MK-801 distribution patterns. In day 21 PCP-treated rats, [^{3}H]MK-801 binding was increased in the hippocampal and septal areas whereas binding was decreased in the motor and sensory cortices, caudate-putamen and nucleus accumbens. Increased [^{3}H]MK-801 binding in the hippocampal and septal areas of day 21 PCP-treated rats, may be one of the mechanisms underlying the increased seizure susceptibility seen in these rats at this age.

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EVALUATION OF THE REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF DEXTROMETHORPHAN AND DEXTRORPHAN IN RHESUS MONKEYS

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Dextromethorphan (DM) is a well-known OTC antitussive agent. In addition, DM and its primary metabolite, dextrorphan (DO), have been shown to have neuroprotective and anticonvulsant properties possibly due to noncompetitive antagonism of NMDA receptors. Because DO may produce its NMDA antagonist effects at the phencyclidinc (PCP)-associated site and due to reports of DM abuse by humans, both were evaluated for PCP-like abuse potential in two animal models. The first study examined IV self-administration of DM (10 - 1000 µg/kg/infusion) and DO (10 - 100 µg/kg/infusion) in rhesus monkeys trained to lever-press for 10 µg/kg infusions of PCP during daily 1 hour sessions. Each DM and DO dose as well as saline was substituted for PCP for four consecutive sessions with values from the last three sessions being used for evaluation. Studies show that in five of the six subjects, at least one dose of DM maintained self-administration levels above saline levels but there was marked variation in responding between subjects as well as within subjects both over the four day substitution series and when doses were retested. One subject consistently had infusion levels similar to saline. For DO, in all subjects at least one dose maintained infusion rates well above saline levels and at or above PCP levels, showing that DO served as an effective positive reinforcer. In a second experiment, four rhesus monkeys were trained to discriminate 0.08 or 0.1 mg/kg PCP, im, from saline under a standard two-lever drug discrimination procedure. DM (0.3 - 10.0 mg/kg, im) yielded partial to full substitution in three of four subjects without altering response rates. DO (0.25 - 8.0 mg/kg, im) substituted completely for PCP in all four subjects at doses which did not greatly decrease response rates. Taken together, these data show that DM has some PCP-like effects in monkeys, but that they are more reliably produced by its metabolite, DO. Thus, DM may have some PCP-like abuse potential in humans but this potential may be associated with or potentiated by metabolism of DM to DO.

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DISCRIMINATIVE STIMULUS EFFECTS OF DEXTROMETHORPHAN

S. G. Holtzman

Dextromethorphan (DXM), the dextrorotatory isomer of levomethorphan, a typical morphine-like opioid, is devoid of most opioid activity. However, DXM is antitussive and has anticonvulsant and neuroprotective effects similar to those of phencyclidine (PCP) and other drugs that bind to the NMDA-type of glutamate receptor. It has only low affinity for the PCP recognition site but high affinity for a subtype of *sigma* site in the brain. The purpose of this study was to characterize pharmacologically the discriminative stimulus effects of DXM in the rat. Dextrorphan, a metabolite of DXM. has PCP-like discriminative effects. Therefore, DXM was injected by the SC route, which minimizes the formation of dextrorphan, and at a dose that did not substitute for PCP in rats discriminating IP injections of 2.0 mg/kg of PCP from saline.

In rats discriminating 30 mg/kg (SC) DXM from distilled water, DXM was slightly more potent SC than it was IP (ED_{50s} for DXM-appropriate lever selection: 8.5 and 14.9 mg/kg, respectively). In contrast, in PCP-trained rats, DXM IP substituted for PCP (ED_{50}: 21.7 mg/kg) but as much as 100 mg/kg of DXM SC had little PCP-like activity. The DXM-trained rats generalized dose-dependently and completely to PCP and to other PCP-like drugs (dizocilpine. dextrorphan), but selected the vehicle-appropriate lever when tested with sigma-site ligands (pentazocine. ditolylguanidine), mu-opioid agonists (morphine, codeine), naltrexone, and non-opioid antitussives (caramiphen, carbetapentane).

These results show that the discriminative effects of SC DXM in the rat are PCP-like and are not mediated by the sigma-binding site or the mu-opioid receptor, or by conversion to dextrorphan. The discriminative and other PCP-like effects of DXM could be mediated by a site on the NMDA-receptor complex that is near, but different from, the PCP-recognition site.

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SIGMA RECEPTOR-MEDIATED MORPHOLOGICAL AND CYTOTOXIC EFFECTS ON PRIMARY CULTURES OF NEURONS

B. J. Vilner and W. D. Bowen

Sigma ligands specifically produced marked changes in the morphology of C6 glioma cells and were cytotoxic upon continued exposure (Vilner and Bowen 1993; Vilner *et al.,* in press). Over 30 compounds which lack sigma affinity but which are ligands for other receptors, enzymes, or ion channels were without significant effect, confirming sigma specificity. Robust effects of sigma ligands over a three day observation period were observed in the range of 30 - 300 uM, with 30 uM being the threshold dose. However, time-dose relationship studies suggested that lower concentrations might produce effects upon longer exposure times. Such studies are precluded with rapidly dividing cell lines since cells will overgrow the system, making gradual effects of the drugs impossible to assess. Also, it was necessary to examine the effects of sigma Iigands in a model system more closely resembling the brain. Thus, we examined the effects of sigma ligands on primary culture of dissociated cells from the rat nervous system. Cerebellum and superior cervical ganglion were obtained from rat pups of age six to eight days and one to two days, respectively. Cortex and spinal cord were obtained from rat embryos of 16-18 days and 12-14 days, respectively. Cells were prepared and cultured using standard techniques for dissociated culture. Over an observation period of 21 - 35 days, sigma ligands were found to produce alterations in the morphology of cells from all of these regions. Similar to observations with C6 glioma cells, initial effects involved alterations of processes, followed by cell rounding or extreme swelling, and cell death. Neurons appeared to be more sensitive than non-neuronal cells which were present in the cultures. Importantly, effects were observed at much lower ligand concentrations compared to C6 glioma cells. For example, in cerebellum, BD737, reduced haloperidol. and fluphenazine produced initial effects at 10 uM after seven days. Effects were seen at only 3 uM after 21 days. BD1008, SH344, LR172, and JL-II-147 (sigma-active aryl ethylenediamines) produced rounding and extreme enlargement of spinal cord neurons after 15 days at a concentration of 3 uM. (+)-Pentazocine, which had only weak effects on C6 glioma cells at 300 uM after 3 days, produced effects on primary cells at 10 - 30 uM after 21 days of exposure. Compounds lacking sigma affinity produced no effects at 30 - 100 uM (except glutamate, as expected). Also, as with C6 glioma cells, adjusting the pH of the medium from normal (pH 7.2-7.4) to acidic (pH 6.5-6.7) was found to almost completely protect cells from the cytotoxic effects of sigma ligands. These results suggest the possibility that sigma receptor-mediated damage might occur to CNS neurons or glia during chronic treatment with typical neuroleptics such as haloperidol. Since sigma receptors occur in high density in certain motor nuclei of the brain, this damage might contribute to neuroleptic-induced motor disorders such as tardive dyskinesia. It may thus be possible to design sigma receptor blockers to attenuate these effects.

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PREPARATION OF AN AFFINITY COLUMN FOR THE PURIFICATION OF *SIGMA* RECEPTORS

L.-I. Tsao and T.-P. Su

An affinity column was prepared for the purification of *sigma* receptors solubilized from rat liver membranes. The ligand chosen was a haloperidol metabolite, 4-(4-chlorophenyl)-4-hydroxypiperidine, **B,** which possesses moderate affinity at *sigma* receptors without affinity for the dopamine D_2 receptor (Bowen *et. al.,* 1990). **B** was coupled to an arm (*N*-BOC-6-aminocaproic acid) in the presence of 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotrazole in *N,N*-dimethylformamide. The protecting group BOC was then removed with 50% (v/v) trifluoroacetic acid in methylene chloride. The resulting compound was then reduced with lithium aluminum hydride in tetrahydrofuran to form the final product, 1-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-6-aminohexane, **D. D** was successfully coupled to Sephadex G-25 via a cyanogen bromide activation (36 mg D covalently linked to 1 g Sephadex). The Ki values of B and D for inhibiting [^{3}H](+)SKF-10047 binding to solubilized *sigma* receptors were 628 ± 45 nM (n = 4) and 2347 ± 429 nM (n = 4) respectively. The affinity column retained a 50% (± 5%, n = 5) of the binding activity when solubilized *sigma* receptors were passed through it. The control column (Sephadex only) retained a 28% (± 3%, n = 5) of the activity. No appreciable amount of protein was retained in either column. Thus, it is possible that the affinity column may have retained a net of about 20% of solubilized *sigma* receptors applied to the column and that, judging from the minimal amount of protein retained by the column, a significant magnitude of purification may have been achieved using this column. Future experiments will attempt to enhance the retention of *sigma* receptors in the column, and their elution from the column. The materials thus obtained will be characterized.

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DIFFERENTIAL SOLUBILIZATION OF SIGMA-l AND SIGMA-2 RECEPTORS FROM RAT LIVER MEMBRANES

C. Torrence-Campbell and W. D. Bowen

We have previously demonstrated that rat liver membranes contain a high density of both sigma-1 and sigma-2 receptors (Bruce *et al,* 1990; Hellewell *et al.,* 1994). These sites are pharmacologically distinct and reside on distinct polypeptides of M_r = 25 kDa and 21.5 kDa, respectively by sodium dodecyl sulfate polyacrylamide gel electrophoresis after photoaffinity labeling with [^{3}H]azido-DTG. In an attempt to purify these receptors, we have investigated the effect of solubilization. Rat liver membranes (P2 membranes) were solubilized in 10 mM Tris-HCl, pH 7.4 containing 7 mM CHAPS (105,000 x g supernatant = extract 1). The 105,000 x g pellet (pellet 1) was washed once, and then extracted a second time, giving extract two and pellet two. The various resulting fractions were assayed for sigma binding characteristics, using [^{3}H](+)-pentazocine to label sigma-1 sites and [^{3}H]DTG in the presence of 1 uM dextrallorphan to label sigma-2 sites. Assays were carried out in a final volume of 0.5 ml with 100-180 ug protein for 120 min at 25°C; with CHAPS extracts, the final detergent concentration was 0.35 mM. Non-specific binding was determined with 10 uM haloperidol. Both of the CHAPS extracts and resultant pellets contained sigma-1 and sigma-2 receptors, as indicated by pharmacological profiles upon competition studies. While others have solubilized sigma-1-like sites from various tissues, including rat liver (McCann and Su 1991), this to our knowledge is the first demonstration of soluble sigma-2 receptors. The Kd and Bmax values for sigma-1 activity in the original P2 membranes were 8.3 ± 0.7 nM and 5,333 ± 572 fmol/mg protein; Kd and Bmax for sigma-2 activity were 19 ± 0.17 nM and 9,190 ± 800 fmol/mg protein. There were no significant changes in the affinity of the two sites in the subsequent soluble and particulate fractions. However, while the sigma-1 and sigma-2 Bmax values in extracts and pellets were generally on the same order as those of P2 membranes, the actual ratio of the Bmax values for sigma-2 to sigma-1 sites varied markedly across fractions. The Bmax ratio of sigma-2/sigma-1 binding in extract one and extract two was 0.86 and 0.68 respectively, lower than the ratio of 1.7 in the original P2 membrane fraction. However, the ratio in pellet two was 3.8, twice that of the original P2 membranes. Furthermore, the Bmax value for sigma-1 sites in pellet two did not change, whereas the sigma-2 Bmax increased 1.8-fold relative to the original P2 membranes. Preliminary experiments using Triton X-100 and cholate gave similar results. Taken together, these data suggest that sigma-2 sites are somewhat more resistant to solubilization relative to sigma-1 receptors and other membrane proteins and therefore become slightly enriched in the particulate fractions. This may indicate different modes of association with the cell membrane for sigma-1 and sigma-2 receptors.

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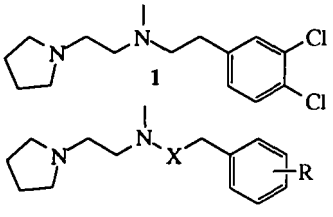
SYNTHESIS AND EVALUATION OF ARYL-SUBSTITUTED N-(ARYL-ETHYL)-N-METHYL-2-(1 PYRROLIDINYL)ETHYLAMINES FOR SIGMA RECEPTOR AFFINITY

Y. Zhang, W. D. Bowen, W. Williams, X. S. He, B. R. de Costa, and K. C. Rice

Recent studies have shown that the sigma-2 subtype of sigma receptor plays an important role in mediating the motor effects of sigma ligands. Data from previous studies revealed that the arylethylenediamine σ ligand **1** possessed high affinity for both σ_1 and σ_2 receptors. It had also been shown that the σ_1 and σ_2 binding are greatly affected by the nature and orientation of the aromatic halogenation of that series of compounds. It was therefore of interest to synthesize a series of class **1** compounds with variation on aromatic substitutions (2-16) to study their sigma binding activity.



2. X=CO, R=*o*-OMe; **3.** X=CO, R=*m* -OMe
4. X=CO, R=*p*-OMe; **5.** X=CO, R=*o* -NO_2
6. X=CO, R=*m*-NO_2; **7.** X=CO, R=*p* -NO_2
8. X=CH_2, R=*o*-OMe; **9.** X=CH_2, R=*m* -OMe
10. X=CH_2, R=*p*-OMe; **11.** X=CH_2, R=*o* -NO_2
12. X=CH_2, R=*m*-NO_2; **13.** X=CH_2, R=*p* -NO_2
14. X=CH_2, R=*o*-NH_2; **15.** X=CH_2, R=*m* -NH_2
16. X=CH_2, R=*p*-NH_2

No	σ_1	σ_2	No	σ_1	σ_2	No	σ_1	σ_2
2	5457±686	3170±144	7	869±3.5	317±144	12	6.37±1.63	95.2±0.7
3	3101±20	1114±55	8	15.7±2.1	144±0.89	13	4.26±0.92	62.7±0.1
4	2223±61	1215±95	9	23.8±1.7	209±22	14	291±38	640±25
5	736±121	1494±129	10	30.3±1.4	256±2.3	15	579±35	2235±260
6	1854±177	539±0.76	11	7.74±0.88	311±3.6	16	276±13	973±77

Binding data show that, overall, the ethylenediamine compounds **8-16** had higher affinity than the acetamides **2-7** at both σ_1 and σ_2 sites labled by [^{3}H]-(+)-pentazocine and [^{3}H]-DTG in the presence of dextrallophan respectively. The nitro-substituted compounds possessed higher potency than the corresponding methoxy or aromatic amino compounds, indicating that an electron-withdrawing group on the aromatic region may generally favor sigma binding affinity. Among the ethylenediamine series, **11-13** showed the highest potency and selectivity at σ_1 binding site. Interestingly, the arylacetamides were more selective on σ_2 binding than the diamine series, with *m*-NO_2 amide **6** nearly 3.5 fold more selective at σ_2. This high preference on σ_2 binding is probably a result of structural rigidity from an amide function. On the other hand, the carbonyl function may allow molecular interaction between the σ ligands and a group present in the σ_2 receptor which does not occur at the σ_1 receptor site. Further studies are currently underway to improve σ_2 affinity while maintaining selectivity.

REFERENCES: Available upon request of senior author.

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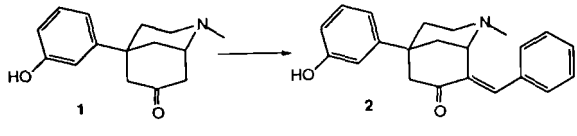
INTRODUCTION OF AN E-8-BENZYLIDENE MOIETY IN THE 2-METHYL-5-PHENYLMORPHAN SYSTEM ABOLISHES OPIOID EFFECTS AND AFFORDS A NEW CLASS OF POTENT SIGMA RECEPTOR LIGANDS

C. M. Bertha, M. V. Mattson, J. L. Flippen-Anderson, R. B. Rothman, H. Xu, X.-Y. Cha, K. Becketts, and K. C. Rice

After several years of intensive and conflicting research, the σ receptor was classified as a non-opioid entity independent from the PCP binding site. This receptor is widely distributed in the brain and the periphery and has been implicated in many physiological processes. It has been shown that many antipsychotic drugs have affinity for σ receptors. Whereas some believe that these receptors are directly responsible for the therapeutic action of neuroleptics and antipsychotics, others have contended that σ receptors contribute to the motor side-effects associated with these drugs. Suppport for the connection with motor effects comes from studies that show motoric alteration upon microinjection into sigma receptor rich brain motor nuclei. The determination of the structure and function of the σ receptor and its physiological role(s) has been hampered by the unavailability of selective ligands.



We have developed a new class of selective σ receptor ligands that are E-8-benzylidene derivatives of the synthetic opioid 2-methyl-5phenylmorphan. The derivatives can be prepared by reaction of the appropriate aldehyde under Claisen-Schmidt conditions with the known 2-methyl-5-(3-hydroxyphenyl)-morphan-7-one (**1**). The attachment of the E-8-benzylidene group to the (+)-(1,5S)-**1** omer producing (-)-(1S,5S)-**2** decreased the affinity at μ receptors by 11-fold while increasing the affinity for σ receptors by 81-fold (K_i = 9.4 nM). Compound (-)-**2** has an affinity for the σ receptor that is about 140-fold greater than its enantiomer indicating an enantioselective interaction. In addition, (-)-**2** has low affinity for PCP sites (> 100 μM) and muscarinic receptors (7.4 μM). Thus, these compounds constitute a new class of selective σ ligands and should prove useful as tools for the further elucidation of the structure and function of these receptors.

REFERENCES:

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MURINE PERITONEAL MACROPHAGE TUMORICIDAL ACTIVITY IS INHIBITED BY INHALED ISOBUTYL NITRITE

L. S. F. Soderberg and J. B. Barnett

Isobutyl nitrite is a drug of abuse popular among male homosexuals. Frequent abuse of nitrite inhalants has been correlated with seropositivity to human immunodeficiency virus (HIV) (Seage et al., 1992) and with the incidence of Kaposi's sarcoma among AIDS patients (Haverkos *et al.,* 1985). To determine if inhalants were immunotoxic, mice were exposed to 900 ppm isobutyl nitrite in an inhalation chamber 45 min/day for 14 days. When mice were tested three days later, they had compromised T-dependent antibody (32.2 + 3.5% of control) and cytotoxic T cell responses (53.6 + 2.1% of control). In addition, such exposure impaired the tumoricidal activity of activated peritoneal exudate macrophages (41.0 + 12.8% of control) as measured using a standard 51Cr-release assay with P815 tumor cells. This reduction in tumoricidal activity was not due to reductions in tumor cell binding (98.6 + 5.1% of control), but did correlate with inhibition of inducible nitric oxide (71.6 + 1.2% of control). Similar exposures did not inhibit NK cell mediated cytotoxicity (99.0 + 2.8% of control). The macrophage tumoricidal activity of mice exposed to isobutyl nitrite remained compromised for at least seven days following the termination of exposures. It is possible that inhalant abuse, by compromising three major immune mechanisms. could reduce resistance to infectious diseases, including HIV and the putative agent of Kaposi's sarcoma.

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ABUSE POTENTIAL EVALUATION OF VOLATILE SOLVENTS: A FIRST ATTEMPT

R. L. Balster, E. B. Evans, M. E. Tokarz, J. Hamilton, and S. E. Bowen

We have hypothesized that the abuse potential of certain types of inhalants could be evaluated in animals by determining the overlap in their profile of behavioral effects with that of CNS depressant drugs and other depressant-like abused inhalants. For our first attempt to evaluate a solvent with an unknown abuse potential we tested ISOPAR E. ISOPAR E is a mixture of predominately C8-C9 isoparrafinic hydrocarbons that is being used more and more frequently as a solvent in industrial and consumer products, including typewriter correction fluids. Nothing is known about the potential for abuse of products containing this solvent. We compared the effects of ISOPAR E and the abused inhalant 1,1,1-trichloroethane (TCE) in six procedures. All the animal work was done in SWISS mice. 1) ISOPAR E was less volatile than TCE. 2) ISOPAR E produced a somewhat different profile of effects than did TCE as assessed with a functional observational battery. 3) Unlike TCE. ISOPAR E did not affect performance on a test of motor coordination. 4) TCE and ISOPAR E produced concentration-related decreases in fixed-ratio performance with recovery from TCE being somewhat more rapid. 5) ISOPAR E produced cross dependence in TCE-dependent mice. 6) Both TCE and ISOPAR E produced substantial levels of ethanol-lever responding in a drug discrimination procedure, although the ethanol-like effects of ISOPAR E only occurred at response rate decreasing concentrations. Overall, there was a poorer separation of behavioral and lethal concentrations for ISOPAR E than for TCE. Although a somewhat different profile of behavioral effects was obtained with ISOPAR E and TCE, we cannot say with certainty if enough similarities may exist with abused inhalants to predict that ISOPAR E would be subject to depressant-like abuse. Nonetheless, the feasibility of preclinical abuse potential of inhalants is demonstrated.

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THE EFFECTS OF ABUSED INHALANTS ON LOCOMOTOR ACTIVITY IN MICE

S. E. Bowen and R. L. Balster

The present study was designed to determine if acute inhalation of vapors from various classes of volatile compounds differed in their ability to produce excitatory and/or depressant effects. Using locomotor activity as the dependent measure, concentration differences and magnitude of effect were determined for the following six solvents: toluene (250-8,000 ppm), 1,1,1-trichloroethane (500-14,000 ppm), methoxyflurane (100-6000 ppm), isoamyl nitrite (150-900 ppm), flurothyl (100-900 ppm), and ISOPAR E (1000-4000 ppm). Test sessions lasting 30 minutes took place daily in static exposure chambers with solvent exposure occurring twice a week (Tuesday and Friday). Toluene, 1,1,1-trichloroethane, and methoxyflurane, three vapors that have been characterized as having depressant properties, initially produced concentration dependent increases in locomotor activity with methoxyflurane displaying the greatest increases. Biphasic results were obtained with higher solvent concentrations in that locomotor activity which was initially increased by solvent exposure was followed by a decrease in activity as the test session continued or as concentration levels increased. Conversely, only decreases in locomotor activity were observed for both flurothyl and isoamyl nitrite, despite the fact that flurothyl is a convulsant vapor at higher concentrations. ISOPAR E, a newer commercial solvent with unknown behavioral effects, produced concentration dependent increases in motor activity similar to that of the "depressant" vapors but without biphasic effects. These data suggest that qualitative and quantitative differences exist in the effects of various vapors and that locomotor behavior is an effective tool for discerning these differences. These results are also consistent with other data showing a common profile of behavioral effects of certain abused inhalants and anesthetics.

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EFFECTS OF DIFFERENT DOSES OF NALOXONE ON THE SUBJECTIVE AND PSYCHOMOTOR EFFECTS OF NITROUS OXIDE IN HUMANS

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Naloxone, an opiate antagonist, attenuates nitrous oxide-induced antinociception (Berkowitz *et al.,* 1977; Yang *et al.,* 1980; Quock *et al.,* 1993). This suggests that the analgesic effects of nitrous oxide are at least in part mediated via the opioidergic system. In the present investigation, we tested the hypothesis that naloxone, an opiate antagonist, attenuates the mood-altering (*i.e.,* subjective) and psychomotor-impairing effects of nitrous oxide. Two double-blind, randomized trials, using three intravenous doses of naloxone or saline-placebo and 30% nitrous oxide in oxygen or 100% oxygen-placebo were conducted in healthy volunteers whose ages ranged from 21-35 years. Experiment One (N=9) tested a range of naloxone doses used clinically to reverse opiate-induced respiratory depression (0, 0.01, 0.1, 1.0 mg/70 kg) and Experiment Two (N=8) included a dose approximately 25 times higher than that needed to reverse opiate-induced respiratory depression (0, 1.0, 3.0, 10 mg/70 kg). Ten minutes into a 35 minute inhalation period in which subjects were inhaling 30% nitrous oxide or 100% oxygen, a challenge dose of naloxone (or saline) was given. Nitrous oxide increased VAS ratings of “feel drug effect,” “carefree,” “drunk,” “sedated,” and “high,” and decreased psychomotor performance in both experiments. Naloxone had no effects by itself in either experiment, and for the most part, did not significantly interact with nitrous oxide-induced changes in mood or psychomotor performance. These results suggest that the opioidergic system is not involved in mediating the subjective effects of nitrous oxide.

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ADDICTION RESEARCH IN HISTORICAL PERSPECTIVE

C. J. Acker

BUILDING A DRUG DEVELOPMENT INFRASTRUCTURE: In 1928, the National Research Council's Committee on Drug Addiction launched a project to solve the opiate addiction problem by developing a nonaddicting opiate analgesic to replace morphine in medical practice. In the 1920s, cooperative arrangements among U.S. academic scientists and pharmaceutical firms to develop new, clinically useful drugs were being formed. The Committee on Drug Addiction created an early example of chemists, pharmacologists and clinicians working together toward a single therapeutic goal. These scientists were also united by the aim of studying structure-activity relationships in physiologically active compounds. Both in its scientific aims and in its institutional-layout, the Committee on Drug Addiction project was inspired by the work of Paul Ehrlich in the first decade of the twentieth century. Ehrlich argued for the existence of drug receptors in the body, and his Institute for Experimental Therapy in Frankfort, Germany, exemplified cooperative work among chemists and pharmacologists.

TESTING FOR ADDICTIVENESS: A METHODOLOGICAL HURDLE: Organic chemist Lyndon F. Small headed the Drug Addiction Laboratory at the University of Virginia, which produced hundreds of compounds for testing. Compounds went from the chemical laboratory to the University of Michigan, where Nathan B. Eddy headed a group of pharmacologists. Compounds were initially screened for toxicity and analgesic effect. No sure method was known for determining addictiveness. When Dihydrodesoxymorphine-D (Desomorphine) was shown to be a strong analgesic with low toxicity, Eddy began chronic administration to cats, dogs and monkeys to test for addictiveness. Results regarding tolerance or withdrawal symptoms were inconclusive. Cornell pharmacologist Robert Hatcher suggested to the Committee on Drug Addiction that any drug which suppressed the opiate withdrawal syndrome was probably also addictive. Working with addicted federal prisoners, Public Health Service physician Clifton Himmelsbach devised the morphine substitution test based on Hatcher's suggestion. First, Himmelsbach quantified the morphine withdrawal syndrome. He ranked symptoms by severity and plotted their onset against time. To test Desomorphine for addictiveness. Himmelsbach first stabilized addicts on morphine doses sufficient to prevent withdrawal symptoms. Then he switched them to Desomorphine. Only a few mild symptoms appeared. When he withdrew Desomorphine, the resulting withdrawal syndrome closely matched that for morphine. Nathan Eddy duplicated this procedure with monkeys, with similar results. Though not used clinically, Desomorphine was important in devising the first reliable test for addictiveness in opiates.

METOPON: JOINING CLINICAL UTILITY AND SCIENTIFIC VALIDATION: Metopon was the first compound from Lyndon Small's laboratory to be developed as a clinically useful analgesic. It was clearly less addictive than morphine. Subjects developed mild to moderate withdrawal symptoms when they were switched from morphine to Metopon. When Metopon was withdrawn, symptoms were significantly less severe than those associated with morphine withdrawal. Metopon was used clinically as an analgesic until the early 1950s. More importantly, it had shown that analgesic potency and addictiveness could vary independently of each other. This finding supported the view that a drug's activity was a function of its molecular structure. THE MOVE TO NIH: By 1939, when Committee on Drug Addiction group moved to the National Institute of Health, the methods of "classical pharmacology" had been well developed for opiates and their derivatives. Creating dose-response profiles for compounds and modifying chemical structure to enhance or diminish known drug effects were established goals. The move to NIH eliminated the geographical separation between groups. It also marked a shift from Rockefeller Foundation funding to federal funding. The Committee on Drug Addiction continued under National Research Council auspices, undergoing several name changes, until 1976, when it became an independent scientific organization. In 1991, it assumed its present form as the College on Problems of Drug Dependence, a scientific membership organization.

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REPORTING AND REPRESENTATION OF SOCIODEMOGRAPHIC GROUPS IN COCAINE PHARMACOTHERAPY STUDIES

D. A. Gorelick and I. D. Montoya

Cocaine abuse affects all segments of the U.S. population, but the representation of various sociodemographic groups as patients in studies of cocaine abuse pharmacorherapy has never been evaluated. In light of recent FDA and NIH regulations requiring adequate representation of women and minorities in clinical trials, we assessed sociodemographic representation in 61 reports of outpatient pharmacotherapy for cocaine abuse published in refereed, English language journals between 1983 and 1993. Representativeness was compared with the epidemiology of frequent cocaine use in the 1990 NIDA National Household Survey of Drug Abuse (NIDA-HS). There were 41 (67.2%) open-label, 19 (31.1%) double-blind, and one (1.6%) unspecified reports, using 30 different pharmacologic treatments. Seven (11.4%) studies did not report on age, two (3.2%) omitted sample size, nine (14.7%) gender, 24 (39.3%) race, 46 (75%) education, 49 (80%) employment status, 55 (91%) sociodemographic status. No article reported ethnic/cultural characteristics. There was under-representation of 12-25 year olds, Hispanics, and the South and West areas of the U.S.; and over-representation of 26-35 year olds, unemployed, high school or college graduates, and the Northeast. These findings show that important sociodemographic data about subjects is often not reported, and raise issues of the quality of research reports, generalizability of results, social equity, and accessibility for certain groups in cocaine abuse pharmacotherapy research.

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ETHNIC AND GENDER FACTORS IN ADDICTION RESEARCH

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There is an increased need for addiction researchers to enhance their understanding of ethnic and gender factors to provide adequate solutions to the problem of drug abuse. For example, federally funded research now mandates a study design with ethnic and gender representation appropriate to the goals and objectives of the proposed project. Certain scientific practices have, however, acted to restrict progress. One practice with severe negative consequences was the conduct of the Tuskegee experiment of untreated syphilis in the negro male, a major source of African American frustration and discontent with the American health and scientific enterprise. Another restriction was the utilization of exclusively male populations in intervention or research projects. We examined the forces that dissuade the participation of African American females in substance abuse treatment and addiction research. Results of a literature review and initial findings from a survey of African American females indicate that the distrust of health professionals and researchers continues. In addition, gender must be taken into account as there are fundamental role, identify, and self-esteem issues that interact with the overall level of ethnic discontent and distrust.

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ACT UP/NEW YORK'S NEEDLE EXCHANGE PROGRAM

G. Elbaz

"Dead addicts cannot be treated" summarized the activists' philosophy. That philosophy motivated the creation of the ACT UP's Needle Exchange Program (A.U.N.E.P) in February of 1990. The same year, drug users represented an increasingly large portion of AIDS cases. Activists involved in the A.U.N.E.P were themselves ex- or recovering IV users. They included Spanish speakers, men and women of color, HIV+ individuals, gay men and lesbians. With a budget of $17,000 every six months, they operated a "roving" team in the West Bronx, East Harlem, Lower East Side and Brooklyn, reaching out to over 1,000 drug users each week. Activists provided clean needles, bleach kit, information on safe drug use, availability of rehabilitation centers, safe sex information as well as condoms. Provided needles were marked with a specific color indicating the site of the Exchange, and a tally of the returned needles was kept. The return rate was about 60%. The A.U.N.E.P generated much controversy. New York State is one of 12 states that require prescription for the sale of drugs, and activists faced up to three years in prison. Additionally, African-American community leaders staunchly opposed the A.U.N.E.P. Using civil disobedience, activists planned to be arrested on the 2nd of March, 1991. A few months later, they used their trial--with the help of the media--as public forum to expose the issue and raise public awareness. Using the "public health necessity" defense, and supported by many drug experts, activists were acquitted. In July of 1992, the State of New York gave a special public health emergency waiver for the distribution of clean needles. Presently, the American Foundation for AIDS Research (AmFAR) and the AIDS Institute provide funding for the Needle Exchange Programs throughout the State of New York.

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ACTIVISTS AND SERVICE PROVISION: AN ANALYSIS OF AN ILLEGAL NEEDLE EXCHANGE

K. D. Henson

This paper, based on participant-observation research with an underground needle exchange organization in Los Angeles county, focuses on the conflicting agendas of advocacy and service work within an activist staffed and run program. The exchange, founded as a working committee of the AIDS activist group ACT UP/Los Angeles in the summer of 1992, became an independent organization in late 1993. Operating mobile sites one afternoon and one evening per week, the exchange reaches less than 1% of Los Angeles' injection drug users.

While the activists were highly committed, the exchange confronted organizational problems and resource deficiencies which constrained and/or compromised attempts to meet their stated service goals of providing injection drug users with access to clean works and treatment. In particular, problems in program implementation and operation such as the rapid introduction, interruption, and discontinuation of exchange sites and/or the frequently short and inconsistent hours of operation hindered efforts to provide access to sterile injection equipment. In addition, inadequate knowledge of the treatment industry and absent linkages with gatekeepers hampered the successful operation of the exchange as a "bridge to treatment" for injection drug users.

The problems encountered by this underground exchange indicate that effective needle exchange programs need consistent and appropriate sites, staffing, operating hours, and funding. The ability of needle exchange programs to focus scarce resources on the primary goals of harm reduction, however, is constrained by current state and local law.

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ADULT ATTENTION DEFICITS DISORDER AND SUBSTANCE ABUSE: A SELECTIVE REVIEW OF MMPI FINDINGS

A. M. Horton, Jr.

Attention Deficit Disorder (ADD) is usually considered as a disorder that first arises in children. In brief, these children are considered to have problems with motor activity and paying attention. There has been a realization that contrary to previously held notions, all ADD symptoms are not outgrown as the child becomes an adult (*i.e.,* motor overactivity does appear to decline) but that ADD persists into adult life and also may result in a higher incidence of drug abuse disorders. Recent research studies have attempted to explore various aspects of adult attention deficit disorder and substance abuser subtypes. One method has been to investigate personality differences. The majority of these studies have used the Minnesota Multiphasic Personality Inventory (MMPI), the best validated objective measure of personality available today. This paper selectively reviews this literature on adult ADD from the standpoint of treatment planning issues. Many of these studies have identified differences in substance abuser personality functioning as measured by MMPI clinical scale profiles. Adult ADD-diagnosed groups have demonstrated clinically significant levels of psychopathology on the MMPI profiles. In one important study, an alcoholic group with ADD and an alcoholic group with ADD and drug abuse had no significant differences between the groups. On the other hand, the two-point MMPI codes for a group of alcoholics with ADD but not drug abuse = 4 - 8 (*i.e.,* Pd and Sc), and for a group of alcoholics with both drug abuse and ADD = 4 - 8 (*i.e.,* Pd and Sc). Regardless of whether or not the subject groups contained drug abusers or not, the ADD-diagnosed groups demonstrated clinically significant levels of psychopathology on the MMPI profiles. Relative to the implications of the group MMPI profiles some comments seem warranted. Both of the groups that included ADD alcoholics or ADD alcoholics and drug abusers had 48/84 profiles. This MMPI two-point code suggests a person who is angry, rebellious, and self-defeating. These rather dramatic findings suggest a particular ADD MMPI profile may emerge regardless of whether or not the subject is a drug abuser. These results would suggest that ADD symptoms may be an important factor to consider when selecting treatment options for substance abusers.

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KAPPA FAILS TO CORRECT FOR CHANCE AGREEMENT WHEN DRUG-USE SELF-REPORTS ARE VALIDATED BY A SINGLE URINE SAMPLE

S. J. Robbins and R. N. Ehrman

In validation studies of drug use self-reports, the kappa statistic is commonly used to evaluate agreements between the results of urinalysis and subject reports. Kappa is defined as $(p_o - p_e) / (100 - p_e)$ where p_o represents the percent of agreements observed and p_e represents the percent of agreements expected by chance. In a typical calculation of kappa, each subject contributes a single data point representing either agreement or disagreement between a self-report and a urinalysis sample. However, the use of this score as an index of subject accuracy is misleading. In general, kappa will provide an overestimate of subject accuracy whenever symmetrical numbers of subjects have high and low levels of drug use.

Imagine that multiple observations are collected from each subject and that all subjects accurately estimate their frequency of drug use. If levels of drug use are uniformly high or low for all subjects, then a high number of agreements between individual self-reports and urine samples will be expected by chance. However, if some subjects have very high rates of use and others have very low rates, then the rate of use across subjects at a given point in time will be intermediate and pe will be low. Kappa will be much higher in the latter case than in the former. Consider two groups of subjects with identical levels of accuracy as measured by; a) their accuracy at matching their frequency of drug-use self-reports to the frequency of drug-positive urines; and b) their level of exact agreement between individual self-reports and urinalysis samples. If one group contains only subjects with high rates of use, and the other group contains both abstinent subjects and relapsing subjects, then different kappa scores will result despite identical levels of individual accuracy. Both simulations and empirical observations support this claim.

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COCAINE ADDICTION AS A NEUROLOGICAL DISORDER

M. D. Majewska

Chronic cocaine use seems to be associated with lasting or permanent neurological and psychiatric deficits. Cocaine abuse can lead to seizures, neuropathies. cerebral infarction, hemorrhages, multifocal or global cerebral ischemia and brain atrophy, secondary to myocardial infarction. Cocaine abusers show lasting deficits in cerebral circulation and glucose metabolism, consistent with hypfrontality, and psychiatric abnormalities, such as paranoia, depression, anhedonia, apathy and cognitive deficits. Several symptoms observed in cocaine abusers suggest deficiencies in dopamine. Preclinical observations after multiple administrations of cocaine revealed deficiencies in dopamine turnover and transmission with loss of dopamine uptake sites in the nucleus accumbens and frontal cortex. Continuous administration of cocaine in rats (3-5 days) resulted in axonal degeneration extending from the habenula along the fasciculus retroflexus toward ventral tegmentum (VTA). Clinical observations in PET and post-mortem studies revealed decreases in the density of dopamine receptors and transporters, suggesting possible degeneration of dopaminergic nerve-terminals. The mechanisms for the neurotoxic effects of cocaine may be synergistic actions between metabolites of catecholamine autooxidation, oxygen free radicals, and glutamate.

Cocaine-induced neuropathies may contribute to the development of neurochemical cocaine-dependency and be responsible for the high rate of relapse. Some pre-existing neuropathies may also increase individual's vulnerability to stimulant addiction. This notion is supported by preclinical findings showing that lesions of dopamine neurons in the VTA increases amphetamine self-administration in rats. Hence, it seems logical to include addiction to cocaine/stimulants within the category of neurological disorders. Consequently, the selection of effective medications should focus on repairing the neurological damage and/or compensating for neurochemical deficiencies.

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RAPID COMPUTERIZED DETERMINATION OF PUPIL DIAMETER FROM IMPERFECT VIDEO IMAGES

H. L. Kaplan

Pupil constriction (miosis) is an important measure of acute opiate effects. Using existing hardware to digitize a video image of the eye under infrared illumination, we developed new software to fit an ellipse (not a circle — the pupil may be viewed off-axis) to the pupil image:

Step 1: Convert the 480x512 pixel, grey scale digitized image of non-square pixels to 192x256 square pixels, tally the histogram of pixel intensities, and merge adjacent histogram bins to eliminate minor extrema and isolate one large peak on the left; call the upper boundary the dark/light threshold.

Step 2: Divide the image into squares, identify the squares containing at least one dark pixel, and find the largest connected set of squares.

Step 3: Find the edges of the dark region within the connected set of squares, find the medians of the centerpoints of the horizontal and vertical dark pixel spanning lines, and take the intersection of the medians as the centroid.

Step 4: From the centroid. select points at equal angles around the boundary as targets for the ellipse fit, and estimate starting values for its parameters.

Step 5: Iteratively refine the fitted ellipse, evaluating it on the best-fitting 30 out of 40 boundary points in order to reject interruptions (such as reflections of the infrared LEDs), using the Nelder and Mead simplex algorithm because the goodness-of-fit statistic is a non-linear function of the parameters.

Step 6: Take the major axis of the ellipse as the pupil diameter, after adjusting for the calibration of the optical system.

Including manual image adjustment, execution of the fitting algorithm, image compression to facilitate subsequent halftone printing, and disk storage, this process takes well under one minute, making it suitable for studies of opiate analogues with short durations of action.

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COMPARISON OF STATISTICAL METHODS FOR ANALYZING REPEATED MEASURES DATA

L.J. Felch, M.E. Di Marino, and K.C. Kirby

There are a number of techniques which can bc used to analyze within session time course effects of drugs, such as raw scores, peak and area under the curve. The present study uses meta-analysis to examine the statistical power of 13 techniques in six studies of precipitated opioid withdrawal.

Power analysis is crucial to the planning and design of efficient and effective studies. Information on effect sizes derived from meta-analyses can be used to provide good estimates of power for future research. This study also illustrates a method of meta-analysis that can be used to estimate effect sizes for power calculations.

A range of measures was chosen for the meta-analysis including subject ratings and observer ratings of subjects' responses to drug, as well as physiological measures. Data were analyzed by a number of different methods including raw scores, change from baseline, four methods of calculating peak response, three methods of calculating area under the curve, slope, and variance. Data were analyzed separately for each study by repeated measures ANOVA with Huynh-Feldt corrections for violations of the sphericity assumption. Effect size was calculated for each F-test conducted. A meta-analysis was then conducted comparing the effect sizes for each study using a repeated measures ANOVA with variable and method of data analysis as the factors. Tukey's posthoc tests were conducted to assess differences in power among methods of data analysis.

Overall, there were no significant differences in effect size for peak, area under the curve, or the condition effect for the time course analyses. However, effect sizes for subject-rated measures were significantly larger for peak analyses (E.S.=0.90); for physiological measures, the condition effects for the time course analyses had the largest effect size (E.S.=0.95).

The robustness of effect sizes in these small N studies demonstrates the efficiency and power of repeated measures designs. The average effect sizes calculated in this meta-analysis can be used in the planning of future studies involving precipitated opioid withdrawal.

We plan to investigate the relative power of methods of data analysis in studies involving drugs with different profiles of effects, including benzodiazepines and stimulants.

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TUBERCULOSIS KNOWLEDGE AMONG NEW YORK CITY (NYC) INJECTING DRUG USERS (IDUs) AND SEXUAL PARTNERS OF IDUs

M. Marmor, H. Wolfe, D. Des Jarlais, and A. Moss

Our objective was to determine the status of tuberculosis (TB)-related knowledge among injecting drug users (IDUs) and sexual partners of IDUs. Subjects were participants in a cohort study and originally were enlisted from three Manhattan (NYC) methadone maintenance treatment programs (MMTPs), a community outreach campaign, and from persons who took part in previous studies of IDUs. The present data were obtained during 11/92 - 2/93, a period when we were engaged in HIV vaccine preparedness studies and hence oversampled HIV-seronegative subjects.

Five hundred and sixty-nine subjects, including 494 IDUs and 75 sexual partners of IDUs, responded to a questionnaire on TB. Thirty-two percent were female; median age was 39(range 18 - 66) years; 39% were African-American, 35% Hispanic, and 24% Caucasian; 16% lived in a relative or friend's residence, 11% in a shelter, 4% in a hotel or room rented on a weekly basis, and 3% on the streets. Eighty-eight percent gave a history of injecting illicit drugs, 50% reported injecting drugs and 41% reported using crack in the six months prior to interview; HIV seroprevalence was 7%. Twenty-nine percent of subjects gave a history of TB skin test reactivity or active TB, and 6% a history of active TB. Record review of a subsample found 90% agreement with these self-sports.

While 93% of subjects identified TB as airborne, only 53% identified it as exclusively airborne. Twenty-four percent of subjects responded correctly to three items measuring knowledge of the distinction between infection and active disease; the remaining 76% believed that a positive skin test inevitably resulted in active disease, and/or that someone with a reactive TB skin test can infect others. Subjects reporting a history of a reactive TB skin test were more likely to respond correctly to all three items. Forty percent of subjects did not understand the importance of medication adherence.

NYC IDUs and their sexual contacts are at high risk of tuberculosis. While some have a good level of TB-related knowledge, many are misinformed about the difference between infection and active disease. These misunderstandings may interfere with TB diagnosis and medication adherence. TB education must be integrated into drug treatment programs and other services provided to IDUs, sexual contacts of IDUs, and others at risk for TB.

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HEPATITIS C VIRUS SEROLOGY IN PARENTERAL DRUG USERS WITH CHRONIC LIVER DISEASE

D. M. Novick, K. J. Reagan, T. S. Croxson, A. M. Gelb, R. J. Stenger, and M. J. Kreek

Chronic liver disease (CLD) is a common complication of parenteral drug use, and liver cirrhosis is frequent in users of both parenteral drugs and alcohol. In 1978-83, we studied 88 parenteral drug users with sufficient evidence of CLD to warrant liver biopsy. Sera from these patients were frozen in multiple vials and stored for later studies. Hepatitis C antibody (anti-HCV) was determined by first generation ELISA, and samples with boderline reactivity were also tested with second generation ELISA. Confirmatory testing with recombinant immunoblot assay (RIBA) was done in 40 patients. Hepatitis B surface antigen (HBsAf) was determined by radioimmunoassay. Parenteral heroin was used by 41, heroin and cocaine by 46, and cocaine alone by noted in 63 (72%); six (7%) were former abusers. Cirrhosis was found in 33 (38%), chronic active hepatitis in 17 (19%), and alcoholic hepatitis in nine (10%). Anti-HCV was detected in 86 (98%), and all 40 tested were RIBA-positive. HBsAg was present in six (7%). We conclude that HCV infections is almost universal in parenteral drug users with CLD. The combination of HCV and alcohol abuse may contribute to the high frequency of cirrhosis.

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SEROPREVALENCE OF HEPATITIS A, B, C, AND D MARKERS AND LIVER FUNCTION ABNORMALITIES IN INTRAVENOUS HEROIN ADDICTS

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Acute and chronic hepatitis is known to be prevalent in intravenous heroin addicts. This study was done to determine which viral types primarily produce chronic hepatitis and liver function abnormalities in addicts. Three hundred eighty-three (383) intravenous heroin addicts with a mean age of 37.7 ± 8.9 years and who had been addicted for a mean of 14.3 ± 9.6 years were selected for study. All were admitted to 18 outpatient treatment clinics throughout California in October and November 1993. Subgroups were tested for antibodies to hepatitis A (anti-HAV), by IGG and IGM, B core (anti-HBc), B surface (anti-HBs), C (anti-HCV), D (anti-HDV), and B surface antigen (HBsAg). The majority were also tested for serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactic dehydrogenase. total bilirubin, globulin, albumin, A/G ratio, and platelet count. One or more antibody markers were found in 360 of 383 (94.0%) subjects. The seroprevalence of each marker was: anti HAV (40.7%); anti-HBc (73.6%); anti-HBs (46.7%); anti-HCV (93.6%); anti-HDV (9.6%). and HBsAg (3.5%). No single case was positive for IgM, anti-HAV, or for both HBsAg and anti-HDV, indicating active hepatitis A or D infection. Abnormal liver enzymes, serum proteins, total bilirubin, and platelet count were found to be abnormal to some degree in 5.3 to 44.8% of anti-HCV cases suggesting active, chronic infection. Among anti-HCV cases, elevated total bilirubin or a low platelet count was invariably associated with one or more liver enzyme and protein abnormalities. Only the small group (6.4%) of subjects negative for anti-HCV had normal, mean ALT and AST levels. While acute hepatitis may be frequent and caused by various viral types, HCV is the primary form of chronic hepatitis found in long-term intravenous heroin addicts. Over 40% of anti-HCV cases demonstrate one or more serum, liver function abnormalities indicating active, infectious liver disease that has the potential to be contagious and progress to cirrhosis, liver failure, and hepatocellular carcinoma. Ways to minimize the impact of HCV in the intravenous addict population should be sought.

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MOUSE STRAIN IS A MAJOR VARIABLE IN *IN VITRO* IMMUNOSUPPRESSION BY OPIOIDS

T. K. Eisenstein, J. J. Meissler, Jr., M. W. Adler, E. B. Geller, and T. J. Rogers

We have previously shown that spleen cells taken from C3HeB/FeJ mice 48 hours post *in vivo* morphine pellet implantation are suppressed in their *in vitro* responses to sheep red blood cells (SRBC). Simultaneous implantation of a naltrexone pellet blocked the suppression. A major question raised by these observations is whether the opioids act indirectly, or act directly on the immune cells. The current studies used a completely in vitro assay system to compare the effects of opioids in C3HeB/FeJ and C57BL/6J mice. Spleen cells were removed from mice which had been injected two weeks prior with SRBC. These mice received no opioids *in vivo*. Dissociated spleen cells taken from each of the two mouse strains were exposed to graded doses of morphine ± naloxone or to U50,488H ± norbinaltorphimine (nor-BNI) for five days in a Mishell-Dutton culture with added SRBC as antigen. Immune responsiveness was assessed by enumerating the number of plaque-forming cells (PFCs) per culture. The results showed a profound difference in the effect of the opioids on the spleen cells of the two mouse strains. Spleen cells of C3HeB/FeJ mice were suppressed approximately 50% in the number of PFCs both by morphine and by U50,488H at 10^{-5} M. The effect of both agonists was dose dependent and the effect could be titered out to 10^{-10} M. Suppression by morphine was blocked by naloxone and suppression by U50,488H was blocked by nor-BNI. In contrast, spleen cells taken from C57BL/6J mice were not suppressed by either opioid at concentrations as high as 10-5 M. Similar results were obtained when data were pooled from several different experiments or when the responses of the two mouse strains were compared in the same experiment. These studies confirm our previously published work with BALB/c mice showing suppression by opioids *in vitro*. Together, the results establish 1) that exogenous μ and κ agonists can have direct suppressive effects on mouse spleen cells, and 2) that mouse strain is a major variable in evaluating the *in vitro* immunomodulatory effects of opioids.

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MORPHINE SUPPRESSES IMMUNE RESPONSES TO MNrgp120/HIV-1 IN MICE: POTENTIAL RELEVANCE FOR AIDS VACCINES

P. A. Virsik and J. L. Bussiere

Clinical trials with the AIDS vaccine recombinant glycoprotein 120 from the MN strain of HIV-1 (rgp120) are being conducted in intravenous drug users (IDU) because they are a high risk group for infection with HIV-1. Given that certain drugs of abuse, particularly opioids, have been shown to be immunosuppressive in animals and man, the possibility exists that immune responses to rgp120 may be altered in IDU compared to other high risk groups. To evaluate this possibility, the effects of morphine (MOR) on immune responses to rgp120 formulated with various adjuvants, and a non-specific antigen keyhole limpet hemocyanin (KLH), were tested in a murine model. Female C3H/FeJ mice were implanted with a 75-mg MOR pellet on day zero, and vaccinated SC with 200 µL of rgp120 (75 µg/mL) with Alum, QS-21 or IFN- γ/QS-21, and 5 mg/ml KLH on days zero and seven. Control mice received rgp120 with Alum (150 µg/mL), QS-21 (50 µg/mL) or IFN-γ (2000 U) with QS-21. Primary immune responses to rgp120 were measured on day 14 by an ELISA, or a delayed-type hypersensitivity (DTH) response as measured by footpad swelling 24 hours after challenge with rgp120 or KLH.

Mice treated with MOR had reduced antibody titers to rgp120 on day 14 (58% of control) and to KLH (22% of control). Footpad swelling in response to KLH was not decreased in morphine-treated mice on day 15, however, DTH responses to rgp120 were suppressed to 35-50% of control. There were no significant differences in the amount of MOR-induced suppression of antibody or DTH responses among the three groups. However, QS-21 and IFN -γ/QS-21 give a significantly greater antibody response in morphine-treated mice compared to Alum controls. In addition, antibody titers to rgp120 with MOR/IFN-γ/QS-21 were significantly higher than with MOR/QS-21 alone, which were significantly higher than with Mar/Alum. Thus, in mice, these adjuvants may increase antibody responses even in the presence of opioids, which could minimize the immune suppression. DTH responses to rgp120 were significantly greater in the QS-21 and IFN-γ/QS-21 treated groups compared to mice receiving Alum. There was no significant difference in DTH responses in morphine-treated mice regardless of which adjuvant was used.

To validate this model, we compared rgp120 vaccine responses in mice and humans. This murine model of opiate-induced immunosuppression does not seem to mimic the clinical scenario in IDU. This may be because of different immune responses between mice and humans to rgp120, and because of the multitude of other factors which need to be considered in IDU. To date, trials with similar antibody titers to rgp120 as other high risk groups, in contrast to the results seen in the murine model.

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MEDICATION ADHERENCE REQUIREMENTS FOR IDUS WITH HIV DISEASE

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The epidemiology of AIDS indicates that there will be an increasing number of severely ill drug users in need of medical treatment. Medications for HIV disease are available, but they require that patients adhere to the treatment regimen. In prior work (Wall et al., CPDD 1992) we demonstrated, among methadone patients prescribed zidovudine (AZT) at San Francisco General Hospital (SFGH), that 56% were not adhering to AZT, evidenced by self-report or biological indicators. In a clinical trial (Wall et al.. CPDD 1993) we showed that on-site dispensing of AZT at the methadone clinic produced a positive effect of limited duration. Here we provide updated information on AIDS medications in addition to AZT. In Fall 1993 we reviewed charts of a random 30 of the 107 patients with HIV disease in methadone treatment at SFGH. The subject population was comprised of 59% men, mean age of 49 years, and of varied ethnicity (48% African-American, 38% Caucasian, 14% Hispanic). Ninety-six percent were prescribed medications (mean=3.58 medications in addition to methadone, range=0-9). The most frequently prescribed medications were AZT (30% of patients received this anti-retroviral), trimethoprim-sulfamethoxazole (23% received this PCP prophylaxis), albuterol (16% received this bronchial dilator), and ibuprofen (16% received this anti-inflammatory agent). By category, the most frequently prescribed medications were anti-infectives (50% of patients), psychiatric medications (37%). antiretrovirals (30%), and cardiovascular medications (27%). The prescribed regimens for each medication ranged from 1-5 times daily. Patients were prescribed 0-24 pills or capsules per day (mean=6.35). Adherence was essentially left up to the patient: Of the 111 prescriptions written, four were dispensed routinely with methadone; patients were expected to take the other 107 on their own. The results indicate that AIDS patients are being prescribed complicated regimens of medications to treat HIV and prevent secondary opportunistic infections. To assist patients in adhering to the medications, special interventions may be needed that combine on-site dispensing with behavioral treatments to improve adherence outside the clinic setting.

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CAN WE IDENTIFY WHAT IS ASSOCIATED WITH THE STABILITY OF IDU WILLINGNESS TO BE IN PREVENTIVE HIV VACCINE EFFICACY TRIALS?

K. Meyers, D. S. Metzger, A. T. McLellan, H. Navaline, and G. E. Woody

As preventive HIV vaccine efficacy trials approach, a critical practical question has been the willingness of high-risk populations to participate in the trials. Our previous work with intravenous drug users (IDUs) who are part of Project Jumpstart, a vaccine preparedness initiative co-sponsored by NIAID and NIDA, illustrate that appoximately 52% are willing to enroll. We have found these initial reports of willingness to be significantly related to engagement in HIV risk behaviors, treatment status, and trust in government. While these initial indications of willingness are encouraging, we are unsure whether willingness is stable over time. Of the 471 subjects, 402 or 85% had complete one-year data obtained at quarterly intervals. While 43% of these subjects were consistent in their responses, only 18% consistently reported that they would be willing to be one of the first to try a vaccine. Proportionately more of those subjects with stable willingness reports had a high school education ($p<.01$), with proportionately more of those who remained willing feeling sure that they knew what vaccines were ($p<.01$). Interestingly, those subjects who remained willing to be in the trials also reported living with other IDUs ($p<.02$) and scored lower on measures of psychological distress ($p<.01$) as compared with other subjects. Implications of these findings in relation to recruitment for preventive HIV vaccine efficacy trials, trial education, and *most importantly, informed consent* will be discussed.

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RELATIONSHIP OF DRUG ABUSE AND HIV SEROSTATUS TO NEUROPSYCHOLOGICAL FUNCTIONING IN MINORITY MEN

M. Quiroga, M. J. Selby, S. J. Ireland, and R. Malow

Introduction: Prior research has yielded inconsistent results concerning the relationship of drug use and neuropsychological functioning among asymptomatic HIV seropositive individuals. It has been hypothesized that drug abuse produces neurotoxic and immunosuppressive effects that may exacerbate the vulnerability of the central nervous system to HIV. The present study examined the effects of drug use and serostatus on neuropsychological functioning among African American and Hispanic men.

Methods: Subjects were 335 incarcerated adult males who showed no evidence of organic brain dysfunction or psychosis. Based upon interviews and HIV serostatus testing, subjects were classified into four groups: 1) seronegative drug abusers (NDAs; N=75). 2) asymptomatic seropositive drug abusers (PDAs; N=97). 3) seronegative nondrug abusers (NNAs; N=54), and 4) asymptomatic positive nondrug abusers (PNAs; N=109). Subjects were administered a neuropsychological test battery designed to be sensitive to the cognitive deficits commonly associated with HIV infection. Medical and demographic data were also collected.

Results: No significant differences hctwecn seropositive (N=206) and seronegative (N=129) subjects or between NDAs and NNAs on any of the neuropsychological measures. However, PDAs were more impaired than PNAs on WAIS-R Digit Symbol ($F = 4.2$, $p < .01$), Rey Copy ($F = 5.1$, $p < .05$), Rey Recall ($F = 4.8$, $p < .01$). Trails B ($F = 4.8$, $p < .05$), and verbal fluency (FAS; $F = 5.7$, $p < .01$). Subjects did not differ on any of the demographic or medical variables.

Discussion: These results with minority subjects are consistent with previous findings with non-minority subjects showing no significant differences between 1) asymptomatic seropositive and seronegative control subjects and 2) seronegative drug and nondrug abusers. Significant differences between seropositive drug and nondrug abusers on measures of psychomotor speed, complex visuomotor ability, the recall of complex nonverbal material, and verbal initiation suggest that although recovery of neuropsychological functioning may occur with abstinence, the introduction of HIV may intenupt or supersede this recovery.

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RELATIVE ANALGESIC POTENCY OF MU AND KAPPA OPIOIDS IN AMPHIBIANS: A UNIQUE ASSAY FOR KAPPA OPIOID ACTION?

C. W. Stevens, A. J. Klopp, and J. A. Facello

Systemic administration of opioid agents produces a well-defined analgesia in mammalian models and in the clinic. It is not known if similar mechanisms of analgesia exist for lower vertebrates This study examined the analgesic effects of eleven opioids; six *mu,* one mixed agonist-antagonist, and four *kappa*-selective agents; following systemic (s.c.) administration in Northern grass frogs, *Rana pipiens.* Analgesic effects estimated by the threshold to produce a wiping response to a cutaneous, chemical stimulus using the acetic acid test (AAT). All agents produced a dose-dependent and long-lasting analgesia, which was blocked or reduced by pretreatment with naltrexone. Comparison of ED50 values gave a relative potency as listed in the Table below:

Opioid agent	ED50[a]	95% C.I.[b]	R. P.[c]
fentanyl	1.4	0.9-2.3	61.6
CI-977	5.8	2.8-11.8	14.9
levorphanol	7.5	5.1-11.1	11.5
U50488	8.5	4.8-15.3	10.2
methadone	19.9	10.4-37.8	4.3
bremazocine	44.4	27.1-72.9	1.9
morphine	86.3	64.7-115.0	1.0
buprenorphine	99.1	58.5-168.0	0.87
meperidine	128.1	82.0-200.0	0.67
codeine	140.3	65.9-299.0	0.62
nalorphine	320.9	220.0-467.0	0.27

[a] *ED_{50} in nmol/g, s.c.*
[b] *95% Confidence Interval of the ED_{50}*
[c] *Relative Potency, calculated as ED_{50} morphine/ED_{50} opioid agent.*

Correlation of log ED50 values in amphibians to those reported for mouse hot plate (HP) and writhing test (WT) was significant for *mu* opioids on the AAT and both HP and WT, but not significant when the *kappa* opioids were included in the analysis. These data suggest that the analgesic action of *mu* opioids in amphibians faithfully predicts that obtained in rodents, but that the amphibian model may be unique for assessment of *kappa* analgesia.

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UNIQUE EFFECTS OF THE δ_2-OPIOID AGONIST DELTORPHIN II WITH δ_1 AND μ-AGONISTS IN INBRED MOUSE STRAINS

G. I. Elmer, J. Evans, and J. H. Woods

INTRODUCTION: Genetically defined inbred strains provide a unique opportunity to test the pharmacology of μ and δ–opioid agonists and their interactions. For example, in two inbred mouse strains, C3H and CBA, the δ_1 agonist DPDPE is a fully efficacious (ED50 ~ 10 nmole) analgesic while the δ_2 agonist deltorphin II is inactive (1-50 nmole). Conversely, the μ agonist morphine acts like a &agonist in CXBH mice; morphine is antagonized by the δ antagonist naltrindole but not by the μ antagonist ß-FNA. These three inbred mouse strains (C3H, CBA, CXBH) and the DBA and CXBK inbred mouse strains were used to investigate the interactions of the δ_2 subtype with δ_1 and μ-agonists.

METHODS/RESULTS: The effects of deltorphin II (i.c.v.) on DPDPE and morphine analgesic dose-effect curves were determined in the five inbred mouse strains. Deltorphin II did not shift the DPDPE dose-response curve in any of the five inbred strains. Thus, deltorphin II is not unique in its pharmacology due to partial agonist properties but is pharmacologically and genetically distinct in its mechanism of action. Deltorphin II (subeffective doses) produced greater than a 3-fold shift to the left in DBA and CXBK morphine dose-response curves consistent with previously demonstrated μδ interactions. In the two strains lacking δ_2 agonist effects (CBA, C3H) and the strain in which morphine acts via δ mechanisms (CXBH), deltorphin II (up to 10 nmole) did not shift the morphine dose-response curve.

DISCUSSION: The behavior genetic method is an analytical approach to pharmacology that provides information not only concerning the influence of genotype on a chosen phenotype but can also be used to dissect closely related mechanisms. To this end, the present results support the independent inheritance and separate mechanisms underlying δ_1 and δ_2 agonist sensitivity. In addition, the unique pharmacology of DPDPE- and deltorphin II-induced antinociception in several of the inbred strains (CBA, C3H) provided an opportunity to exclude potential partial agonist properties of deltorphin II. Lastly, interactions of the μ/δ systems were consistent with pharmacogenetic differences in δ_2 agonist-induced analgesia. These data highlight the utility of inbred mouse strains in opioid pharmacology and the genotype dependent effects of opioids.

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EXPOSURE TO VOLATILIZED OPIOIDS PRODUCES ANTINOCICEPTION IN MICE

A. H. Lichtman and B. R. Martin

Although the illicit use of heroin by smoking has recently gained in popularity among drug addicts, the abuse potential of smoking other opiates is presently unknown. Therefore, the purpose of the present study was to develop a rodent model to assess the potencies of volatilized opiates using a nose only exposure system. Six mice at a time were placed in individual animal holders which were attached to a manifold connected to a heated U-shaped pipe. A quantity of drug was then delivered into the pipe; five minutes later the subjects were removed from the holders and evaluated in the tail-flick test 15 minutes after exposure. Although each subject was exposed to only a fraction of the volatilized drug, ED_{50} values were calculated using the starting amount of drug as the independent variable. The antinociceptive potencies of opioids administered by inhalation and i.v. injection together with their potency relative to heroin are presented below.

Drug	Inhalation Exposure ED_{50}	potency relative to heroin	Intravenous Administration ED_{50}	potency relative to heroin
heroin	1.0 (0.5 to 1.9)	1	0.35 (0.17 to 0.72)	1
morphine	21 (11.8 to 38.9)	0.05	1.5 (0.7 to 3.1)	0.23
fentanyl	0.04 (0.02 to 0.08)	25	0.009 (0.005 to 0.018)	39
mepetidine	15.4 (10.8 to 22.1)	0.06	7.3 (4.2 to 12.6)	0.05
codeine	19 (7.7 to 45.6)	0.05	10.6 (6.6 to 17.2)	0.03

*with 95% confidence limits.

The relative potencies of both fentanyl, codeine, and meperidine compared to heroin were similar for both routes of administration. In contrast, the relative potency of morphine was substantially reduced after inhalation exposure. These results demonstrate that a variety of opioids are capable of producing pharmacological effects when volatilized suggesting the potential for their abuse.

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IRREVERSIBLE MU OPIOID ANTAGONIST CLOCINNAMOX REVEALS ETONITAZENE TO BE HIGH-AFFINITY, LOW-EFFICACY AGONIST

G. Zernig, J. W. Lewis, and J. H. Woods

Etonitazene is routinely used in behavioral assays as a high-potency mu opioid agonist. As the potency of any agonist is determined by its *in vivo* affinity as well as its efficacy, this study determined both by applying the method of partial irreversible antagonism. Clocinnamox was used as the irreversible inhibitor of etonitazene's effects in two tests of antinociception, i.e. the mouse warm-water tail withdrawal assay (TW) and the mouse writhing (WR) assay. Data were analysed according to Zernig *et al.,* (1994). Etonitazene's efficacy was 7.1 ± 2.0 in TW and 7.5 ± 0.7 in WR. The efficacies of the three other tested opioid agonists were: Morphine, 3.9 ± 1.3 in TW, 11 ± 4.7 in WR; fentanyl, 19 ± 6.0 in TW, 30 ± 2.3 in WR; NIH 10741 (RTI-4614-14, (2S,3R,4S)-cis-N-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-pipe-ridyl]-N-phenylpropanamide, synthesized by Dr. George Brine), 27 ± 5.9 in TW, 37 ± 1.0 in WR. Thus, etonitazene proved to be an agonist of only moderate efficacy in both assays. Interestingly. Comer *et al.,* (1992) had shown that the pA_2 for naltrexone in TW using morphine as the agonist was only 5.9, whereas in WR it was 7.7 (Comer 1992). Accordingly. in the present study etonitazene's apparent *in vivo* dissociation constant, KA, was 0.63 mg/kg in TW and 0.05 mg/kg in WR. These findings suggest that thermal and visceral antinociception in the mouse are mediated by different opioid receptor subtypes. Due to both its low efficacy and high affinity, etonitazene was the only mu opioid agonist in the mouse writhing assay that allowed complete separation of opioid- from non-opioid-induced inhibition of writhes.

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APPARENT AFFINITY ESTIMATES FOR OPIOID ANTAGONISTS IN RATS TREATED WITH CLOCINNAMOX OR CHRONIC MORPHINE

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The potency and effectiveness of opiate agonists can be reduced by repeated treatment with opiate agonists or acute treatment with irreversible opiate antagonists. This reduction in agonist potency and effectiveness may result from changes in affinity or relative efficacy at μ opioid receptors. This hypothesis was tested by measuring the apparent affinity of the antagonists naltrexone (NTX) or nalbuphine (NLB) for μ opioid receptors in rats treated with either a single dose of the irreversible antagonist clocinnamox (CAM) or repeated doses of morphine (MS), respectively. In addition, the potencies of the μ agonists MS and fentanyl (FE) were compared following CAM treatment in non-tolerant and MS-tolerant rats. Sprague-Dawley rats (n=60) were trained to discriminate 3.2 mg/kg MS and saline, s.c., under a FR-15 schedule of food delivery. Under control conditions, apparent pA_2 values for NTX and NLB as antagonists of the stimulus and rate-altering effects of MS were 7.8 and 5.4 mol/kg, respectively. In CAM-treated rats (10 mg/kg, 24-h ptt.), NTX (0.032-3.2 mg/kg) dose-dependently antagonized MS, with apparent pA_2 values of 7.0-7.3 mol/kg. In rats treated with 20 mg/kg/day MS for 7-14 days, NLB (1.0-32 mg/kg) dose-dependently antagonized MS, with apparent pA_2 values of 5.0-5.4 mol/kg. These data suggest that CAM or repeated MS treatment alone fail to alter the apparent affinity of an antagonist for μ receptors. CAM treatment alone increased the doses of MS and FE required for MS-like stimulus effects by 6 and 2-fold, respectively, and increased the doses required for rate-decreasing effects by 5-fold. MS treatment alone (20 mg/kg/day for 5.5 days) increased the doses of MS and FE required for MS-like stimulus effects by 3-fold, and the doses required for rate-decreasing effects by 2-fold. The combination of repeated MS treatment and CAM treatment further increased the doses of both MS and FE required for MS-like stimulus and rate-decreasing effects by 2 to 4-fold. Furthermore, in tolerant rats, the slope of the MS dose-response curve following CAM treatment was significantly shallower than slopes of control curves. This suggests 1) that the combined treatments had produced a maximum rightward shift, and 2) that further decreases in receptor number (through irreversible antagonism or repeated agonist treatment) would produce only decreases in maximal effect without further decreases in potency. Potency ratios in tolerant and non-tolerant rats suggested that repeated MS treatment may reduce both the affinity and relative efficacy of μ agonists for their receptors.

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DIURNAL CYCLE AND FLAVOR EFFECTS ON OPIOID ANTINOCICEPTION IN INFANT RATS

K. F. Green, R. J. Beitner, C. E. Schlundt, and S. O. Werner

Opioid antinociception (OAN) in rats has been reported to vary with exposure to flavored fluids and with time of day. The effect of flavored fluids on OAN appears to depend on age: adult rats typically show reduced morphine-OAN after flavor ingestion (Lieblich *et al.,* 1983), whereas infant rats typically show direct elicitation of OAN (Blass 1992). One of the differences in work with adults vs infants is the use of nonnutritive vs nutritive fluids, respectively. Thus our first purpose was to examine OAN in infants after exposure to both types of fluids. The effect of time of day also appears to depend on age: the rodent pattern of greater sensitivity to pain during the light hours was found to be greater in younger (1-2 months) than in older mice (Kavaliers and Hirst 1983). Thus our second purpose was to seek diurnal changes in pain sensitivity in infant rats. Finally, our third purpose was to determine whether the opioid activity evoked by a relatively brief exposure to flavors would be affected by opioid activity produced by the diurnal cycle. Would the effects add, or would the prolonged night-time opioids produce tolerance-like effects?

Two hundred and ninety Wistar rat pups, ten days old, were drawn from 53 litters. They were tested two hour into the light or dark phase of a 12-12 light-dark schedule. Pups were further assigned to one of nine conditions: five with flavors (water, saccharin, sucrose, milk, and milk preceded by naloxone at 0.5 mg/kg) plus four controls for procedural stress. Fluids were infused for three minutes via a plastic cannula inserted through the anterior floor of the mouth. Paw lift latencies from a 48.5 degree C surface were then measured. Effects were evaluated with two-way factorial analysis of variance followed by individual comparisons of cell means.

Control groups for procedural stress did not consistently show increased paw lift latencies attributable to either stress or time of day. Groups infused with water, saccharin, and milk (but not sucrose) had longer latencies at night than in the morning. and did not differ from each other. Latencies in these flavor groups were longer than those of controls at night but generally not in the morning. Naloxone latencies were less than saline latencies when morning and night groups were combined,

The effectiveness of naloxone confirms that milk yielded OAN and suggests that the antinociception elicited by the nonnutritive fluids was also opioid. In control pups the lack of consistently longer latencies at night may indicate that diurnal variation in opioids is not great or that we did not test at optimal times. In flavor groups the long latencies at night suggest that opioids activated by flavors and by diumal variation combine additively to determine overall levels of OAN.

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THE ROLE OF SEROTONIN IN THE ANTINOCICEPTIVE EFFECTS OF MU AND KAPPA OPIOIDS

K. R. Powell and L. A. Dykstra

In this study, we examined the role of serotonin (5HT) in the antinociceptive effects of the kappa opioids. U50,488 and spiradoline, and the mu opioids. morphine and I-methadone, in squirrel monkeys responding under a titration procedure. Under this procedure, shock was scheduled to increase once every 15 seconds from 0.0 to 2.0 mA in 30 steps. Five responses on a lever during the 15-second shock period terminated the shock for 15 seconds, after which the shock resumed at the next lower intensity. U50,488, spiradoline. morphine and I-methadone were examined alone and in combination with three or more of the following drugs: 8-OH-DPAT and ipsapirone ($5HT_{1A}$ agonists), NAN-190 ($5HT_{1A}$ antagonist), ketanserin, pirenperone and LY 53857 ($5HT_2$ antagonists), DOI ($5HT_2$ agonist) and MDL 72222 ($5HT_3$ antagonist). When administered alone, U50,488, spiradoline, morphine and *l*-methadone increased median shock level (MSL), whereas 8-OH-DPAT, ipsapirone, NAN-190, ketanserin, pirenperone, LY 53857, DOI and MDL 72222 generally did not alter responding within the dose-ranges tested. When administered in combination with the higher doses of ketanserin, pirenperone and LY 53857, the dose-effect curves for U50,488 and spiradoline were shifted leftward. 8-OH-DPAT also shifted the U50,488 dose-effect curve leftward, whereas 8-OH-DPAT did not alter the effects of spiradoline. Furthermore, the effects of U50,488 were not altered by DOI or MDL 72222. When administered in combination with morphine, 8-OH-DPAT and ipsapirone attenuated the effects of the highest dose of morphine. Unlike the effects of morphine, the effects of I-methadone were not altered by the $5HT_{1A}$ agonists. Finally, the effects of morphine were not altered by NAN-190, ketanserin or MDL 72222. These data support a role for the $5HT_2$ receptor system in the antinociceptive effects of kappa opioids and for the $5HT_{1A}$ receptor system in the antinociceptive effects of morphine and U50,488, but not other mu or kappa opioids.

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BEHAVIORAL EFFECTS OF THE DELTA OPIOID AGONIST BW373U86 IN RHESUS MONKEYS

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The behavioral effects of BW373U86, a non-peptidic, systemically active delta opioid agonist (Chang et *et al.,* 1993), were examined in rhesus monkeys, in tests of suppression of food-maintained response rates (Negus *et al.,* 1993a), drug discrimination, intravenous self-administration and thermal antinociception. BW373U86 (s.c., 0.032-0.32 mg/kg), the mu agonist alfentanil (0.0032-0.032 mg/kg) and the kappa agonist U69,593 (0.00032-0.01 mg/kg) all produced dose-dependent suppression of food-maintained response rates under a FR30 schedule. The selective delta antagonist naltrindole (NTI, 1.0-10.0 mg/kg) antagonized the effects of BW373U86 with high potency (apparent pA_2 value=6.5), whereas it was less potent in antagonizing alfentanil (apparent pK_B value=5.1); NTI was ineffective against U69,593. BW373U86 was not generalized by animals trained to discriminate the mu agonist alfentanil or the kappa agonist EKC from vehicle, and did not produce reinforcing effects in an i.v. self-administration procedure (dose range: 0.01-0.32 mg/kg/inj). BW373U86 was ineffective in the warm water (50°, 55° C) tail withdrawal assay of thermal antinociception, but was dose-dependently effective against the thermal allodynia (in 42°C water) produced by tail injection of bradykinin (0.1 µg; see Negus *et al.,* 1993b). This anti-allodynic effect of BW373U86 was also antagonized by NTI (1.0 mg/kg). BW373U86 therefore appears to cause delta-receptor mediated effects in some assays in rhesus monkeys; it has a novel constellation of behavioral effects that differ from either mu or kappa agonists in rhesus monkeys.

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SUBANESTHETIC DOSES OF NITROUS OXIDE REDUCE COLD PRESSOR-INDUCED PAIN IN HUMANS

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Nitrous oxide (N_2O) has analgesic properties as determined in both animal and human research. The purpose of our study was to determine if the cold pressor test (Chen et al., 1989) is a sensitive pain assay to measure N_2O analgesic effects in humans. Subjects (N=10) participated in four sessions, and in each session the effects of one of four concentrations of N_2O (0, 20, 30, 40% in oxygen) were assessed. Duration of inhalation was 40 minutes, and within each session, subjects immersed their non-dominant arm in water (2-3°C) twice for three minutes (10 and 30 min intra-inhalation). Pain intensity and aversiveness (measured on a verbal scale of 0-10, 0 = "not at all" and 10 = "extremely painful/bothersome") and pain quality (measured by short-form McGill's Pain Questionnaire [SF-MPQ]) were assessed during the forearm immersions. Mood (measured by a series of visual analogue scales [VAS]) was assessed in the presence and in the absence of the cold water immersion. Self-reported pain intensity and aversiveness and SF-MPQ ratings of "sharp pain" and "throbbing pain" and a VAS rating of "unpleasant bodily sensation" were significantly reduced by N_2O ($P < 0.05$) in a dose-dependent manner. N_2O had a number of effects on mood (e.g., increased VAS ratings of "coasting," "high," "carefree," "stimulated," "elated," and decreased VAS ratings of "in control of body"). In general, pain did not alter these effects. Results from our study indicate that the cold pressor test, used by researchers as a model of experimentally induced tonic pain, is a sensitive assay to measure the analgesic properties of N_2O in humans.

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CARDIORESPIRATORY EFFECTS OF COCAINE-HEROIN COMBINATIONS IN THE ANESTHETIZED RABBIT

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Co-administration of cocaine (COC) and heroin (HE) is a common practice among drug abusers. It is generally accepted that cocaine is a cardiorespiratory stimulant, while heroin is a potent respiratory depressant without remarkable effects on the cardiovascular system. We hypothesized that a combination of cocaine and heroin may delay and minimize the effects of each drug on the cardiorespiratory system. Nine groups (n = 4 each) of anesthetized (pentobarbital 35 mg/kg) rabbits were infused with cocaine (0.075, 0.15 or 0.5 mg/kg/min), heroin (0.075, 0.15 or 0.5 mg/kg/min) or a combination of cocaine and heroin at the same doses. Within five minutes after the beginning of the infusion, respiration ceased for the heroin and COC + HE groups. Artificial ventilation (adjusted to maintain expired CO_2 at baseline values) was immediately instituted for these groups. In contrast, cocaine alone produced a dose-dependent increase respiratory rate. No significant changes in either blood pressure or heart rate were observed for any of the groups at the five min time period. Sixty minutes into the continuous infusion period, cocaine and heroin alone at the lower doses produced only minimal changes in blood pressure and heart rate. However, at both the lower doses the combination of cocaine and heroin tended to produce greater decreases in blood pressure and heart rate than either drug alone. At the highest dose tested, all three groups produced comparable effects. At the 60 minute time period, heroin alone continued to suppress respiration and while cocaine alone produced even larger increases in respiration than at the five minute time period, cocaine was still not able to antagonize the respiratory depressant effect of heroin. At the 0.5 mg/kg/min dose cocaine alone and the COC + HE combination produced a clear increase in QRS duration. No change in QRS was noted for heroin. These results suggest that, at the doses tested, cocaine was unable to reverse the respiratory depressant effects of heroin. Likewise, heroin was not able to antagonize the local anesthetic effect of cocaine as reflected in the QRS widening. Further, at the lower doses the combination of cocaine and heroin appeared to produce supra-additive effects on hemodynamics. The mechanism for this interaction is unclear.

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KAPPA OPIOID RECEPTOR AGONISTS PREVENT SENSITIZATION TO THE REWARDING EFFECTS OF COCAINE

T. S. Shippenberg and C. H. Heidbreder

The repeated administration of cocaine (COC) can lead to an enhancement of its conditioned rewarding effects (e.g. sensitization). Such sensitization is associated with a transient increase in basal dopamine (DA) overflow within the nucleus accumbens and it has been postulated that this increase underlies the development of this phenomenon. The acute administration of kappa opioid receptor agonists inhibits the activity of mesolimbic DA neurons. The existence of a tonically active kappa-opioidergic system which regulates basal DA release within the nucleus accumbens has also been demonstrated. In view of such findings, we have employed an unbiased place preference conditioning procedure in order to determine whether manipulations of kappa opioid systems can modify the development of sensitization to the rewarding effects of COC.

Male Sprague-Dawley rats (200-250g) received once daily injections of saline or COC (10 mg/kg; ip) for five days. Additional rats received COC on days one and two and U69593 (0.16 mg/kg; sc) or its vehicle 15 minutes prior to COC on days three through five. All injections were conducted in a room distinct from that of place conditioning. Conditioning sessions (2 drug; 2 saline) were conducted 72 hours later on days eight and nine. Tests of conditioning were conducted on day ten. COC (1.0 - 10.0 mg/kg) was ineffective as a conditioning stimulus in saline pretreated rats. In rats, however, which had previously received COC for five days, a marked place preference in response to COC doses of 5.0 mg/kg and greater were seen. This enhanced response to COC was prevented by the kappa agonist U69593. Thus, regardless of the COC dose used for conditioning, no drug-induced place preference was observed in animals which had received the repeated COC treatment in combination with U69593. ICV administration of the selective kappa opioid receptor antagonist, nor-binaltorphimine, 24 hours prior to the commencement of COC treatment, did not, by itself, modify the enhancement of COC-induced place conditioning. However, in animals which had received nor-binaltorphimine and U69593 in combination with COC, an enhancement of COC place conditioning was again seen.

These findings confirm that the repeated administration of COC leads to an enhancement of its conditioned rewarding effects. Furthermore they demonstrate that a kappa opioid receptor agonist given in combination with COC can prevent the development of this phenomenon. The effects of the kappa agonist were antagonized by the ICV administration of nor-binaltorphimine and mimicked by ICV U69593 suggesting the specific involvement of kappa opioid receptors located within the central nervous system.

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EFFECT OF THE DELTA OPIOID ANTAGONIST NALTRINDOLE ON COCAINE DISCRIMINATION AND SELF-ADMINISTRATION IN RHESUS MONKEYS

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The effects of the delta opioid antagonist naltrindole (NTI) were evaluated on the discriminative stimulus effects and reinforcing effects of cocaine in rhesus monkeys. In the drug discrimination experiment, four monkeys were trained to discriminate 0.40 mg/kg cocaine from saline in a food reinforced, two lever, drug discrimination procedure. Cocaine alone produced a dose-dependent increase in responding on the cocaine-appropriate key. Pretreatment with delta-selective doses of NTI (0.32-3.2 mg/kg) had no effect on the cocaine dose-effect curve of approximately 1/2 log unit in the other two monkeys. These antagonist effects were not monotonically related to dose; the intermediate dose of NTI (1.0 mg/kg) was as effective as or more effective than lower or higher doses. Furthermore, upon redetermination, pretreatment with 1.0 mg/kg NTI did not shift the cocaine dose-effect curve in any of the four monkeys.

In the cocaine self-administration experiment, four monkeys were trained to self-administer cocaine (0.032 mg/kg/inj) or food. Substitution of saline or other cocaine doses (0.001-0.1 mg/kg/inj) yielded a typical inverted-U shaped dose effect curve for each monkey. Pretreatment with delta selective doses of NTI (0.1-3.2 mg/kg) for ten consecutive days suppressed self-administration of a dose of cocaine on the ascending limb of the cocaine dose-effect curve (0.01 mg/kg/inj) by up to 50 to 100% in three of the four monkeys. However, intermediate doses of NTI (0.32-1.0 mg/kg) were more effective than lower or higher doses. Furthermore, upon redetermination, these intermediate NTI doses were found to be either less effective or ineffective in decreasing cocaine self-administration. NTI had no effect on cocaine self-administration in one monkey, and little effect on food self-administration in any of the four monkeys.

In summary, these findings indicate that delta-selective doses of NTI antagonized both the discriminative stimulus and reinforcing effects of cocaine in some, but not all, monkeys. Intermediate NTI doses were as effective as or more effective than either higher or lower doses, and the antagonist effects of NTI appeared to decrease with repeated determinations.

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ETHANOL COTREATMENT INCREASES BLOOD AND BRAIN COCAINE LEVELS IN MICE

I. R. Tebbett, D. L. Phillips, R. D. Harbison, and S. M. Roberts

There are conflicting reports in the literature concerning the effects of alcohol on the pharmacokinetics of cocaine. Previous studies of the metabolism of cocaine *in vitro* in mouse and human liver have found that the enzymatic hydrolysis of cocaine to benzoylecgonine is inhibited by ethanol (Roberts *et. al.,* 1993). Correspondingly, hepatic hydrolysis of benzoylecgonine were diminished and cocaine concentrations increased by cotreatment with ethanol *in vivo.* The present study extends these observations by examining the effect of ethanol cotreatment on cocaine blood and brain concentrations. Mice were administered a single dose of cocaine (10 mg/kg, i.p.) with or without a concurrent ethanol dose (2 g/kg, p.o.). These doses were selected to yield blood cocaine and alcohol concentrations relevant to human substance abuse. Ethanol concentrations in blood and cocaine and benzoylecgonine concentrations in both blood and brain were measured over time. Ethanol cotreatment resulted in a significant increase in peak cocaine concentrations in the brain. Peak cocaine concentrations in both tissues occurred somewhat earlier in the ethanol cotreated mice. Increased cocaine concentrations were also reflected in cocaine tissue AUC's which were approximately 3-fold greater in both blood and brain in mice co-administered ethanol. Blood benzoylecgonine concentrations were somewhat lower in ethanol treated mice, but brain benzoylecgonine concentrations were significantly greater than in mice treated with cocaine alone. These observations suggest that ethanol can significantly alter the pharmacokinetics of cocaine, which could account, at least in part for reports of increased toxicity of cocaine when combined with alcohol. This may be associated with an inhibition of cocaine metabolism in the presence of alcohol and/or changes in the absorption and distribution of the drug.

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CNS STIMULANTS PRODUCE CROSS-TOLERANCE TO COCAINE IN AN FR2 SCHEDULE OF COCAINE SELF-ADMINISTRATION

R. L. Peltier and M. W. Emmett-Oglesby

This experiment determined whether the chronic administration of *d*-amphetamine or methamphetamine would result in cross-tolerance to cocaine in a low value FR (FR2) self-administration paradigm. Rats were implanted with indwelling jugular catheters and were allowed to self-administer cocaine (0.25 mg/injection) on an FR2 schedule of reinforcement, 15 reinforcers each day, until stable baseline responding was observed. A dose-response curve for cocaine self-administration was then obtained for each rat using a multi-dose procedure. This procedure employs an FR2 schedule with a maximum of 24 reinforcers. The reinforcers were divided into three blocks of eight with each block of reinforcers providing a different dose of cocaine (i.e. reinforcers 1-8 = 0.5 mg/inj, 9-16 = 0.25 mg/inj, 17-24 = 0.125 mg/inj). After dose-response data were obtained, rats were randomly assigned to one of two groups. One group received injections of d-amphetamine (0.32, 1.0 or 3.2 mg/kg, s.c.) twice daily for seven days, while the other group received injections of methamphetamine (0.32, 1.0 or 3.2 mg/kg, s.c.) twice daily for seven days. During this chronic regimen, the rats were not allowed to self-administer cocaine. Twenty-four hours following the last chronic injection, a cocaine dose-response curve was reobtained. There was a significant shift to the right of the post-chronic dose-response curves for cocaine self-administration for the hightest dose (3.2 mg/kg) of both *d*-amphetamine and methamphetamine given chronically. Following seven days without testing or training, all rats spontaneously returned to baseline rates of cocaine self-administration. These data show that chronic treatment with a CNS stimulant of the amphetamine type produces dose dependent cross-tolerance to cocaine in a self-adminstration paradigm.

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MODULATION OF COCAINE-INDUCED SENSITIZATION BY NITRIC OXIDE

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Increasing evidence suggests the involvement of excitatory amino acids in psychostimulant-induced sensitization, and our recent studies indicate that blockade of brain nitric oxide synthase (NOS) abolishes the development of cocaine-induced sensitization in mice (Itzhak 1993, 1994). To further establish the role of nitric oxide (NO) in the process of sensitization to cocaine, the effects of L-NAME and L-Arginine (L-Arg), an inhibitor and a substrate of NOS, respectively, on the convulsive response to cocaine was investigated. Male Swiss Webster mice were divided into six groups and the following drugs were administered i.p., once a day, for seven days: 1) saline before cocaine (40 mg/kg), 2) L-NAME (100 mg/kg) before cocaine, 3) L-NAME + L-Arg (300 mg/kg) solution before cocaine, 4) L-NAME + D-Arg (300 mg/kg) solution before cocaine, 5) saline before L-Arg + cocaine solution, 6) saline before D-Arg + cocaine solution. Results indicate the following: (i) L-NAME completely abolished the development of cocaine-induced seizures. (ii) L-Arg, but not D-Arg, partially reversed the protective effect of L-NAME against cocaine-induced seizures. (iii) L-Arg, but not D-Arg, markedly intensified the development of cocaine-induced seizures.

To determine whether repeated exposure to cocaine induces super-sensitization of the NMDA receptor - which may lead to the activation of brain NOS - saline and cocaine-treated animals received a challenge dose of N-methyl-D,L-aspartate (NMDLA; 200 mg/kg, i.p.) 24 hours after the drug treatment was stopped. While only 10% of the control animals experienced seizures and death, 50% of cocaine-treated animals died after the administration of 200 mg/kg NMDLA.

Taken together, the present study provides *in-vivu* evidence for the role of NO in the process of sensitization to cocaine and supports the view that increased sensitivity of the NMDA receptor following exposure to cocaine leads to activation of NOS. Manipulation of NMDA/NOS pathway may therefore provide protection against cocaine toxicity.

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EFFECTS OF A NITRIC OXIDE SYNTHASE INHIBITOR ON THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE AND ON SUBSTITUTION PROFILES OF DA- AND NMDA-RELATED DRUGS

K. M. Kantak and M. A. Edwards

A number of nitric oxide (NO) synthase inhibitors have been described and their effects appear to mimic to some degree those of NMDA antagonists by preventing the formation of NO and the subsequent release of glutamate. To learn more about the behavioral pharmacology of NO synthase inhibitors and their interactions with cocaine, the present study characterized the influence of the NO synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME) on the discriminative stimulus (DS) effects of cocaine and on the cocaine-like DS effects of other DA- and NMDA-related drugs. Drug substitution tests with cocaine, the DA releaser (+)-amphetamine, the DA uptake inhibitor GBR 12909, the noncompetitve NMDA antagonist dizocilpine and the competitive NMDA antagonist NPC 17742 were conducted one hour following pretreatment with either saline or 100 mg/kg L-NAME in rats trained to discriminate 10 mg/kg cocaine from vehicle. Cocaine (0.1-17.8 mgkg), as well as (+)-amphetamine (0.01-1.0 mg/kg) and GBR 12909 (0.3-17.8 mg/kg) engendered dose-related increases in cocaine-lever responses, with each drug reaching a maximum average of > 96% after one or more doses. Following L-NAME pretreatment, the dose-effect curves for cocaine, (+)-amphetamine and GBR 12909 were shifted, in a non-additive manner, to the left by 1/2 to 1 log-unit. Unlike the findings with these DA-related drugs, L-NAME pretreatment did not alter the shape or position of the dose-effect curves for either dizocilpine (0.01-0.1 mg/kg) or NPC 17742 (1.0-17.8 mg/kg), which primarily engendered saline-lever responses. These results suggest that under certain conditions, L-NAME may indirectly enhance DA neurotransmission to augment the DS effects of cocaine and other drugs that have cocaine-like effects.

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THE HPA AXIS AND COCAINE SELF-ADMINISTRATION

N. E. Goeders and G. F. Guerin

We have previously reported that rats without control over electric footshock presentation (non-contingent shock) will intravenously self-administer cocaine at lower doses and higher rates than rats exposed to the same schedule of response-contingent footshock or that were never shocked (Goeders and Guerin 1994), suggesting an involvement of stress in the etiology of cocaine self-administration. In addition, we found significant positive correlations between the number of infusions delivered with the 0.125 mg/kg/infusion dose of cocaine and plasma corticosterone measured before the first exposure to the cocaine self-administration component of the multiple schedule. These correlations appeared to roughly correspond with the acquisition, or lack thereof, of self-administration with this dose. This relationship between stress-induced elevations in plasma corticosterone and cocaine self-administration has been investigated in an additional 33 triads (*i.e.,* 99 rats). A small percentage of these rats acquired self-administration with the lowest dose of cocaine (*i.e.,* 0.031 mg/kg/infusion, n = 7), while the majority of rats acquired self-administration with the 0.125 mg/kg/infusion dose as previously reported (Goeders and Guerin 1994). There were significant differences in the locomotor response to novelty measured before exposure to electric footshock between the rats that acquired cocaine self-administration with the 0.031 mgkg/infusion dose vs those from the same triads that did not, while there were no differences between rats that did or did not acquire self-administration at the 0.125 mg/kg/infusion dose. These data suggest that individual factors (Piazza *et al.,* 1989), which may or may not be associated with contingent vs non-contingent electric footshock, were likely involved in extremely low dose cocaine self-administration for this small percentage (*i.e.,* 7%) of the rats tested. On the other hand, plasma corticosterone resulting from the different treatment conditions was significantly increased in rats that acquired cocaine self-administration with the 0.125 mg/kg/infusion dose compared to rats from the same triads that did not. These data further suggest an important role for stress and/or stress-related hormones in cocaine reinforcement.

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EFFECTS OF COCAINE AND CORTICOTROPIN RELEASING FACTOR (CRF) ON PULSATILE ACTH AND CORTISOL RELEASE IN OVARIECTOMIZED RHESUS MONKEYS

Z. Sarnyai, N. K. Mello, J. H. Mendelson, M. Erös-Sarnyai, P. Nguyen, M. Kelly, H. Gelles, and Y. G. Cheng

Cocaine stimulates ACTH secretion by a corticotropin-releasing factor (CRF)-dependent mechanism in male rats, rhesus monkeys and in humans. The extent to which cocaine's stimulation of ACTH is modulated by gonadal steroid hormones is unknown. We examined the effects of acute cocaine on the pulsatile release of ACTH and cortisol in ovariectomized (OVX) rhesus monkeys and compared its effects to stimulation with corticotropin-releasing factor (CRF). Venous blood samples were collected at 2 min intervals for 60 min prior to and after cocaine (0.4 an 0.8 mg/kg) and CRF (1.0 and 10 µg/kg) administration. Cluster analysis procedures were used to evaluate the pulsatile characteristics of ACTH and cortisol release. After placebo administration, an ACTH pulse frequency of 3 peaks/hr was detected. Plasma cocaine levels peaked at 92 ± 3.0 and 201 ± 60 ng/ml after intravenous administration of 0.4 and 0.8 mg/kg of cocaine, respectively. Low (0.4 mg/kg) and high doses (0.8 mg/kg) of cocaine did not stimulate the pulsatile release of ACTH in OVX females. Instead, 0.4 mg/kg of cocaine decreased ACTH incremental peak height and valley levels compared to pre-cocaine values and a higher dose of cocaine produced no changes in ACTH release. Bolus injection of low dose of CRF (1.0 µg/kg, iv) significantly increased ACTH incremental peak height and a higher dose of CRF (10 µg/kg, iv) increased ACTH peak amplitude, percentage increase in peak amplitude. area under the peaks, incremental peak heights, as well as ACTH valley level and nadir. ACTH pulse frequency did not change after CRF administration. Pulsatile release of cortisol was 2.7 peaks/hr under placebo conditions and did not change after cocaine. Cortisol pulse amplitude was increased after low and high doses of CRF. High doses of CRF (10 µg/kg) also increased the mean level of cortisol valleys. The frequency of pulsatile cortisol release remained unchanged after CRF treatment.

In summary, we found that CRF, but not cocaine, stimulated pulsatile ACTH and cortisol release in OVX rhesus monkeys. The profound ACTH response to CRF challenge suggests that the CRF-sensitivity and the ACTH release capacity of the anterior pituitary corticotroph cells were intact. The lack of stimulatory effects of cocaine on HPA axis may be due to the absence of gonadal steroids in ovariectomized monkeys.

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THE RELATIONSHIP OF COUNSELOR AND PEER ALLIANCE TO DRUG USE AND HIV RISK BEHAVIORS IN A SIX-MONTH METHADONE DETOXIFICATION PROGRAM

S. L. Tunis, K. L. Delucchi, K. Schwartz, P. Banys, and K. Sees

Therapeutic alliance is defined as a collaboration between therapist and patient. It has predicted symptom reduction in therapy, but has not been studied in substance abuse treatment. Another type of alliance remaining unexplored is peer alliance. The purpose of this study was to examine both types of alliance for predicting outcome for opiate addicts in a six month detoxification program. Assessments were monthly from about day 90, including a 30-day follow-up. Counselor alliance was assessed with the California Therapeutic Alliance Scale. We also used two subscales to assess peer relationships. We predicted that greater alliance would be related to remaining in treatment, less drug use, and fewer HIV risk behaviors.

Neither counselor nor peer alliance was related to treatment retention. No differences existed in either type of alliance for those who did or did not use cocaine. For opiate use, results were similar to those above for the first three assessments. At time four (day 180), however, higher levels of both types predicted no opiate use in the previous 30 days. HIV risk scores were calculated for needle-sharing and for sexual risk. Again, we found no relationship between alliance and outcome in the early and middle stages of the methadone taper. For time four, alliance with counselor predicted both fewer and less frequent needle-sharing behaviors. For the follow-up, level of counselor alliance was related to only behavior frequency. Peer alliance was also related to fewer needle-sharing behaviors at time four, as well as to more frequent risky sex in the month after treatment.

Conclusions: For this sample enrolled in a six-month methadone program, we found evidence for the importance of both types of alliance in the final stages of methadone taper. Substance abuse researchers and clinicians may want to test approaches that can improve counselor alliance. Patients may also benefit from counseling that addresses ways in which drug use and other risky behaviors may be influenced by peer alliance.

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EFFECTIVENESS OF INTEGRATING ENHANCEMENTS TO STANDARD METHADONE TREATMENT FOR SUBJECTS AT HIGH RISK FOR HIV TRANSMISSION

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This was a preliminary examination of the effectiveness of integrating a set of enhancements into standard methadone treatment in terms of ability for staff to consistently deliver the intervention and of subject response. Subjects were 175 severely opiate dependent individuals who met at least one HIV high risk criteria: (1) HIV seropositive (n=11); gay or bisexual male (n=14); sex worker (n=70); sexual partner of any of the above (n=50). Subjects were randomly assigned in blocks to either a standard methadone or an enhanced methadone condition and their outcomes tracked for 8 consecutive months. Enhanced subjects also received tangible enhancements (transportation vouchers for the first 90 days) and psychosocial enhancements (more available and more skilled counselors; access to psychiatric services; and access to psycho-education groups on topics of womens' issues, cocaine abuse and dependence, and HIV-related concerns). Outcome variables were days in treatment, methadone dose levels, number of counseling sessions, and monthly urine toxicology.

Results showed enhanced and standard subjects retained in treatment for similar periods (206 vs 189 days). More enhanced subjects (15.1%) provided urines negative for drugs of abuse than standard subjects during month 1 (5%; X^2=4.78, df=1, p<.05) and slightly so during month 2 (37.1% vs 24.3%; X_2=3.14, df=1, p<.10). This difference correlated temporally with provision of transportation vouchers to enhanced subjects. Independent of condition, higher average modal methadone dose levels correlated with completion (n=109) of the 8 months (58.3 ml vs 50.73 ml; t=3.09, df=123.1, p<.01). Subjects received similar numbers of counseling sessions (16.6 vs 14.6; n.s.) and only 24.7% of enhanced subjects sought psychiatric services.

Interventions tested in this project were able to be implemented consistently and seemed appropriate to the clinical presentation of this group of subjects, despite showing little effect on outcomes. Because of the severe nature of their opiate dependency, interventions oriented toward subjects' immediate concerns (*e.g.,* methadone medication, transportation services) had most effects in terms of retention. With this population, the type of counseling interventions selected appeared to have no detectible effect on drug use outcomes.

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ACUPUNCTURE AS AN ADJUNCT TO SERVICES PROVIDED AT METHADONE TREATMENT FACILITIES

T. R. Jackson, E. A. Wells, O. R. Diaz, V. Stanton, and A. J. Saxon

Acupuncture is currently being studied as an adjunct to chemical dependency treatment in various locations and with a number of different types of programs and clinical populations. The goal of this project was to test the feasibility of using acupuncture in the initial stages of methadone maintenance/ methadone detoxification in order to achieve decreased acuity and duration of withdrawal symptoms, increased retention, increased stability, and decreased drug use of methadone clients. Over several months 60 opiate addicts (35% of the clients eligible), most multiply drug dependent, were recruited. Volunteers did not differ from refusers in any demographic variable. These subjects, while receiving standard methadone treatment, were randomly assigned to either specific or non-specific acupuncture treatment. The subjects and all research and clinical staff were blind to the condition assignment; only the acupuncturist providing the treatment was aware of the condition. Subjects received bilateral five point acupuncture and a point detector was used to differentiate needle placement between the two conditions. Acupuncture sessions were held once daily prior to methadone dosing. Data concerning subjects' attendance at methadone treatment services, methadone dose level, attendance at acupuncture sessions, and dates of discharge from treatment were gathered from client charts. Questionnaires regarding mood, physiological responses to acupuncture, and withdrawal symptoms were administered to subjects immediately prior to and following each acupuncture session. Subjects left a urine sample for drug urinalysis and completed self-rating scales on drug use and cravings and withdrawal symptoms weekly. Our study indicates a need to define an acceptable inert placebo for use in future studies; our research failed to find differences in drug use, either by urinalyses or self-report, between the specific and non-specific groups. In addition, the non-specific group reported less craving for opiates and cocaine then the specific group. Our findings, when comparing the acupuncture subjects with an historical control group of methadone patients at the same clinic who did not receive acupuncture, suggest that acupuncture reduces cocaine use among methadone patients but that future studies in this area need to standardize methadone doses in subjects.

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OUTCOMES FROM DIFFERING LEVELS OF INTERVENTION IN A METHADONE MAINTENANCE PROGRAM

J. M. White and C. F. Ryan

This study is a preliminary report on an evaluation of a public methadone program designed to incorporate differing levels of intervention and supervision. Clients enter a low intervention stream (Stream A) which provides counselling services on demand only; they are not required to be abstinent from illicit opioids and urines are not checked. A second stream (Stream B) is similar to the traditional methadone program, providing counselling for each client and requiring abstinence confirmed by urine testing. Participation in Stream B is associated with privileges such as methadone dispensing at a local pharmacy and take-home doses. Clients have the option of remaining on Stream A or may choose to change to Stream B. A third stream, Stream C, is associated with greater privileges, but is accessible only after some months of abstinence on Stream B.

After six months on the program, approximately 60% of clients had moved from Stream A to Stream B. Comparison of characteristics at entry showed that those choosing to remain on Stream A had used larger amounts of heroin, had a greater proportion of heroin using friends and engaged in more property crime. Their drug-using histories revealed a more rapid change from first use to first daily use of heroin. Preliminary results suggest that Stream A may attract a different group of heroin users compared to the traditional methadone program.

In both those who remained on Stream A and those who transferred to Stream B, participation in the program resulted in a number of changes. These included decreased heroin use, decreased benzodiazepine use, decreased property crime and drug dealing, and improved health status as shown by the SF-36 health questionnaire. Long term follow-up of the subjects will determine if these changes are maintained.

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A MODIFIED THERAPEUTIC COMMUNITY METHOD FOR METHADONE-MAINTAINED CLIENTS: EFFECTIVENESS AND CLIENT CORRELATES OF OUTCOME

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The Passages clinical program is an enhanced day-treatment program for methadone clients based on modified therapeutic community (TC) methods. Passages operates at two methadone clinics in the New York metropolitan area: a private clinic in Queens and a hospital-based clinic in Nassau County. Modifications to the TC approach that were implemented included greater emphasis on outreach and advocacy, reduction in the intensity of personal and interpersonal interactions, the replacement of confrontation with affirmation, graduated and guided implementation of all new expectations, and greater responsiveness to individual differences. The Passages clinical program runs four full days a week, and is composed of morning meetings, groups, seminars, communal lunch, recreational activities, and daily job assignment.

Passages (and TCs in general) view drug abuse as a disorder of the whole person, reflecting problems in conduct, attitudes, and emotional management. Therefore, the goal of treatment is the development of a prosocial lifestyle marked by alcohol ard drug abstinence, the elimination of AIDS-related risk behavior (needle use, sexual activity) and antisocial behavior (criminal activity), and the cessation of negative patterns of behavior and thinking (psychological dysfunction) that predispose the individual to drug use/abuse.

To study the effectiveness of the Passages clinical program, a research project compared Passages members with methadone-maintained clients who were not in any enhanced treatment. Data collected included face-to-face structured interviews, self-administered psychological scales, and administrative records. The primary research questions addressed were: 1) Is the Passages clinical program effective in reducing drug use, other risk behaviors, criminal activity, and psychological dysfunction? and 2) What significance does retention in Passages have in predicting treatment success?

Multivariate regression analyses, controlling statistically for possible initial group differences, indicated that Passages membership was associated with reductions in drug use (cocaine and heroin). Passages members who remained in the Passages program for at least six months were shown to be the key subgroup exhibiting improvement. Compared to nonpassages clients, retained Passages members showed significantly greater reductions in drug use (cocaine, heroin, and injection of either/both cocaine and heroin), needle use, criminal activity, and psychological dysfunction (Manifest Anxiety scale).

In summary, Passages members who remained active in the clinical program for at least six months registered greater overall levels of improvement. Since any reduction in drug use involving injection behavior may decrease the risk of contracting or spreading the AIDS virus, these findings have significant import for the policy debate about enhancing methadone treatment.

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RETENTION IN METHADONE MAINTENANCE BY DURATION IN TREATMENT AND REASON FOR DISCHARGE

K. J. Besteman, L. Greenfield, A. De Smet, B. T. Yates and J. Filipczak

Studies of retention in substance abuse treatment programs have generally focused on characteristics which predict retention duration. In the present study, patients' reasons for leaving were assessed in addition to their length of slay in the program. Indicators of treatment retention outcome were analyzed for a sample of methadone maintenance patients, including pre-treatment characteristics (n=304) and early in-treatment measures (n=250) analyzed for patients' first two weeks in the program. Retention was studied over a 10 month period. Patients included in the study were admitted prior to July 1, 1993, giving all S's the possibility of up to a 10-month stay in treatment prior to analysis. Patients who did not complete at least one month in the program were excluded from analyses on early in-treatment variables.

Retention was evaluated in two ways: (1) time in treatment and (2) reason for discharge. Time-in-treatment categories include Short duration (0 to 2.9 months), Medium duration (3 to 9.9 months), and Long duration (10 or more months). Reason-for-discharge categories include Drop (voluntary withdrawal prior to 10 months), Push (detoxification and discharge for noncompliance prior to 10 months), and Stay (10 or more months in treatment). Both methods of retention assessment proved useful, yielding different sets of indicators.

Pre-treatment indicators significant ($p<.05$) on both measures include: frequency of cocaine use, number of criminal convictions, and hours of employment per week. Pre-treatment indicators significant only on the time-in-treatment measure include: frequency of crack use, number of months spent in prison, total income from illegal sources over the past 12 months, and current employment status. Pre-treatment indicators significant only on the reason-for-discharge measure include: frequency/amount of alcohol use and prior participation in a maintenance program. Early in-treatment (first 2 weeks) variables were: positive urinalysis results for cocaine and opiates, number of individual counseling sessions, and total minutes of individual counseling. Early urinalysis results were significant on both retention measures. Number of individual sessions was significantly related to time in treatment, but total minutes of individual counseling was not significant on either measure.

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DRUG ABUSE TREATMENT OF NARCOTIC AND/OR COCAINE ABUSING PAROLEES

T. E. Hanlon, D. N. Nurco, R. W. Bateman, and T. W. Kinlock

This is an interim report of an ongoing long-term evaluation of the feasibility and effectiveness of a program of counseling and social support offered to male and female parolees from Baltimore City identified as either narcotic addicts or heavy cocaine abusers and required to participate in a drug abuse program in the community as a condition of parole. The study, which involves random assignment to treatment, was designed to isolate the separate effects of a combined social support/urine monitoring program offered to these parolees in which counseling, client advocacy, and case management are prominent features (E Group). Two control groups (U and C Groups) are being used in this study, the first of which receives weekly urine monitoring along with routine parole supervision and the second routine parole supervision alone. Principal outcomes in this evaluation, involving a one-year observation period, are such measures as time to first drug use, type of drug use, re-addiction, self-reported criminal activity, arrest, parole violation, incarceration, and compliance and retention in the program. Outcome data are presently available for 266 parolees who have completed the one-year parole period.

The average time in treatment for the E Group subjects was 6.6 months and 5.3 months for U Group subjects. The completion rates were 28% and 18%, respectively. Results for the total sample indicate that 47% of the parolees were arrested within the one-year parole period and 28% were incarcerated. There were no differential treatment group effects for these outcomes. There were, however, differences between males and females, with the rates for males for both arrests and incarcerations being two to three times those for females. Drug use comparisons for the E and U Groups, both of which received weekly urinalysis, showed equivalent illicit drug use, approximately 80% of both groups having used illicit drugs at least once. On a self-report measure of drug abuse, 3 1% of the E Group, 23% of the U Group, and 42% of the C Group reported at least one period of addiction during the year. Positive test results for weekly urine analyses served to reduce program compliance ratings made by parole officers for E and U Group parolees. In contrast, 60% of the Group C parolees were not required to submit urine specimens at any time during the one-year period. There were significant treatment group differences favoring E Group subjects on problem measures dealing with employment and home relationships.

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MEDICAL MAINTENANCE: A FIVE YEAR EXPERIENCE

E. C. Senay, A. C. Barthwell, R. Marks, and P. Bokos

Medical Maintenance (MM), as we define it, consists of one counseling session, one doctor visit and one random urine screen per month. Subjects have 13 day take home doses of methadone. To control for diversion, S's coming in for random urine screens must bring in their unused bottles for inspection. ASI's are obtained every six months. S's must have a six month period of drug free urines and good performance in standard treatment to be eligible for MM. We have five years of data on two sets of subjects. The first set, the pilot group (N = 130), was studied for a one year period. S's were assigned randomly to MM or to control (C) groups, on a two thirds MM, one third C basis. Seventy-three percent of S's completed the study year in good standing. No differences were found between groups. Control S's continued under standard conditions in their clinics of origin for six months and then moved to the experimental clinic under the MM paradigm for the second six months. Two blind HIV tests resulted in 0% and 4% positive, respectively, rates substantially below the 20 to 40% found in opiate injectors not in treatment in Chicago, indicating that MM S's are a distinct subset of IDU's. Without exception, S's were very satisfied with MM. Our IRB concurred with our judgement that return to standard conditions would have constituted a hardship and permitted us to continue S's in the MM condition beyond the one year study period. MM, compared to standard practices, resulted in substantial savings in counselor and nursing time.

We obtained a NIDA grant for a two year study of the paradigm described above but regulatory interaction between NIDA, FDA and DEA delayed the study with the result that we only obtained data for one year on new S's (N = 99). Sixty-seven percent of these S's completed the study year and there were no differences between MM and C groups. Thus, we replicated the findings of the pilot study. In the second study we continued to follow S's from the pilot study (N = 75), and obtained data on them for periods totaling three to five years. Eighty percent of pilot S's finished three to five years in the study in good standing. In a total group of 229 S's, followed for one to five years, there were three instances of criminal activity, a remarkable record given the histories of the individuals involved in this research. Conclusion: there is a subset of MM patients who can perform well in treatment with lower requirements for counseling and pick ups than current regulations require without significant risk of diversion. In addition, resources can be freed up to be applied to the needs created by the HIV epidemic.

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THE ROLE OF SOCIAL RELATIONSHIPS IN ADDICTIVE BEHAVIOR: AN EXAMINATION OF AN IN-TREATMENT AND OUT-OF-TREATMENT SAMPLE

L. R. Goehl, D. S. Metzger, H. Navaline, G. E. Woody, and A. R. Childress

While recent research has demonstrated that social relationships have a significant impact on substance abuse treatment, the effect found has not been consistent. Additionally, the role of social relationships has not been examined in substance abusers who are not receiving treatment. In a prospective study of 222 opiate addicts (Risk Assessment Project; 138 in-treatment and 84 out-of-treatment), the effect of social relationships on addictive behavior was examined. Supportive, satisfying, and drug-free social networks were expected to have a positive impact on outcome for both in and out-of-treatment subjects. Baseline and follow-up measures assessed quantitative and qualitative network features. Outcome data included SCL-90, BDI, ASI scores, high-risk behavior, and drug use frequency. Network size per se was not significantly associated with outcome. There were, however, significant differences in network size between in-treatment (M=5.8) and out-of-treatment subjects (M=4.8) (t=-2.3, df=216, p=.022) and between baseline (M=5.4) and 18 month follow-up (M=3.8) (t=6.74, df=221, p=.000). Importantly, drug use in the network was significantly associated with outcome at follow-up. Thus, subjects with drug using relatives and without drug-free friends had higher levels of depression, psychiatric symptoms, drug use, needle sharing, and lower family/social functioning at follow-up. For the in-treatment group, drug use in the network was significantly associated with higher levels of depression, psychiatric symptoms, and drug use. For the out-of-treatment group, drug use in the network was significantly associated with decreased family/social functioning and higher levels of drug use. Female network members were significantly associated with being in treatment, less high-risk behavior, fewer symptoms of psychological distress, and increased perceived influence of the network. Higher perceived satisfaction with the network was significantly associated with less drug use, better family/social functioning, and fewer symptoms of psychological distress. These results indicate that social network variables, particularly drug use in the network and perceived quality of the network, are important predictors of outcome for drug abusers in and out of treatment.

AFFILIATION:

Treatment Research Center, University of Pennsylvania, and VA Medical Center.

VOCATIONAL ENHANCEMENT: OVERVIEW OF FINDINGS OF ONE RESEARCH DEMONSTRATION PROJECT

P. H. Kleinman, R. B. Millman, M. L. Lesser, H. Robinson, P. Engelhart, C. Hsu, and I. Finkelstein

This paper reports selected findings of the Comprehensive Vocational Enhancement Program (CVEP) for Methadone Maintenance Treatment Programs project, a five year research demonstration project funded by NIDA. currently in its last year. The program was implemented in a methadone program in the New York metropolitan area. The CVEP is a nine-stage program, which starts with orientation and assessment, and proceeds through job search, job acquisition and job stabilization. Time in each stage is planned to be variable, and total time in the program may be as long as two years. Most sessions are scheduled on an individual basis. and emotional support is offered as well as task-oriented activities. Data presented here are based in part on 289 clients who consented to participate in the CVEP, and in part on 113 clients retained in the larger methadone program for at least 18 months.

A number of important findings have emerged. **First,** substantial numbers of methadone treatment clients will voluntarily participate in a well-conceived and well-run vocational rehabilitation program. In this project, 80% of the patients who consented to participate voluntarily attended at least one treatment session, and fully 47% attended 11 or more sessions. **Second,** results in the employment area were mixed. Participation in the program resulted in some noteworthy "success stories" of program participants who obtained good jobs even though they appeared to be poor candidates for vocational progress. However, there were no statistically significant differences in measures of work involvement between program participants and program non-participants. **Third,** program participants were significantly more likely than non-participants to be abstinent from cocaine, as determined by urinalysis results, at the 18 month follow-up period. The dose-response relationship is clear and linear, and holds even with control on baseline cocaine use, self-esteem, and level of psychiatric symptomatology. The meaning of these findings and their implications for treatment and treatment research are discussed.

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AFFILIATION:

Cornell University Medical College, North Shore University Hospital, National Association on Drug Abuse Problems, Greenwich House Methadone Treatment Programs

MOTHER-INFANT INTERACTION BETWEEN COCAINE ABUSING PARENTS AND THEIR THREE AND SIX MONTH OLD INFANTS

L. C. Mayes, R. Feldman, R. H. Granger, and R. Schottenfeld

How parental cocaine abuse affects parents' ability to respond contingently and reciprocally to their infant during mutual interactions has not been extensively studied. The face-to-face interactions of 29 cocaine-abusing mothers and their prenatally exposed infants at three and six months of age were compared to those of 23 non-cocaine using mothers. Groups were similar in terms of maternal ethnicity but differed in terms of maternal education and associated drug use (alcohol, tobacco, and marijuana) as well as infant birthweight. Interactions were scored by coders blind to the mother's drug use status for 14 maternal behaviors reflecting reciprocity, adaptation, consistency, and resourcefulness. Eight infant behaviors were coded measuring level of alertness, vocalizations, affective range, and infant responsiveness. Cocaine-using mothers showed significant differences from non-cocaine using mothers in 10 of 14 behaviors. Cocaine-using mothers less often elaborated on the infant's behavior, used fewer vocalizations, and showed less consistency and verbal fluency in their responses. During the interactions, the infants of cocaine-using mothers showed significant differences in three of the eight behaviors. The infants were less sociable, less likely to initiate an interactive bid, and more likely to look away. Between three and six months, cocaine-using mothers were significantly more likely to show more impaired interactive behaviors while non-cocaine-using mothers became more coordinated and responsive in their interactions.

The significant interaction between age of assessment and drug-use status pertained after covarying the analyses for associated maternal drug use and perinatal and sociodemographic factors. These findings are discussed in terms of their implications for a biologic-environment interaction model for the effects of pre- and postnatal cocaine exposure on early infant development.

AFFILIATION:

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BIRTH OUTCOME NOT CORRELATED WITH LATE-TERM COCAINE EXPOSURE WITHIN AN EXPOSED SAMPLE

P. R. Marques, A. S. Tippetts, and D. G. Branch

A sample of 163 cocaine-positive, newly post-partum, public assistance women (28 ± 4 years age) were identified by urine toxicology screens, and referred by hospital healthcare workers for random assignment to drug treatment (residential, outpatient, non-treatment comparison). Infant hair, maternal hair and urine cocaine were measured at intake and at four month intervals; social and psychometric instruments (BSI, DLC, ASI, HOME, NCAST, Rosenberg, Sarason, Beck) were administered at eight month intervals. All measures were collected at project entry along with birth outcome data. Hair cocaine (mean ± sd) was found to be 365 ± 426 (mother) and 290 ± 324 ng/10mg (infant); two extreme outliers were removed from the data set. This report focuses on infant outcome. Hospital charts showed these infants as a group to be small with 31% < 2500 gm birth weight (bw); full-term mean bw = 2904 gm, total sample bw = 2624 ± 711 (sd), N = 144; full-term head circumference (hc) = 32.7 cm, total sample hc = 31.9 ± 2.1 cm; full term body length (bl) = 48.5 cm, total sample bl = 46.7 ± 3.9 cm. (Fewer infants, N = 76 and 63. had the latter measurements in their charts.) These birth size variables are intercorrelated with $r \geq .84$. Can measured third trimester cocaine exposure (estimated from hair) explain these outcome findings?

Hair cocaine estimates from both mother and infants were reported earlier to be well-correlated ($r = .48$. $P < .0005$, $N = 132$); such hair samples are believed to reflect approximate last trimester exposure. The first post-natal infant hair sample also correlated with other exposure measures such as maternal urine cocaine metabolite ($r = .33$, $N = 128$, $P < .0005$), and somewhat but weakly with maternal 30 day self-report ($r = .21$, $N = 129$, $P < .02$). While only hair and meconium can provide reliable long term exposure estimates, neither mother nor infant hair samples can be considered reference standards. To minimize error in either one exposure estimate, a single factor solution representing both hair samples was created to strengthen the estimate. The degree of relation between exposure and birth outcome was then assessed and results showed that virtually none of the variance in birth outcome can be explained by degree of exposure using the factor score, nor by using the raw hair cocaine data from either mother or infant. It's concluded that birth size outcome differences within the sample cannot be directly attributed to maternal cocaine use. Examination of other variables in the data set from the baseline ASI, BSI, Social Support, Millon, Beck, NCAST Teaching, Feeding or HOME found none to be significantly associated with poorer birth outcomes, only pre-natal care predicted outcome ($r = .35$). Birth size differences are therefore presumed to reflect a diffuse composite of poor health and poor self-care more so than late trimester cocaine exposure.

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CAREGIVING INFLUENCES ON THE DEVELOPMENT OF INFANTS BORN TO COCAINE-ADDICTED WOMEN

J. Howard, L. Beckwith, M. Espinosa, and R. Tyler

The present study investigated the influences of maternal personality characteristics/disorders on parenting behaviors, and how these behaviors, in turn, were related to children's development. Prior research has shown that the most significant mediating factors that affect individual differences in caregiving among non-addicted women are the women's personal psychological resources, including personality characteristics and/or disorders. A group of 70 cocaine-abusing women were identified during pregnancy. At intake, the Addiction Severity Index was administered to quantify drug use, and the Millon Clinical Multiaxial Inventory was administered to describe DSM-III axis two personality characteristics and axis one clinical disorders. (Both of these are self-report measures.) To evaluate later parenting behaviors, home observations of 47 infants living with biological mothers and 23 infants living with alternative caregivers were made six months after delivery, scored by mother-infant interaction rating scales. Also at six months, children's cognitive development was assessed in the laboratory using the Bayley Scales of Infant Development. Maternal personality characteristics/disorders during pregnancy that were negatively associated with quality of mother-infant interaction at six months were histrionic, narcissistic, paranoid, bipolar-manic, drug abuse/drug problems and psychotic delusions. Poorer quality of mother-infant interaction, in turn, was associated with lower infant Bayley Mental Development Index scores. In summary, mothers who reported more histrionics, narcissism, paranoia, bipolar-mania, drug abuse-related problems, and psychotic delusions during pregnancy were less sensitive caregivers later, and their infants performed less well cognitively.

Further, mothers of the 23 infants living with alternative caregivers were similar to the mothers who retained custody of their children in age, education, number of children, and personality characteristics/disorders. Alternative caregiver-infant interaction at six months was not different from that found in the mother-infant dyads. Yet, those infants in alternative care situations performed significantly less well cognitively than those cared for by their mothers.

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MATERNAL PSYCHOSOCIAL CHARACTERISTICS OF PREGNANT COCAINE DEPENDENT WOMEN: RESIDENTS VS. OUTPATIENTS

M. Comfort, K. Kaltenbach, and A. Smith

Clients in residential and outpatient programs are being compared in a NIDA Research Demonstration Project for pregnant cocaine dependent women and their infants. At enrollment subjects were pregnant (≤ 24 weeks.), using cocaine (non-opiate) and 18 years of age or older. The treatment programs provide comprehensive obstetrical and psychosocial services. This report includes 64 women active in treatment: residents (MSP) n=32; outpatients (OPS) n=32. There were no differences between groups in age (X=28 years.) or race (86% African American). MSP women reported higher education (11.8 vs. 10.8 years, F=3.45, p <.05). The average profile of lifetime substance use for both groups included cocaine (X = 6.2 years), alcohol (X = 7.7 years) and marijuana use (X = 5.3 years), with 83% reporting previous treatment episodes. Intake assessments showed no differences between groups in depression or locus of control, but more psychiatric symptoms were reported by MSP women (p <.0125). Significantly higher stress was perceived by MSP women at intake (t = 2.37, p <.05) and at eight months of pregnancy (t = 4.42, p <.05), while parenting self esteem showed no differences between groups. Family members were the leading sources of support for both groups. Correlations between intake characteristics and months in treatment (X = 6 mos) showed moderate associations. The results suggest that, except for education, stress and psychiatric symptoms, women in residential and outpatient programs were similar in personal characteristics and time spent in treatment. Further analyses of case studies and treatment success factors are being conducted.

AFFILIATION:

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CHANGES AND STABILITY IN FAMILY FUNCTIONING IN PERINATAL ADDICTS

D. L. Haller, K. S. Ingersoll, K. S. Dawson, and S. H. Schnoll

This study examined family characteristics of perinatal addicts in treatment in three areas over time: family of origin, current family, and current partner relationship. Subjects were 125 addicted women in perinatal outpatient treatment; 84% were African-American, 15% Caucasian, and 1% Native American. Most were unemployed, unmarried polysubstance abusers.

Measures: The Relationship Assessment Form (RAF) assessed "codependent" behavior such as needing the other's approval for self-worth, blaming external forces for a partner's behavior, etc. The RAF Total's internal consistency in this sample was an acceptable .71 (Cronbach's alpha). The Family of Origin Scale (FOS) assessed the perceived psychological health of an individual's family of origin. The Self-report Family Inventory (SFI) evaluated the health of the current family. Each subject completed a comprehensive intake interview with her therapist during the first week of treatment to provide demographic and psychosocial information. Subjects completed family measures at intake, after five months of treatment, and six and twelve months post discharge.

Results: At Intake, perinatal addicted women endorsed roughly half of the RAF items, indicating moderate codependent behavior, and resembled distressed psychiatric patients on the FOS and SFI. Few changes occurred from pretreatment to posttreatment. At followup points, family of origin perceptions were unchanged from intake, current family functioning deteriorated, but RAF scores decreased, reflecting improvements in Total codependent behaviors, lowered dependence for self-worth, less likely to orient life around the other, and less likely to blame external forces for the other's behavior.

Conclusions: Our findings are mixed with regard to changes in family functioning. We found limited, transient changes in family functioning in three domains. These findings may result from problems in the unit of intervention and measurement in this study. The program did not provide family therapy per se, but targeted intervention and measurement at the addicted mother alone. This strategy may have limited efficacy despite its multicomponent nature. Additionally, the instruments used were normed on nonsubstance-abusing, two-parent families, and may need additional refinement for use in the perinatal addicted population. The fact that families tended to deteriorate may reflect a return to drug use at followup, or result from subjects' denial of problems before treatment but willingness to admit them posttreatment.

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DRUG WITHDRAWAL DURING PREGNANCY - FETAL EFFECTS

M. A. E. Jarvis, J. S. Knisely, and S. H. Schnoll

As many as 15% of pregnancies are complicated by drug or alcohol dependence. While post-natal effects have been described, there is little information available regarding the fetal effects of *in utero* exposure to drugs and drug withdrawal. At the Medical College of Virginia, we have been recruiting women in their second and third trimesters who wish to be withdrawn from drugs to participate in investigations of the effects of drug withdrawal on the fetus. The women are admitted to the Clinical Research Center, are tapered with medications causing cross-tolerance to their drugs of choice (where possible) and are monitored using biophysical profile, uterine and umbilical doppler ultrasounds, fetal movement counts as well as other measures.

Previous reports of data from these studies showed the presence of an *in utero* abstinence syndrome during abrupt withdrawal from cocaine. This abstinence syndrome is marked by increased maternal perception of fetal movement (fetal movement counts) and increased variability in the maternal-placental blood flow (umbilical s/d ratio). Abrupt withdrawal from cocaine has not been seen to be associated with fetal distress.

Current work extends these studies to other drugs and drug combinations. It is the rare chemically-dependent person who uses only one drug, making investigations of combinations very important. Since these are ongoing studies, numbers of subjects in these groups are very small at this time, and thus, information must be interpreted with caution. As with cocaine, an increased variability of umbilical doppler readings was seen with women using alcohol (withdrawn on phenobarbital). Little change was seen in women using opioids (withdrawn on methadone) or in women using combined opioids and cocaine (withdrawn ***on*** methadone). The significant increase in fetal movement counts observed in cocaine-dependent women was not reported by polydrug users. Also, no significant indications of fetal stress have been seen in any subjects, and all biophysical profiles have been reassuring.

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PERINATAL OUTCOMES OF INFANTS BORN TO DRUG DEPENDENT WOMEN ENROLLED IN A MULTI- MODALITY TREATMENT PROGRAM

K. Kaltenbach, M. Comfort, and A. Smith

This study assessed perinatal outcomes for 182 drug exposed infants born to women receiving treatment in a comprehensive outpatient program. The program includes obstetrical, medical, psychiatric, and psychosocial services, methadone maintenance treatment and drug free treatment for non-opiate dependent women. Data were analyzed according to maternal drug use: Group 1, methadone maintained women with no other drug use (n=21); Group 2, methadone maintained women who used other illicit drugs excluding cocaine (n=36); Group 3, methadone maintained women who used other illicit drugs including cocaine, (n=66); Group 4, cocaine dependent women who used cocaine and other drugs excluding opiates (n=24); and Group 5, cocaine dependent women who remained drug free (n=35). Mean birthweight for term infants was 3005 gms; for preterm infants, 2260 gms. Preterm infants did not differ in birthweight, length or head circumference as a function of maternal drug use. Differences between groups were found for term infants in birthweight (Kruskal Wallis=p .004). Mann Whitney U tests revealed infants in group one had smaller birthweights than infants in groups five. Groups 2 and 3 had a higher incidence of prematurity (p=.03). These data suggest the outcome of infants of women maintained on methadone differs as a function of concurrent poly-drug abuse and the outcome of infants exposed to cocaine differ as a function of concurrent opiate use. When investigating infant outcomes it is most important that maternal drug use be differentiated not only according to primary drug and/or poly-drug use, but according to specific combinations of maternal drug use.

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THE RELATIONSHIP BETWEEN ADDICTION SEVERITY AND A FIVE FACTOR MODEL OF PERSONALITY IN PREGNANT COCAINE ABUSERS

S. A. Ball and R. S. Schottenfeld

Previous research has found an association between substance abuse and the personality traits of high impulsivity, sensation seeking, and emotionality, and low sociability. The current study assessed the relationship between a biologically-based five factor model of personality and substance abuse severity and psychiatric symptoms in cocaine abusing pregnant women. Ninety-one predominantly single, unemployed, African-American women seeking prenatal care at an inner city hospital were administered the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ). the Addiction Severity Index (ASI), and the Beck Depression Inventory (BDI). The ZKPQ consists of five scales measuring the following basic dimensions of personality: 1) Impulsive Sensation Seeking (ImpSS); 2) Neuroticism-Anxiety (N-Anx); 3) Sociability (Soc); 4) Aggression-Hostility (Ag-Hos); 5) Activity (Act). Scores on the five factors of personality were normally distributed and cocaine abusing pregnant women scored lower than the predominantly white standardization sample of college women only on Soc. Pearson correlations were used to assess the relationship between each continuous personality measure and ASI and BDI severity scores. T-tests analyzed personality trait differences between those reporting the presence vs. absence of significant psychiatric symptoms in the past 30 days and lifetime.

Results indicated that N-Anx was positively correlated with ASI Drug ($r=.28$), Legal (.37), Family (.39), and Psychiatric (.47) severity and BDI scores (.50). Ag-Hos was correlated with ASI Legal ($r=.24$) and Psychiatric (.32) severity and BDI scores (.44). Act ($r=-.27$) and Soc (-.32) were negatively correlated ASI Drug Severity. Subjects reporting a history of recent and lifetime depression, anxiety, suicidality, and violence scored higher on N-Anx and ImpSS ($p<.05$). A history of suicidality, violence, and criminal arrests was also associated with higher Ag-Hos. Scores on the personality dimensions were not related to recency of drug use. The current findings support the importance of psychopathic and negative affect personality traits in this sample of cocaine abusing women. Subtyping substance abusers based on a five factor model of personality may provide important information for understanding etiology, predicting treatment response, and identifying high risk individuals.

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Available upon request of senior author.

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COST-EFFECTIVENESS OF COMPREHENSIVE CARE FOR DRUG-ABUSING PREGNANT WOMEN

J. H. Lee and D. Svikis

Several studies have shown behavioral incentive programs to be an effective strategy for promoting drug abstinence in outpatient programs, but little research has addressed the issues of program retention. The present study examined the effectiveness of an incentive program targeting program attendance. Forty-eight substance abusing pregnant women were given the opportunity to earn seven tickets to the Baltimore National Aquarium (worth $21.00) by completing seven consecutive days of full programming following transfer from inpatient to outpatient programming. The number of patients attending full programming was calculated for the first seven days following transfer and then again for 30 days post transfer. A control sample of 47 patients, not offered the incentive program, consisted of all admissions for the two months prior to start-up of the incentive program. Twenty-five percent of patients offered the ticket incentive attended full programming for seven consecutive days post-transfer as compared to only 9% of patients not offered the ticket incentive. More importantly, 100% of those patients who earned aquarium tickets were still in treatment 30 days following transfer as compared to only 33% of controls. The results of this report demonstrate the effectiveness of behavioral incentives in the treatment of pregnant drug abusing women in improving program retention.

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HOSPITALIZATION OF CHILDREN BORN TO COCAINE-USING MOTHERS

B. W. C. Forsyth, J. M. Leventhal, and K. Qi

Lengthy hospitalizations of infants of cocaine-using mothers are costly and often cited as a potential cost-saving outcome of treatment programs. To determine whether these children also spend more time in hospital beyond the newborn period and the extent to which prematurity accounts for differences, we identified 137 children of cocaine-using women who attended the Yale-New Haven Hospital prenatal clinic. For each case, a control child of a non-cocaine-using mother (two independent notations in the mother's record) was matched for race, billing status, maternal age and parity (control 1). Whenever a case was premature, a premature, second control (control 2) was identified. All hospital stays before age two years were reviewed and the Pediatric Appropriateness Evaluation Protocol was used to categorize medically unnecessary days. The sample was mainly black (82%) and on Medicaid (97%). The results are as follows:

	Case	Control 1	Control 2	
Proportion premature	23%	7%	23%	
Birth: mean hospital days	7.8	3.9**	6.5	(Difference
% med. unnec.	14.0	2.0	3.0*	from case
< 2 yrs: mean hospital days	2.0	1.1	0.8*	* P<.05
% med. unnec.	21%	9%	5%	**P<.01)

We conclude that cocaine-exposed infants spend more time in the hospital even beyond the newborn period. Although in newborn admissions prematurity accounts for a large part of this difference, it is not a major factor with later admissions.

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OPIOID PEPTIDE AND RECEPTOR mRNA LEVELS IN THE RAT BRAIN DETERMINED BY TCA PRECIPITATION OF mRNA: cRNA HYBRIDS

R. Spangler, Y. Zhou, E. Unterwald, V. Yuferov, A. Ho, and M. J. Kreek

We have utilized a sensitive and quantitative mRNA assay to measure levels of opioid receptor and peptide mRNA simultaneously in selected rat brain regions. The results shown in Table I are for six brain regions: OLF - olfactory tubercle; NAC - nucleus accumbens; CPU - caudate putamen; AMY - amygdala; HYP - hypothalamus; SN - substantia nigra. ND indicates that no specific mRNA was detected when 75% of a total region was assayed for that gene. The mRNA densities are expressed as attomole specific mRNA/microgram total RNA.

Tab I	Enkephalin	Dynorphin	Mu	Kappa
OLF	3.9 ± .40	ND	0.14 ± .02	ND
NAC	22 ± 1.5	4.1 ± .30	0.29 ± .04	0.59 ± .11
CPU	46 ± 3.0	4.5 ± .34	0.31 ± .04	0.47 ± .12
AMY	2.8 ± .14	0.41 ± .02	0.20 ± .01	0.26 ± .02
HYP	2.1 ± .12	0.59 ± .04	0.24 ± .02	0.29 ± .03
SN	ND	ND	0.24 ± .01	0.24 ± .02

Pairwise comparison of specific mRNAs in the caudate putamen revealed a significant correlation between the dynorphin mRNA level and the level of kappa mRNA in each animal. On the other hand there was no animal by animal correlation when mu mRNA was plotted as a ratio with either dynorphin or enkephalin mRNA.

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EVALUATION OF A SERIES OF N-ALKYL BENZOMORPHANS IN A CELL LINE EXPRESSING TRANSFECTED δ-OPIOID RECEPTORS

M. E. Abood, R. C. Carter, E. L. May, and L. S. Harris

We have isolated and characterized a δ--opioid receptor cDNA clone from rat brain (Abood, *et. al.,* 1994). When transiently expressed in COS cells or stably transfected in CHO cells, the clone shows high affinity opioid binding with selectivity for δ-opioids. Transfection of individual opioid receptors in CHO cells provides a pure, homogeneous population essential for screening drug candidates. We used this system to evaluate the affinity of a series of (-)-5 , 9 α-dimethyl-2-hydroxy-N-substituted-6,7-benzomorphans at the cloned δ-opioid receptor. [^{3}H]Diprenorphine was used to measure opioid receptors in P_2 membrane preparations. [^{3}H]Naltrindole was used to confirm the δ-specificity of the cloned receptor. Both compounds gave a Bmax of 1159 fmol/mg and Kd of 0.12-0.5 nM. Competition assays were performed with 1 nM [^{3}H]diprenorphine and 0.1 to 10 μM displacing ligands. Our results suggest that the benzomorphan compounds display a range of affinities (<30 nM to >4 μM) for the δ-opioid receptor in the cell line. The rank order of potency was C6>C4>C8>C7=C1>C5>C2>C3>C9>C0>C10. The rank order of potency at the cloned rat δ receptor does not correlate well with that of antinociception in the mouse tail flick test ($p<.05>.025$) in this class of compounds. Possible reasons for the lack of correlation include the predominance of "μ" opioid receptors for mediation of antinociception and the probable "δ2" subtype of the cloned receptor. Support for the former reason comes from subsequent experiments demonstrating a very good correlation ($p<.001$) between the rank order of affinity of these compounds in a cell line expressing cloned mouse μ opioid receptors with that of antinociception. In sum, transfected cell lines provide a useful model for testing novel pharmaceuticals.

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NEW RECEPTOR SELECTIVE OPIOID AGONISTS AND ANTAGONISTS, DERIVED FROM SYNTHETIC COMBINATORIAL LIBRARIES

C. T. Dooley and R. A. Houghten

Synthetic combinatorial libraries are composed of tens of millions of compounds arranged as mixtures. Using a synthetic peptide combinatorial library (SPCL) (Houghten *et. al.,* 1991) made up of L-amino acids, we have recently identified the acetalins, peptide ligands that inhibit the binding of ^{3}H-DAMGO to receptors in crude rat brain homogenates, and are potent antagonists in the guinea pig ileum assay (Dooley *et. al.,* 1993). They have inhibitory activities in the 5-10 nM range at the μ receptor site, were found to be inactive at the κ_1 and κ_2 receptor sites, and showed a 10-fold preference for μ over δ sites. A similar library composed entirely of D amino acids was also screened and iterations were performed to obtain individual peptides. One of the individual peptides, Ac-rfwink-NH_2, had high affinity for μ_1 and μ_2 receptors (16 nM and 41 nM, respectively) receptors, moderate affinity for κ_3 (288 nM) receptor, and was not active at the highest concentration tested for δ, κ_1, and κ_2 receptors. This peptide was an agonist in the guinea pig ileum and mouse vas deferens assays. The peptide produced analgesia in mice when administered i.c.v., 3 nmol induced 100% antinociception for two hours which decreased to 35% in five hours. The peptide also produced analgesia in mice following i.p. administration (10 mg/kg of the peptide produced antinociception virtually identical to the same dose of morphine). These libraries are currently being tested in δ and κ selective assays, mixtures from the same library show different selectivities for the different receptors. Thus we can expect individual peptides derived from these mixtures to have high selectivities for a particular receptor.

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A 14ß-NITROCINNAMOYL DERIVATIVE OF DIHYDRO-CODEINONE AND ITS CORRESPONDING N-CYCLOPROPYL-METHYL ANALOGUE ACT AS SHORT-TERM MU-SELECTIVE AGONISTS AND LONG-TERM MU-SELECTIVE ANTAGONISTS

J. M. Bidlack, K. P. Hill, A. Sebastian, and S. Archer

We have previously reported that 5ß-methyl-14ß-(2-nitro-cinnamoy1amino)-7,8-dihydromorphinone (MET-CAMO) and its corresponding N-cyclopropylmethyl derivative (N-CPM-MET-CAMO) were μ-selective irreversible opioid antagonists, devoid of agonist properties in the mouse tail flick test. (Jiang *et al.,* J Pharmacol Exp Ther 268:1107-1113 1994). In the present study, we investigated the receptor binding properties, and the short-term and long-term effects of 14ß-(2-nitrocinnamoylamino)-7,8-dihydrocodeinone (CACO) and its N-cyclopropylmethyl analogue (N-CPM-CACO) in the mouse 55°C-water tail flick test. Both CACO and N-CPM-CACO produced wash-resistant inhibition of μ opioid binding without altering ∂ or κ binding to bovine striatal membranes. Pretreating membranes with 50 nM of either compound followed by extensive centrifugal washes, reduced the B_{max} value for [^{3}H]DAMGO binding by 75% without altering the K_d value in comparison to control membranes. In the mouse tail flick test, an i.c.v. injection of CACO produced short-term μ-selective antinociception that was dose-dependent with a maximal analgesic effect obtained with 10 nmol. A single 1-nmol i.c.v. injection of CACO administered from 8 to 72 hours before testing suppressed morphine-induced antinociception, but had no effect on antinociception mediated by ∂ or κ opioid receptors. N-CPM-CACO also produced μ-selective short-term antinociception and long-term antagonism of morphine-induced analgesia. N-CPM-CACO was more potent than CACO in producing short-term antinociception. However, both compounds were equipotent in producing long-term antagonism of analgesia mediated by the μ opioid receptor.

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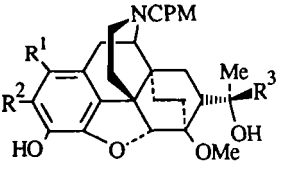
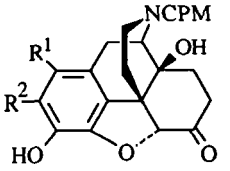
THE EFFECT OF AROMATIC SUBSTITUTION ON THE ACTIVITY OF SOME STANDARD ANTAGONISTS AND PARTIAL AGONISTS

J. W. Lewis, S. M. Husbands, C. Smith, M. Myers, P. A. Bradley, A. S. Haynes, and P. T. Taylor

The effect of aromatic substitution in 4,5-epoxymorphinans on opioid receptor subtype activity has not been previously investigated. We have prepared and evaluated 1-chloro and 2-nitro derivatives of naltrexone, diprenorphine and buprenorphine.



R^1=Cl,R^2=H,R^3=^{t}Bu
R^1=Cl,R^2=H,R^3=Me
R^1=H,R^2=NO_2,R^3=^{t}Bu
R^1=H,R^2=NO_2,R^3=Me



R^1=Cl,R^2=H
R^1=H,R^2=NO_2

From binding studies and mouse vas deferens it appears that, for naltrexone and diprenorphine, the effect of 1-chlorination is to enhance affinity at the μ, κ, and δ receptor sites. For buprenorphine the affinity has remained unchanged at κ and δ sites, while at μ there is a 10-fold drop in affinity and also a drop in intrinsic activity. For each compound *in vivo* activity is lower than predicted from the *in vitro* results. This is particularly true for the orvinols buprenorphine and diprenorphine and may be due to increasing lilpophilicity beyond the optimum. 1-Chloronaltrexone displayed high potency in the mouse (10 x naltrexone) but on moving to a higher species (rhesus monkey) the potency dropped to half that of naltrexone. However it remains a potent *in vivo,* relatively lipophilic, antagonist of possible use in a depot preparation for opiate addict treatment.

The effect of 2-nitration is to substantially reduce affinity at all three receptor types. This was particularly evident with buprenorphine and diprenorphine, each showing a reduction in affinity of between two and three orders of magnitude, while naltrexone was least affected, the loss in affinity being limited to one order of magnitude. From bioassay results (GPI) it appears that diprenorphine has retained κ intrinsic activity while buprenorphine has lost activity at the μ receptor. *In vivo* neither 2-nitrobuprenorphine nor 2-nirtodiprenorphine show any appreciable agonist or antagonist activity. Surprisingly in both mouse and rhesus monkey 2-nitronaltrexone displayed the characteristics of a low affinity partial agonist. As yet this activity has not been fully characterised but is most likely due to activity at the μ receptor.

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ANTINOCICEPTIVE PROFILE OF SNC 80, A HIGHLY SELECTIVE, NON-PEPTIDIC DELTA OPIOID AGONIST

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INTRODUCTION: The discovery of opioid analgesics which act via non-mu (μ) mechanisms has been a goal of opioid research for many years. Opioids acting via delta (δ) opioid receptors appear to have potential therapeutic advantages over μ opioid agonists including (a) limited (or no) abuse potential; (b) antinociceptive activity in most animal models; (c) decreased (or no) development of physical dependence; (d) lack of depression (and possible stimulation) of respiratory function and (e) little (or no) induction of constipation. These indications have been derived from studies with opioid peptides which have high selectivity for δ opioid receptors including [D-Pen^2, D-Pen^5]enkephalin (DPDPE) and [D-Ala^2, Glu^4]deltorphin. Systemic administration of these peptides is generally not feasible due to limited blood brain barrier penetration. The development of systemically-active, non-pcptidic opioid δ agonists is thus a desirable research objective. Recently, the pharmacology of BW 373U86 has been reported (JPET. November 1993). This non-pcptidic opioid agonist has selectivity for δ opioid receptors. The present studies assess the pharmacology of SNC 80, an enantiomer of BW 373U86.

METHODS: **Mouse vas deferens (MVD) and guinea pig ileum (GPI) bioassays:** Dose-response curves for inhibition of electrically stimulated contractions in each tissue type were constructed for SNC 80, DPDPE and [D-Ala^2, Glu^4]deltorphin. **Antinociceptive testing:** Male ICR mice were tested in the warm water tail-flick test following administration of intracerebroventricular (*i.c.v.*), intrathecal (*i.th.*) or intraperitoneal (*i.p.*) injections of SNC 80.

RESULTS: IC_{50} values for SNC 80 in the MVD and GPI bioassays were 2.73±0.5 and 5457±2052 nM. respectively. The GPI/MVD ratio of IC_{50} values for SNC 80 was approximately 2000 compared to DPDPE (1800) or [D-Ala^2, Glu^4]deltorphin (17000) selectivity ratios. The δ-selective antagonist ICI 174,864 (1 μM) and μ-selective antagonist CTAP (1 μM) produced 236- and 5.34-fold shifts in the IC_{50} values for SNC 80, respectivety. SNC 80 produced dose- and time-related antinociception following *i.c.v., i.th.* and *i.p.* administration. The calculated A_{50} values (95% C.I.) were 104.9nmol (63.7-172.7), 69.0 nmol (51.8-92.1) and 57.0 mg/kg (44.5-73.1), respectively. SNC 80 antinociception (*i.c.v.*) was antagonized by *i.c.v.* pretreatment with naloxone (3 nmol, opioid antagonist), ICI 174,864 (4.4. nmol, δ opioid antagonist), naltrindole (10 nmol, δ opioid antagonist), [D-Ala^2, D-Leu^5, Cys^6]enkephalin (DALCE, 4.8 nmol, δ_1 opioid antagonist), [D-Ala^2, Cys^4]deltorphin (3 nmol, δ_2 opioid antagonist), but not by ß-FNA (18 nmol, μ opioid antagonist). suggesting that its antinociceplive actions are produced via activation of opioid δ_1 and δ_2 receptors.

CONCLUSION: Based on its profile in vivo and in vitro, SNC 80 is a highly selective, nonpetidic opioid δ agonist. In mice, SNC 80 produces antinociception after *i.c.v., i.th.* and *i.p.* administration. Furthermore, SNC 80 does not produce convulsions at *i.p.* doses up to 300 mg/kg and al *i.c.v.* doses of 300 nmol/mouse. SNC 80 promises to be a useful compound for the exploration of opioidreceptor pharmacology. Analogues of SNC 80 are also currently under study.

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GENDER AND MENSTRUAL CYCLE INFLUENCES ON COCAINE'S EFFECTS IN HUMAN VOLUNTEERS

S. E. Lukas, M. B. Sholar, M. Fortin, J. Wines, Jr., and J. H. Mendelson

Although men differ from women in their response to many drug classes. drug abuse research has historically been conducted using male subjects. The purpose of the present study was to determine whether women differ from men in their subjective, physiologic and kinetic responses to an acute dose of cocaine. Six male and six female occasional cocaine users provided informed consent and volunteered to participate in this study. The male subjects were studied on one occasion, and the women were studied twice: once during the luteal and once during the follicular phase of their menstrual cycle. After a 30 minute baseline period, all subjects received a 0.90 mg/kg, i.n. dose of cocaine. Blood pressure, heart rate, and integrated plasma cocaine levels were monitored and subjects completed POMS, ARCI, and Visual Analog Scales throughout the two hour study. Subjects reported detection and episodes of extremely good or "euphoric" and extremely bad or "dysphoric" effects after cocaine using an instrumental joystick device. Plasma cocaine levels rose sooner and peak plasma cocaine levels were significantly higher in males. In addition, males had significantly more episodes of "euphoria" and "dysphoria", detected cocaine's effects sooner and experienced cocaine's effects longer than females. However, males experienced only a slightly greater heart rate increase and scores on the ARCI, POMS and VAS were not significantly different. Women who were tested during their luteal phase developed even lower plasma cocaine levels and experienced an attenuated cocaine response than when they were tested during their follicular phase. The results of this study demonstrate that not only are there significant gender differences in cocaine's effects, but that women in their luteal phase (when estradiol and progesterone levels are higher) develop lower plasma cocaine levels than when they are in their follicular phase.

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ALTERED DOPAMINERGIC SYNAPTIC MARKERS IN COCAINE PSYCHOSIS AND SUDDEN DEATH

J. K. Staley, C. V. Wetli, A. J. Ruttenber, W. Lee Hearn, and D. C. Mash

One of the most serious psychiatric sequelae of cocaine abuse is excited delirium, which may be associated with hyperthermia and sudden death. Cocaine-induced excited delirium generally is manifested as a sudden onset of paranoia followed by violent or bizarre activity. The precise mechanism of death in these cases is unknown. Cocaine fatalities have been linked lo hyperthermia, cardiovascular complications, respiratory depression and convulsions. In Dade County, Florida the annual incidence of cocaine psychosis and sudden death parallels the epidemic curve for cocaine overdose deaths. Compared to cocaine overdose deaths without evidence of preterminal excited delirium (ED), the subjects were more likely to be male, to die in police custody, and to survive longer than one hour after the onset of the overdose symptoms. We have used ligand binding and autoradiographic methods to assay for altered regulation of dopamine transporters and D1 and D2 receptor subtypes in cocaine overdose deaths. We have compared ED cases to cocaine overdose deaths (COD) without evidence of preterminal excited delirium and to drug-free and age-matched (control) subjects. Our hypothesis is that cocaine-induced alterations in dopamine transport and receptor signaling may play a role in the neuropsychiatric and lethal effects of cocaine. In comparison with drug-free controls, the high affinity cocaine recognition site on the dopamine transporter (DAT) is elevated in the striatum from COD. Striatal densities of high affinity cocaine recognition sites on DAT were not elevated in the ED subgroup. The density of the D1 receptor subtype was decreased significantly in the caudate, putamen and nucleus accumbens in both COD and the ED subgroup. In contrast to these results, the affinity and number of D2 receptor sites were unchanged from control values in the striatum. However, in the ED subgroup there were marked decreases in the densities of D2 receptors seen in the hypothalamus. In the anterior nucleus of the hypothalamus, an area known to be important for regulating core body temperature, a selective and significant reduction in the density of [^{3}H]-raclopride binding to the D2 receptors was measured in the ED subgroup as compared to both COD and control subjects. Taken together, these results suggest that chronic cocaine abuse may lead to alterations in dopaminergic synaptic markers. We speculate that the apparent defect in the ability of the high affinity cocaine recognition site to "upregulate" in the ED subgroup suggests a diminished capacity for compensatory changes in dopamine reuptake that may "kindle" cocaine psychosis with repeat patterns of "binge" use. The decrease in the number of D1 receptors may result from the indirect agonist effects of cocaine which promote down regulation in receptor expression, contributing to the development of a behavioral tolerance in these subjects. Hypothalamic D1 and D2 receptors have opposing effects on thermoregulation, with the D1 receptor mediating a prevailing increase in core body temperature, while D2 receptors mediate a compensatory decrease. Since the D1 receptors are unaltered, the reduced density of D2 receptors in temperature regulatory nuclei of the hypothalamus may explain the malignant hyperthermia associated with the excited delirium syndrome.

References available upon request.

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AFFILIATIONS: Comprehensive Drug Research Center and the Departments of Neurology, Pathology and Pharmacology, University of Miami School of Medicine, the Dade County Medical Examiner Department, Miami, FL and the Department of Health Sciences and Biometry, University of Colorado, Denver, CO

SPECT IMAGING OF THE DOPAMINE TRANSPORTER IN COCAINE ABSTINENCE: PRELIMINARY STUDIES USING [123-I]ß-CIT

S. E. Best, R. T. Malison, E. A. Wallace, S. S. Zoghbi, Y. Zea-Ponce, R. M. Baldwin, R. B. Innis, and T. R. Kosten

The reinforcing properties of cocaine are thought to be mediated through the dopamine (DA) transporter. Post-mortem binding studies in victims of cocaine overdose suggest that chronic blockade of the DA transporter by cocaine may lead to upregulation of the transporter. We have used the novel radioligand [123-I] methyl 3ß-(4-iodophenyl) tropane-2ß-carboxylate (ß-CIT), a marker for striatal DA transporters (Laruelle *et. al.,* 1994), to study changes in numbers of DA transporters in acute (< 48 hours) and prolonged (two and four weeks) cocaine abstinence.

We have studied six cocaine dependent subjects (ages 23 to 46, two men and four women) who were all actively using cocaine at the time of their entry into this study (mean cocaine use 6 ± 3 grams/week). Each subject received approximately 10 mCi [123-I]ß-CIT intravenously and serial SPECT images were acquired at 24, 27, and 30 hours post-injection using a CERASPECT camera. The primary outcome measure in this study, "V3", is equal to the specific binding divided by non-specific binding (*i.e.,* {striatal - occipital})/(*i.e.,* B_{max}/K_D). In this study, specific binding peaked at 24 to 30 hours post-injection. We therefore report our outcome measure as mean "V3" averaged over the 24, 27, and 30 hour time points. On admission, the mean value of "V3" decreased to 10.2 and 8.6. respectively. Using a within subjects comparison of first and last scans, "V3" decreased an average of 18.6% (range 7.8 to 33.3%) compared to "V3" at baseline ($p = 0.02$, paired t-test).

While the number of subjects studied to date is small, these results suggest that there is a significant decrease in presynaptic DA receptors during abstinence from cocaine.

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LOWER FREQUENCY OF THE DRUG METABOLIZING CYTOCHROME P450 2D6 (CYP2D6) DEFICIENCY PHENOTYPE IN A COCAINE DEPENDENT POPULATION

S. V. Otton, K. Droll, J. Klein, G. Koren, S. Chaudhari, and E. M. Sellers

CYP2D6 is a genetically variable drug metabolizing enzyme absent in 58% of Caucasians (called poor metabolizers, PM) as a result of deleterious mutations in the CYP2D6 gene. PMs exhibit impaired capacity to biotransform drugs which are substrates of CYP2D6. Several abused drugs are substrates of CYP2D6 and it is hypothesized that CYP2D6 activity may be a risk factor in their abuse.

In studies comparing CYP2D6 genotype distributions in a group of abusers of CYP2D6 substrates (codeine, oxycodone, hydrocodone) with non-abusing controls, we also genotyped a group of cocaine abusers to control for any inherent differences between drug users and non-drug users. (-)-Cocaine is an extremely potent inhibitor of CYP2D6 activity *in vitro,* having an apparent Ki value of 0.2 μM (Tyndale *et al.,* 1991) but it does not appear to he a CYP2D6 substrate. Using GC/MS analysis (Zhang and Foltz 1990), we observed no detectable formation of 11 of cocaine's metabolites in incubates of (-)-cocaine with recombinant CYP2D6 enzyme. The results obtained in the oral opiate group will be reported elsewhere.

Subjects (n = 70) fulfilling DSMIIIr criteria for cocaine abuse and n = 75 control subjects who reported no history of regular psychoactive substance use were genotyped by a PCR amplification technique using genomic DNA extracted from whole blood (Heim and Meyer 1990). All subjects were unrelated and reported predominantly Caucasian ancestry. Only 2/70 (or 2.9%) of cocaine dependent subjects had a CYP2D6 genotype associated with PM status, compared to 6/72 (or 8%) in the drug-free control group. The difference in genotype distributions did not reach statistical significance ($chi^2 = 1.90$, df = 2, p = 0.39), and we are continuing to increase our sample size. Although preliminary, these data suggest that CYP2D6 PM status offers protection against developing or maintaining cocaine dependence and that the mechanism does not likely involve the altered biotransformation of cocaine.

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Available upon request of senior author.

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EFFECTIVENESS OF DESIPRAMINE IN TREATING COCAINE DEPENDENCE

R. A. Rawson, S. Shoptaw, M. J. McCann, and S. Minsky

The present study provides data to clarify the role of desipramine in the treatment of cocaine disorders. Ninety-nine subjects meeting DSM-III-R criteria for cocaine abuse or dependence were admitted to the study. All subjects received a set of psychosocial counseling and education services delivered according to the 26 week outpatient Matrix protocol for stimulant abuse treatment. In addition, subjects were randomly assigned to either: desipramine, up to 200 mg for 16 weeks (desipramine group, n=33); placebo tablets for 16 weeks (placebo group, n=35); no medication (Matrix only, n=31). Subjects submitted weekly urine specimens over the 26 weeks of the study. Pill taking subjects provided blood samples monthly to measure plasma desipramine levels. Across all measures of outcome there were no significant differences between the three treatment groups. The outcome data were analyzed according to presence (n=16) or absence (n=52) of desipramine in the plasma. For subjects in which desipramine was detected in the plasma, there was a nonsignificant trend for longer retention in treatment ($p=.08$). Subjects with desipramine present in plasma had significantly lower depression (CES-D) scores during treatment ($p<.05$). The presence of desipramine metabolite was not related to cocaine use as measured by urinalysis data. Those subjects who reported higher rates of pill taking demonstrated significantly longer rates of treatment retention than those whose self reported pill taking was lower. Self reported pill taking behavior did not differ between desipramine and placebo groups. High pill takers had significantly lower percentage of cocaine positive urine samples in treatment than lower pill takers (13% vs. 39%, $p<.01$). High pill takers achieved eight week consecutive blocks of abstinence during treatment at a much higher rate than low pill takers (70% vs. 31%). It is necessary to measure medication in the plasma to definitively assess medication effects, since medication taking behavior may have independent influences on treatment outcome.

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A COMPOSITE SCORE FOR EVALUATING TREATMENT RESPONSE IN COCAINE PHARMACOTHERAPY TRIALS (TES)

W. Ling, S. Shoptaw, R. A. Rawson, and C. J. Klett

Retention and drug use are two common indicators of treatment effects in pharmacotherapy trials. However, each is an incomplete index of treatment outcome. Retention can vary independently of drug use. The reverse can also occur. Moreover, there remains no consensus on how to measure retention and drug use. Most investigators report retention as the number of subjects remaining in treatment divided by the total enrolled. Drug use is measured by self-report and urine toxicology with arbitrary levels of sensitivity as positive or negative. Good outcome is variably defined as negative urines at single time points, a varying number of consecutive clean urines, or consecutive clean days or weeks. Dissatisfaction with these various measures led us to develop the Treatment Effectiveness Score (TES). A patient earns each TES point by attending clinic and giving a "clean" urine. Conceptually, this shifts the focus onto success rather than failure and avoids the explicit imputation of a missing specimen as "dirty". A patient in a 17 week study that requires three urine samples per week can earn from 0 to 51 TES points. Patients may achieve scores of less than 51 in two ways: by providing one or more urines positive for drugs of abuse or by providing fewer than 51 specimens.

This project use the TES to evaluate the relative performance of 159 patients in a 16 week cocaine medication trial and to examine correlations between TES and other commonly used outcome variables. Results showed higher TES scores significantly associated with ability to achieve three and eight consecutive weeks of urine samples negative for metabolite (Kruskall-Wallis H = 105.76, df = 1, $p < .001$; K-WH = 80.61, df = 1, $p < .001$). TES scores at 8 and 16 weeks significantly associated with counseling sessions attended (eight weeks rho = 0.74, n = 98, $p < .001$; 16 weeks *rho* = 0.83, n = 75, $p < .001$). Higher TES associated negatively with lower ASI Drug scale scores at eight weeks (*rho* = -0.72, n = 98, $p < .001$) and 16 weeks (*rho* = -0.48, n = 75, $p < .001$), which indicated better drug use behavior outcomes. These results indicated the TES to be a conceptually encompassing and succinct indicator of treatment outcome in this cocaine pharmacotherapy trial. The TES appears to be a stringent measure of subjects' performance and correlates well with traditional indices of drug use, treatment acceptance, and compliance.

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AFFILIATIONS:

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TREATMENT FOR HOMELESS COCAINE ABUSERS: RETENTION, PROCESS AND OUTCOME

J. B. Milby, J. E. Schumacher, J. M. Raczynski, M. Engle, E. Caldwell, M. Michael, and J. Carr

Homeless substance abusers, randomly assigned to enhanced day treatment plus work therapy and housing components (EC), were hypothesized to show better treatment retention, involvement, and outcome than usual care (UC). Subjects were assessed for alcohol and drug use, homelessness, and employment, at baseline and follow-up (2, 6. and 12-months). The sample (N=176) were primarily male (79.4%). African-American (96.2%). adult (average age=35.8 years), high school educated (average education=12.2 years), and cocaine abusers (71.8%). Most subjects completed some treatment (74.4%, n=131). Subjects were categorized into four treatment intensity groups: No Treatment with 0 contacts/wk. (25.6%, n=45); Low with <.5 contacts/wk. (32.4%, n=57); Moderate with .5 to < 2 contacts/wk. (19.3%, n=34); and High with 2-6.25 contacts/wk. (22.7%, n=40). The Low Intensity group consisted mostly of UC subjects (73.7%, n=42) and the High Intensity group was primarily EC subjects (92.5%, n=37). EC subjects attended significantly more outpatient treatment than the UC subjects (2.42 vs .56 contacts/week, p<.001). Thirty-three subjects received drug-free contingent work experiences (31 EC, 2 UC) and 38 subjects were placed in drug-free contingent housing (26 EC, 12 UC). Wei-Lachin longitudinal analyses revealed EC subjects reported significantly fewer days alcohol use in the past 30 days (p=0.026), fewer positive urine toxicology results for cocaine (p=0.003), and fewer days homeless in the last 60 days (p=0.026) than UC subjects across all follow-up points. No differences between groups in employment were found. However, paired Wilcoxon tests for within groups differences revealed more days employed from baseline to six months for EC (p=0.001) and UC (p=0.021) and from baseline to 12-months for EC (p=0.0001).

This is the first demonstration that homeless cocaine abusers can be retained and effectively treated in an outpatient setting. The enhanced treatment proved to have a positive impact on retention and important outcomes for this population. The intervention, which includes elements to address both the Substance Abuse Disorders and homelessness, is one of the first interventions shown to be sufficient to produce such positive outcomes. Confidence that this complex intervention is truly effective with homeless substance abusers will be strengthened by systematic replication with similar populations.

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AFFILIATIONS:

VAMC and University of Alabama at Birmingham School of Medicine; Birmingham Health Care for Homeless Coalition.

ACTIVE COPING STRATEGIES FOR COCAINE CUE REACTIVITY: TREATMENT OUTCOME

A. R. Childress; R. Ehrman; L. Goehl; and C. P. O'Brien

Cues which have repeatedly signalled drug administration (e.g.. drug-related locations, paraphernalia, persons, or even mood states) can trigger strong arousal and drug craving, potentially leading to relapse. Our initial attempt to address problematic cocaine cue reactivity featured passive cue exposure (to cocaine-related audiotapes, videotapes and paraphernalia) vs. a control condition, with each added to standard psychosocial (inpatient) treatments. Patients receiving the passive cue exposure intervention showed enhanced outpatient retention and reduced cocaine use in the eight weeks following hospital discharge. Despite such benefits, these patients sometimes still experienced craving in response to cues outside the treatment setting, and drug use tended to reinstate cue strength. To circumvent these limitations, we have developed an approach which teaches cocaine patients several ***active coping strategies*** (deep relaxation, delay/behavioral alternatives, negative/positive consequences, aversive/ positive imagery, mastery imagery, cognitive interventions) to counter the craving and arousal triggered by detailed recounting of an individualized craving episode in the presence of a therapist.

In a recently completed trial of this intervention, 48 cocaine outpatients were randomly assigned to a 12-week protocol featuring either the active coping strategies or other control activities (videotapes about family relationships and addiction) which were not craving-focused. Both the experimental and control conditions were added to a standard treatment baseline of weekly drug counseling and regular urine monitoring. Thirty-six of the 48 randomly-assigned outpatients (75%) engaged in treatment, and attendance for treatment sessions was similar (about two-thirds of the scheduled sessions) for each condition. Patients taught active strategies for coping with drug craving had significantly more cocaine-free urines than patients in the control condition, suggesting the potential clinical importance of addressing cue reactivity in drug dependence treatment.

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ONE-YEAR OUTCOME FOLLOWING OUTPATIENT BEHAVIORAL TREATMENT FOR COCAINE DEPENDENCE

S. T. Higgins, A. J. Budney, W. K. Bickel, and D. Ogden

Our group has been assessing the efficacy of an outpatient behavioral treatment for cocaine dependence. The efficacy of this intervention for retaining patients in treatment and establishing initial periods. of cocaine abstinence has been demonstrated in four controlled trials. The purpose of the present study was to examine whether the initial improvements observed with this intervention are maintained during the year after treatment entry. For that purpose, we examined outcomes in 39 cocaine-dependent patients who received treatment. Addiction Severity Index (ASI) scores and urinalysis results were assessed at intake and 6, 9, and 12 months after treatment entry. ASI composite scores on the Drug, Alcohol, Family/Social, and Psych. scales all showed significant improvements that were maintained during follow-up. For example, mean scores on the ASI Drug scale decreased from .24 ± .01 at intake to . 10 ± .01, .09 ± .01, and .09 ± .01 at 6, 9, and 12 month follow-ups ($p < 0.05$). Similarly, the percent of urine specimens that were cocaine negative increased from 46% at intake to 74%. 74%, and 77% at 6, 9, and 12 month follow-ups ($p < 0.05$; missing specimens were treated as positive). These results indicate that the initial clinical improvements observed with this treatment are well maintained during the year after treatment entry, and further suggest that this behavioral approach has promise as an effective outpatient treatment for cocaine dependence.

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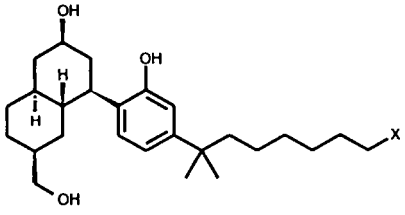
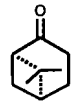
SYNTHETIC STUDIES DIRECTED TOWARDS 18F-LABELED CP-55,244: A POTENTIAL LIGAND FOR IMAGING CANNABINOID RECEPTORS

P. R. Fleming, Z.-Q. Gu, S. Richardson, S. Mirsadeghi, L. S. Melvin, M. R. Johnson, and K. C. Rice

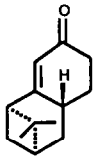
We are currently engaged in a program to synthesize a ^{18}F-labeled derivative of CP-55,244. CP-55,244, a potent nonclassical cannabinoid ligand developed by Pfizer in the early 1980's, is an ideal candidate for a positron emission tomography (PET) ligand. It has high affinity for the cannabinoid receptor and is more stable than classical Δ^9-tetrahydro-cannabinol(THC)-based ligands. The synthesis utilizes R-(+)-nopinone as the enantiomerically enriched starting material. A Robinson annulation of the morpholine enamine of R-(+)-nopinone with methyl vinyl ketone furnished the enone **3.** Treatment of the enone with HCl(g) in acetic acid opened the cyclobutane ring to afford the tertiary chloride **4.** Reduction ($NaBH_4$/pyridine) of the enone **4** followed by oxidation (PCC) and elimination (DBU) gave predominantly **5.** The hydroxy ketone **6** was prepared from **5** in several steps. Further studies will involve the conversion of **6** into an α,β-unsaturated enone suitable for cuprate addition of the aryl fragment and conversion of the coupled product into **1b.**



1a: X = H : CP-55,244
1b: X = F(^{18}F)



2: R-(+)-Noplnone



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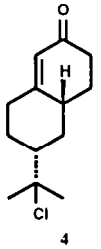

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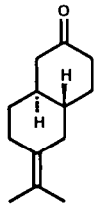

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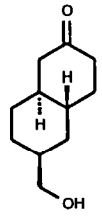

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ANALOGS OF ARACHIDONIC ACID AS POTENTIAL LIGANDS FOR THE CANNABINOID RECEPTOR

J. C. Pinto, D. L. Boring, F. Potie, K. C. Rice, M. R. Johnson, C. Cantrell, G. H. Wilken, and A. Howlett

Anandamide has recently been identified as a putative endogenous ligand for the cannabinoid receptor in the brain(CBR1). Felder and coworkers have explored both the fatty acid and amide moieties of a series of anandamide derivatives to gain information on the binding requirements of this endogenous ligand. While none were found to be more active at the receptor, some had receptor affinities comparable to anandamide. To further probe the structure-activity requirements for CBR1, a series of novel arachidonamides and prostaglandin amides were synthesized and biologically evaluated.

The arachidonamides were synthesized via an acid chloride intermediate that was subsequently treated with a primary amine. The prostaglandin amides were synthesized through a mixed anhydride intermediate. Within the arachidon-amide series, an increase in chain length by one carbon, doubled the potency of the compound. However, further extension of the alkyl chain resulted in loss of activity. Replacement of the hydroxyl group to yield N-propylarachidonamide (7.3 nM) exhibited a three-fold increase in affinity while the N-butyl derivative (30 nM) retained the same activity as anandamide (22 nM). (N-benzyl)arachi-donamide (170 nM) showed an eight-fold decrease in affinity when compared with anandamide. Both the N-(2-methoxyethyl) and the N-(2-formamidoethyl)-arachidonamides exhibited greater than 10 fold loss in affinity while N-(2-aminoethyl)arachidonamide had total loss of activity at CBR1. Within the prostaglandin series, the rigid hair-pin conformations of PGE_2, PGA_2, PGB_2, and PGB_1 had no affinity for CBR1 at concentrations as high as 100um.

In conclusion, substantial loss in binding activity occurs in N-substituted anandamide analogs which have more than four non hydrogen atoms in the alkyl chain. Furthermore, the presence of a hydroxyl group is not necessarily a requirement for binding since when it is replaced with a methyl group the most potent compound in the series was obtained. It appears that the prostaglandin amides do not behave as restricted analogs of anandamide since there was no interaction with the cannabinoid receptor in the brain.

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PHYSIOLOGICAL AND BEHAVIORAL EFFECTS OF ANANDAMIDE, AN ENDOGENOUS CANNABINOID, IN THE RAT

E. A. Stein, S. A. Fuller, W. S. Edgemond, and W. B Campbell

The discovery and characterization of a specific brain receptor that binds cannabimimetic agents (Howlett et al., 1990) and the heterogcnous CNS localization of both the receptor (Herkenham *et al.,* 1990) and its mRNA (Matsuda *et al.,* 1993) led to the search for an endogenous ligand. At least one such ligand, arachidonyl ethanolamide (AEA; anandamide), may be synthesized in brain, binds to rat brain membranes (Hillard *et al.,* 1994) and appears to possess physiological activity (Fride and Mechoulam 1993, Crawley *et al.,* 1993). We thus sought to further characterize the behavioral and physiological effects of AEA in the freely behaving rat.

Anandamide was synthesized from arachidonyl chloride following the method of Devane *et. al.* (Devane *et. al.,* 1992) and prepared fresh each day in an emulphor-ethanol vehicle (1:1) diluted with saline. In rats surgically implanted with chronic femoral arterial and venous catheters, IV AEA exerted profound dose-related, brief duration behavioral and physiological effects. Following 10 and 30 (but not 3) mg/kg, rats became amotoric for up to 4 and 13 minutes, respectively. While catatonic, they displayed a hyper-reflexia to auditory and air puff stimulation. In addition, these doses decreased core temperature by more than 1°C up to 11 and 26 minutes post injection, respectively. An increase in hot plate latency was also seen after 10 (but not 0.3 or 3) mg/kg AEA that lasted less than five minutes.

A rapid, transient bradycardia was seen immediately following drug administration. All three doses were initially equieffective. decreasing HR by about 50-60% within five seconds. This bradycardia lasted for 6, 5 and 11 minutes after the 3, 10 and 30 mg/kg doses, respectively. Anandamide also induced a rapid (5-10 second latency), dose-related (10-30%) hypotension. This effect was also short lived and, when compared to baseline, evolved into a significant hypertensive response beginning at about 30 seconds in both the 3 and 10 mg/kg groups. MAP remained elevated for up to five minutes after the low and two minutes after the middle dose.

Collectively, these data demonstrate that AEA possesses significant biological activity when administered to freely behaving rats and are consistent with those seen following cannabinoid administration. However, in general, AEA's duration of action is much shorter than that seen with the cannabinoids which may be related to the rapid metabolism of the former and slow elimination from the body of the latter.

REFERENCES: Available upon request of senior author.

ACKNOWLEDGEMENTS: Supported in part by grants HL21066 and HL37981 and the Peters Foundation of MCW

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CARDIOVASCULAR EFFECTS OF ANANDAMIDE IN ANESTHETIZED RATS

K. Varga and G. Kunos

Cannabinoids (CANs) have been widely used for their potent neurobehavioral effects. However, they can also affect other physiological functions, including cardiovascular variables in experimental animals as well as in humans. Recent research has indicated that the biological effects of CANs are mediated by specific receptors in the brain and in the peripheral tissues. These receptors recognize and bind not only plant-derived CANs, but also a recently identified endogenous ligand, anandamide (AN), which shares many of the neurobehavioral effects of CANs. In our experiments we tested whether AN also has CANS-like cardiovascular effects in anesthetized rats.

Blood pressure (BP) and heart rate (HR) were monitored in urethane-anesthetized male SD rats via an intra-arterial cannula connected to a pressure transducer and a physiograph. AN was dissolved in a solvent composed of ethanol-emulphor-saline. IV injection of this solvent alone did not cause any change in the cardiovascular parameters.

IV bolus injections of 4 mg/kg AN caused complex, but highly reproducible changes in BP and HR. Immediately after the injection there was a sharp drop in HR which then gradually returned toward baseline level. BP displayed a transient decrease, followed by a brief pressor component and a more prolonged depressor response. These effects were dose-dependent in the range of 0.2 to 20 mg/kg. As reported for CANs, AN also caused readily noticeable respiratory depression with occasional apnea. Retesting the effect of AN in paralyzed, mechanically ventilated animals AN showed the same pattern as in a spontaneously breathing rat. The bradycardiac effect proved to be vagally mediated because either pretreatment of IV methylatropine or bilateral vagotomy completely blocked this effect of AN as well as the initial drop in BP (secondary to the decrease in cardiac output caused by extreme slowing of the heart.) Neither phentholamine nor cervical spinal cord transection could eliminate the pressor effect of AN indicating that this effect is peripherally mediated and does not involve catecholamines. On the other hand, the absence of the prolonged hypotensive component under both conditions indicates that this effect is centrally mediated, probably through a decrease in sympathetic outflow to the vasculature. Earlier reports implicated prostaglandins (PGs) in the hypotensive affect of CANs. Based on these findings we tested the effect of the cyclooxygenase inhibitor, indomethacin (IND), on the cardiovascular effects of AN. IND markedly inhibited the prolonged hypotension suggesting PGs involvement in AN effect.

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ANANDAMIDE AND Δ^9-THC-INDUCED DILATION OF RABBIT CEREBRAL ARTERIOLES IS BLOCKED BY INDOMETHACIN

E. F. Ellis and S. F. Moore

INTRODUCTION AND METHODS

Previous studies of the effect of marijuana on cerebral blood flow (CBF) have found mixed results, with increased CBF a more prevalent finding. Anandamide (arachidonyl ethanolamide) binds to Δ^9-THC receptors and is thought to be the endogenous ligand for the Δ^9-THC receptor. The effect of anandamide (AN) on CBF is unknown, however a constituent of AN, arachidonic acid (AA), is a potent dilator of cerebral vessels. The purpose of these studies was to examine the effect and mechanism of action of AN and Δ^9-THC on the cerebral circulation. We measured the effect of 10^{-13} - 10^{-4} M topically applied AN and Δ^9-THC on *in vivo* cerebral arteriolar diameter in anesthelized rabbits implanted with an acute cranial window chamber.

RESULTS AND CONCLUSIONS

Both AN and Δ^9-THC induced transient, dose-dependent dilation (see figures 1 and 2). Studies with [^{3}H] AN showed that it was 20% metabolized to AA as it passed over the brain surface. Since AA causes dilation via cyclooxygeanse-dependent oxygen radicals, we examined the effect of indomethacin (Indo), a cyclooxygenase inhibitor, and superoxide dismutase (SOD) plus catalase (CAT), which are oxygen radical scavengers. Indo, but not SOD + CAT, blocked AN and Δ^9-THC dilation. L-NAME, an inhibitor of NO synthease, had no effects on

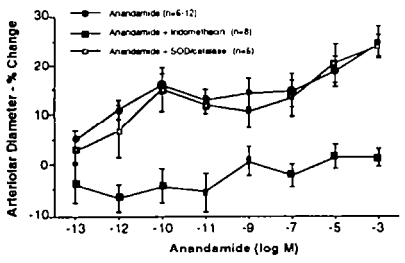

Figure 1

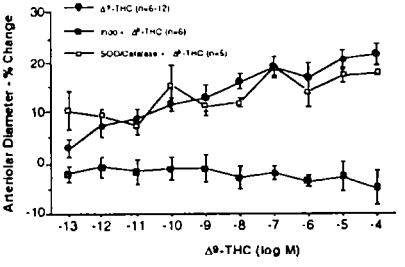

Figure 2

AN or Δ^9-THC dilation. In summary, AN and Δ^9-THC produce dilation by a cyclooxygenase-dependent mechanism. However, unlike dilation produced by topical application of AA, the dilation is not blocked by oxygen radical scavengers. Since AN and Δ^9-THC cause dilation at a much lower concentration than caused by topical AA we believe AN and Δ^9-THC are releasing endogenous AA. Previous literature supports this possibility. Whether the active dilator is a PG or the dilator species is dependent on prostaglandins for synthesis or release is unknown. In summary, AN may be an endogenous modulator of CBF while Δ^9-THC causes increases in local CBF independent of changes in systemic hemodynamics

ACKNOWLEDGEMENTS: Supported by NIDA 08677

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EEG EFFECTS OF WIN55212-2, A STRUCTURALLY NOVEL CANNABINOIDMIMETIC, IN RATS

F. C. Tortella and S. J. Ward

WIN55212-2 is the prototype aminoalkylindole (AAI) cannabinoid possessing stereoselective affinity for the cannabinoid receptor and analgesic activity in rodents. The aim of this study was to characterize the acute EEG (using spectral analyses) and associated behavioral effects of this cannabinoid-like compound in rats. For these studies male S.D. rats were anesthetized (70 mg/kg ketamine and 6 mg/kg xylazine, i.m.) and surgically prepared with a chronic indwelling external jugular vein catheter and frontoparietal electrodes for bipolar recording of cortical EEG activity. During wakefulness, WIN55212-2 resulted in marked disruptions in normal EEG spectral patterns and overt behavior which were dose- (0.125-0.5 mg/kg, i.v.) and time-dependent. The most prominent EEG event associated with WIN55212-2 injections was the immediate induction of high-amplitude synchronized bursts (SBs). These EEG SBs, which persisted for 21 ± 3 minutes at the highest dose tested, resulted in significant increases in EEG spectral power and were distinguished by dual frequency spectral peaks. The "dual peak spectra" was seen as an initial large-amplitude frequency peak centered about 4.6 Hz, and a secondary small-amplitude peak centered about 9.4 Hz. Behaviorally, the EEG SBs were associated with sedation and ataxia, the degree of which was also dose-dependent. In contrast, the spectral power during the post-SB desynchronized awake EEG was significantly reduced to 77% of baseline. The (S) enantiomer, WIN55212-3 (1.0 mg/kg, i.v.), was inactive, suggesting that these effects were stereoselective for the cannabinoid receptor. By comparison, the synthetic cannabinoid levonantradol (0.0625-0.25 mg/kg, i.v.) produced a similar, albeit more potent, EEG and behavioral response. However, spectral analyses revealed the levonantradol-induced EEG SBs to be quantitatively different from WIN55212-2 and characterized by only a "single spectral peak" centered about 5.2 Hz.

These results demonstrate that the AAI WIN55212-2 possesses a cannabinoidmimetic profile in rats which, while similar to other cannabinoids, can be distinguished on the basis of EEG spectral analyses.

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DEVELOPMENT OF A "COMPOSITE" MEASURE OF ALPHA HYPERFRONTALITY FOR USE IN THC RESEARCH

F. Struve, G. Patrick, and J. Leavitt

Previously we reported and replicated significant elevations of Absolute Power, Relative Power and Coherence of alpha activity over frontal-central cortex (a phenomenon we refer to as "Hyperfrontality of Alpha") in chronic THC users as contrasted with non-user controls. A major problem in using quantitative electrophysiological data in human research is the multitude of intcrcorrelated measures that are ohtained. For example, four and possibly more quantitative measures are obtained for four or more frequency bands at 21 or more scalp electrodes. In our laboratory one monopolar electroencephalographic recording yields 464 separate quantitative values. This large multitude of intcrcorrelated measures invites the introduction of spurious significant results and renders efforts to correlate EEG findings with other variables tedious and difficult.

We derived a single "composite" score reflecting alpha hyperfrontality (or the lack of it) by combining equally weighted subscorcs for (1) Alpha Hyperfrontality Absolute Power (AHA), (2) Alpha Hyperfrontality Relative Power (AHR), and (3) Alpha Hyperfrontality Coherence (AHC). To do this Z-scores (from age corrected and Gaussian transformed raw scores) are averaged across electrode groups which are then themselves averaged. An example of the subscore AHA is:

$$AHA = \frac{\frac{(Fp1 + Fp2 + Fpz)}{3} + \frac{(F3 + F4 + Fz)}{3} + \frac{(F7 + F8)}{2}}{3}$$

The three subscores (AHA, AHR, AHC) are in turn averaged to obtain a total alpha hyperfrontality score:

$$AHS = \frac{AHA + AHR + AHC}{3}$$

The total AHS scores significantly ($p<0.001$) separate THC users from non-user controls but the measure does not correlate significantly with years of duration of THC or measures of average number of joints smoked per week. In controlled/paced smoking studies of subjects smoking high dose (3.58%) THC. total AHS scores increase dramatically during smoking, peak during the second half of smoking and return to baseline levels at four hours post smoking. Exposure to low dose (1.77%) THC had only a slight effect on AHS scores and placebo cigarrette did not elevate AHS scores at all.

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CANNABINOID METABOLITE CONCENTRATION IN HUMAN URINE VARIES WITH METHOD OF SAMPLE HYDROLYSIS

P. M. Kemp, I. K. Abukhalaf, B. R. Manno, J. E. Manno, and D. D. Alford

Cannabinoid metabolites, excreted as glucuronide conjugates, must be hydrolyzed for the analysis of the free compounds. This study compared the concentrations of cannabinoids and selected metabolites obtained with three commonly used methods of hydrolysis in human urine following acute exposure to marijuana. Eight healthy human subjects were each asked to smoke a single marijuana cigarette (3.58% THC). Urine was obtained prior to smoking, five minutes after smoking and hourly thereafter for a period of eight hours.

The cannabinoids in 1 mL urine were enzymatically hydrolyzed with the addition of 1 mL of the appropriate phosphate buffer followed by adjustment of the pH to maximize the ß-glucuronidase activity for each species (5.0 for *Helix pomatia,* 6.8 for *Escherica coli).* Five thousand units of each enzyme were added and the specimens were incubated overnight (16 hours) at 37°C. Base hydrolysis was done on 1 mL urine with the addition of 0.5 mL 2N NaOH followed by heating at 60°C for 15 minutes. All hydrolyzed samples, and non-treated controls, were extracted with hexane: ethyl acetate (7:1) and derivatized with BSTFA + 1% TMCS and 1 µL was injected. The HP5890/5972 GC/MS was operated in the electron impact mode, using temperature and inlet pressure programming and selected ion monitoring. The results below were obtained from the urine of one subject taken at one hour post-smoking and run in triplicate for each treatment.

Compound	Control	Base	Mollusk	Bacteria
THC	0.8	1.4	3.1	37.8[a,b]
11-OH-THC	1.0	1.7	4.6	82.2[a,b]
THCCOOH	61.2	59.3	75.1[a,b]	65.4[b]
a=control vs. treatment, $p<0.05$; b=mollusk vs. bacteria, $p<0.05$				

These data demonstrate the species dependent nature of glucuronidase activity in hydrolyzing cannabinoid metabolites (*E. coli* > *H. pomatia*) and that the ether glucuronides of THC and 11-OH-THC must be hydrolyzed enzymatically for analysis of the free compounds.

ACKNOWLEDGEMENT:

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TIME COURSE OF COCAINE-INDUCED ALTERATIONS IN OPIOID AND DOPAMINE RECEPTORS AND TRANSPORTER SITES

E. M. Unterwald, J. M. Rubenfeld, and M. J. Kreek

Cocaine potentiates dopaminergic neurotransmission by binding to dopamine transporter sites and inhibiting the reuptake of dopamine into presynaptic terminals. Previous studies have demonstrated that chronic cocaine administration alters opioid receptor densities (Hammer 1989; Unterwald *et al.,* 1992). The present study investigated the time course of mu opioid receptor upregulation during repeated cocaine administration and determined if mu receptor changes were accompanied by alterations in the density of dopaminc D_1 and D_2 receptors and/or dopamine transporter sites in specific brain regions. Cocaine (45 mg/kg/day) or saline was administered to male Fischer rats three times daily at one-hour intervals to mimic the binge pattern of human cocaine abuse. Mu opioid receptors, dopamine D_1 and D_2 receptors, and dopamine transporter sites were measured in adjacent brain sections after 2.7, and 14 days of treatment using quantitative autoradiography with the selective ligands [^{3}H]DAMGO, [^{3}H]SCH 23,390, [^{3}H]raclopride, and [^{3}H]WIN 35,428, respectively. The density of mu opioid receptors increased over 14 days of cocaine administration in the cingulute cortex, nucleus accumbcns, and rostral caudate putamen. D_1 receptor densities increased over the 14 days of cocaine administration in the olfactory tuberele, nucleus accumbens, ventral pallidum, and substantia nigra. In contrast, binding to D_2 receptors in the olfactory tubercle, rostral nucleus accumhens, and rostral caudate putamen was transiently increased on day seven of treatment which rctumcd to control levels by day 14. Dopamine transporter sites were found to be unaltered after cocaine administration in all brain regions investigated. These results illustrate the complex pattern of changes in neurochemistry that occur as a result of repeated cocaine administration.

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ACKNOWLEDGEMENTS:

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DOPAMINE TRANSPORTER mRNA LEVELS IN THE RAT SUBSTANTIA NIGRA AND VENTRAL TEGMENTAL AREA IMMEDIATELY FOLLOWING AND AT TWO DAYS AND TEN DAYS AFTER "BINGE" COCAINE ADMINISTRATION

C. E. Maggos, R. Spangler, Y. Zhou, E. M. Unterwald, and M. J. Kreek

We hypothesized that cocaine might effect the expression of dopamine transporter (DAT) mRNA. Our initial mapping of DAT mRNA showed the following levels of message in the rat brain (pg DAT mRNA/ug total RNA): caudate putamen 0.075, hypothalamus 0.119, substantia nigra (SN) 8.331, ventral tegmental area (VTA) 5.132, central grey 0.101, pons medulla 0.059.

Sixty day old male Fisher rats were treated under the "binge" paradigm with three i.p. injections at one hour intervals with saline or cocaine (45 mg/kg/d) beginning at 9:30 a.m. as follows.

Group A (n = 12)	Group B (n = 6)	Group C (n = 6)
1. sal x 14 days (d)	sal x 11d+coc3d	sal x 14d+withdraw 10d
2. coc x 14 days (d)	sal x 10d+coc2d+sal2d	coc x 14d+withdraw 10d

After treatment the rats were sacrificed, their brains dissected; regions were homogenized and individually extracted for RNA. The SN and VTA were assayed for DAT mRNA using a modified solution hybridization assay.

	A1	A2	B1	B2	C1	C2
VTA	6.1±0.7	6.3±0.9	5.9±1.1	6.3±1.5	2.2±0.6	2.8±0.4
SN	9:1±1.0	9.8±1:2	7.4±0:7	7.2±1.0	8.2±0.8	8.3±1.1

Mean±SEM in pg DAT mRNA/ug Total RNA

There were no significant differences in DAT mRNA between the saline and cocaine treatment groups within individual protocols. The levels of DAT mRNA in the VTA and SN of saline and cocaine injected animals that had a 10 day withdrawal period were significantly lower than those found in the animals that did not undergo withdrawal for 10 days. Work is underway to further investigate the effect of cocaine on DAT mRNA levels in the caudate putamen, hypothalamus, central grey and pons medulla.

ACKNOWLEDGEMENT:

Dr. Ann Ho for experimental design and data analysis. This work supported by NIH-NIDA (P50-DA05103).

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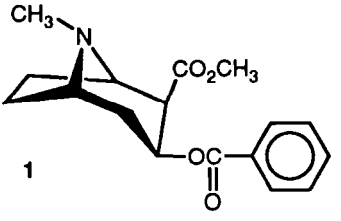
SECONDARY AMINE ANALOGS OF 3ß-(4'-SUBSTITUTED PHENYL)TROPANE-2ß-CARBOXYLIC ACID ESTERS AND N-NORCOCAINE EXHIBIT ENHANCED AFFINITY FOR SEROTONIN AND NOREPINEPHRINE TRANSPORTERS

F. I. Carroll, M. J. Kuhar, T. Kopajtic, E. Yang, P. Abraham, A. H. Lewin, and J. W. Boja

Radioligand binding affinities of *N*-norcocaine (**2**) and six *N*-nor-3ß-(4'-substituted phenyl)tropane-2ß-carboxylic acid esters (**4a-f**) at the DA, 5HT, and NE transporter were measured and compared to those of cocaine **(1)** and 3ß-(substituted phenyl)uopane analogs (**3a-f**). Whereas the absence of the N-methyl group had relatively small effects on affinity at the DA transporter, 4-19-fold and 2–44-fold enhancements in affinity at the serotonin and norepinephrine transporter respectively resulted. *N*-Nor-3ß(4'-iodophenyl)tropane-2ß-carboxylic acid methyl ester (**4d**) with an IC_{50} = 0.36 nM showed the greatest affinity for the serotonin transporter, and *N*-nor-3ß-(4'-ethylphenyl)-tropane-2ß-carboxylic acid methyl ester (**4e**) was the most serotonin selective.



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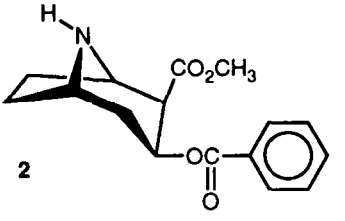

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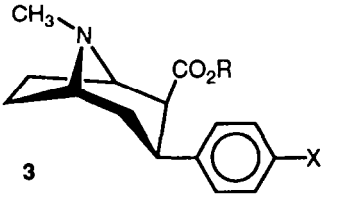

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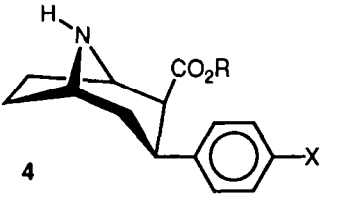

4

(a) R = CH_3, X = H
(b) R = CH_3, X = F
(c) R = CH_3, X = Cl
(d) R = CH_3, X = I
(e) R = CH_3, X = C_2H_5
(f) R = $(CH_3)_2CH$, X = I

AFFILIATION:

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DISCOVERY OF A NOVEL CHIRAL BENZAZEPINE DERIVATIVE, RTI-4793-41, WHOSE ENANTIOMERS BIND POTENTLY AND WITH MODERATE ENANTIOSELECTIVITY TO PCP SITE 2 AND CLONED DA TRANSPORTERS

B. Emilien, C. B. Goodman, C. M. Dersch, J. S. Partilla, J. L. Cadet, D. Vandenbergh, J.-B. Wang, G. R. Uhl, F. I. Carroll, B. Blough, K. P. Constable, and R. B. Rothman

Recently, we reported that RTI-14, a novel pyrrole compound, showed high affinity (IC50 = 38 nM) and selectivity for the MK801-insensitive [^{3}H]TCP binding site (PCP site 2) and moderate affinity for the biogenic amine transporters (BAT). These findings provided further evidence that PCP site 2 may be associated with the BAT system. In the present study, we determined the IC50 values of RTI-14, the novel benzazepine derivative RTI-41 and their enantiomers at PCP site 1 and 2 and the cloned human and rat DA transporters. Using guinea pig membranes, PCP site 1 was labeled with [^{3}H](+)-MK801, while [^{3}H]TCP in the presence of 500 nM (+)-MK801 was used to label PCP site 2. The DA transporter was labeled with [^{125}I]RTI-55. RTI-41 bound potently and selectively to PCP site 2 (IC50 = 15 nM). The enantiomers of both RTI-14 and RTI-41 demonstrated moderate enantioselectivity at PCP site 2. The enantiomers of RTI-41 showed opposite enantioselectivity at PCP site 2 and the DA transporter, supporting the hypothesis that PCP site 2 and the cocaine recognition site on the DA transporter may be different.

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PARTIAL PURIFICATION OF COCAINE RECEPTORS FROM RAT BRAIN

L. P. Raymon and M. E. Eldefrawi

The reinforcing properties of cocaine are due in part to inhibition of amine transport in the brain. Solubilization and partial purification of the transporters using affinity chromatography were realized.

Analogs of cocaine, BTCP and citalopram were covalently linked via a primary amine group to a cross-linked agarose (N-hydroxy-succinimide functional group). A 1% digitonin extract of forebrain synaptosomes was loaded on the affinity column and eluted with buffer to remove non-absorbed proteins. The affinity columns were then eluted with μM to mM concentrations of citalopram, BTCP or cocaine and the eluate concentrated, dialyzed and assayed for binding of [^{3}H]ligands.

Solubilization of transporter proteins with detergents lowers dramatically their affinity for transporter ligands and alters their cocaine sensitivity. Citalopram retained relatively high affinity and was chosen to follow the activity of the soluble transporter proteins. The three affinity chromatography columns yielded fractions that exhibited cocaine-sensitive [^{3}H]citaloprsm binding, confirming the presence of serotonin transporters. The cocaine affinity column resulted in soluble proteins recognizing not only [^{3}H]citalopram, but also [^{3}H]BTCP and [^{3}H]GBR 12935, showing the presence of probably all three amine transporters and an overall purification of 12,000-fold at a recovery of 78% for cocaine-sensitive [^{3}H]citalopram binding. Double staining of SDS-PAGE gels of the various fractions show five distinct bands, including a 70 kD one, but also two higher and two smaller molecular weight bands. Native PAGE was hindered by aggregation of the proteins in the gel.

A Western blot of the gels will reveal if all bands represent transporter proteins.

ACKNOWLEDGEMENT:

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BEHAVIORAL AND PHARMACOLOGICAL DIFFERENTIATION OF DIRECT AND INDIRECT DOPAMINE AGONISTS AND AMONG DOPAMINE UPTAKE INHIBITORS

J. M. Witkin, E. Tirelli, and B. Geter-Douglass

We have developed a method for rapidly differentiating among dopamine agonists *in vivo* that may be useful in understanding their abuse. Indirect dopamine agonists (dopamine releasers and dopamine uptake inhibitors) produced dose-dependent increases in gnawing on corrugated paper in C57B1/6J mice. In contrast, direct agonists did not induce gnawing. The dopaminergic nature of the gnawing response was confirmed in experiments in which a host of non-dopaminergic drugs did not induce gnawing and in which dopamine antagonists blocked gnawing induced by either cocaine or methylphenidate. There was a positive correlation between potencies of a series of dopamine uptake inhibitors to induce gnawing and to mimic the discriminative stimulus effects of cocaine (Terry and Katz, submitted).

Dopamine uptake inhibitors could be further differentiated from one another. In the presence of the GABAA agonists gaboxadol (THIP) or muscimol, gnawing induced by methylphenidate, methamphetamine, nomifensine, indatraline, GBR 12935, mazindol, and amfenolate was potentiated; gnawing induced by cocaine, WIN 35,428, or GBR 12909 was not affected. Effects of direct-acting dopamine agonists were not potentiated by the GABAA agonists. These results suggest potential mechanistic differences in the actions of dopamine uptake inhibitors.

The gnawing procedure may provide a rapid ***in vivo*** screen to differentiate indirect from direct dopamine agonists, with potential predictive utility for important behavioral effects of these drugs in humans. This method appears to be useful also in mechanistic studies of indirect dopamine agonists.

ACKNOWLEDGEMENTS:

We thank Ms. Dawn French for expert technical assistance. We are also grateful to the many pharmaceutical companies for their generous donation of some of the compounds used in this study.

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DIFFERENTIAL RELATIONSHIPS AMONG DOPAMINE TRANSPORTER AFFINITIES AND STIMULANT POTENCIES OF VARIOUS UPTAKE INHIBITORS

S. Izenwasser, P. Terry, B. Heller, J. M. Witkin, and J. L. Katz

Binding to the dopamine transporter and inhibiting dopamine reuptake are considered important factors in regulating the behavioral effects of cocaine. One of the prominent behavioral effects of cocaine and other dopamine uptake inhibitors is the stimulation of locomotor activity. The present study was done in order to more closely examine the relationship between binding to the dopamine transporter, inhibition of dopamine uptake, and this behavioral effect of cocaine and other dopamine uptake inhibitors. The displacement of [^{3}H]WIN 35,428 (CFT) binding and inhibition of [^{3}H]dopamine uptake by cocaine and other uptake inhibitors, were examined in rat caudate putamen and compared with stimulation of mouse locomotor activity. The binding affinities ($K_{0.5}$ values) were highly and significantly correlated with IC_{50} values for inhibition of dopamine uptake for all of the tested compounds. As previously shown, cocaine and several other uptake inhibitors were best fit by two-site binding models, therefore yielding both K_{hi} and K_{lo}, values. The correlation among ED_{50} values for stimulation of locomotor activity and $K_{0.5}$ values for binding for all of the compounds was low but significant ($r=0.477$, $P\leq0.05$). In contrast, when only cocaine and its structural analogs were analyzed, the correlation among potencies for binding and activity was high and significant ($r=0.902$, $P\leq0.01$). For these compounds, the comparison of K_{hi} and ED_{50} values produced an even better correlation ($r=0.949$, $P\leq0.004$). For structurally dissimilar uptake inhibitors, however, there was no significant correlation among potencies for stimulation of locomotor activity and affinity for displacement of [^{3}H]WIN 35,428 binding, regardless of which binding values were used. Thus the stimulation of locomotor activity by dopamine uptake inhibitors does not appear to be related in a straightforward manner to the affinity of these compounds at the dopamine transporter. Further, these findings provide evidence that cocaine analogs may bind to the dopamine transporter in a manner that is fundamentally different from that for structurally dissimilar uptake inhibitors.

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TOPOGRAPHY OF LIMBIC DOPAMINE UPTAKE SITES IN HUMAN AND RAT BRAIN

K. Y. Little, F. I. Carroll, and B. J. Cassin

Previous experiments have demonstrated that binding sites on the dopamine transporter (DAT) are increased in striatum from human subjects abusing cocaine prior to their deaths. It has not been determined if DAT binding is similarly altered in limbic regions thought to subserve emotional and subjective experience, such as the amygdala and hippocampus. Dopaminergic innervation of these regions is sparse, and specific, high affinity radioligands for the DAT have not been available. [^{125}I]RTI-121 is a newly synthesized radioligand with reportedly high affinity and selectivity for the DAT, especially versus the serotonin transporter. The present experiments examined the selectivity and anatomical distribution of [^{125}I]RTI-121 binding in human and rat limbic brain, emplying quantitative autoradiography.

[^{125}I]RTI-121 binding was detected in the hippocampus and amygdala which appeared to label DAT sites in humans and rats. A number of factors indicated that these binding sites were located on the DAT: 1) the binding was displaced by (-)cocaine, 30 μM, (60-70%), and WIN 35428, 1μM, (~80%); 2) the binding was not displaced by citalopram, 1 μM; 3) the binding was distributed in a unique anatomical pattern, similar to D_2 receptors; 4) the anatomical pattern was different from [^{125}i]RTI-55, which labels 5-HT transporter sites with high affinity; 5) the binding was Na+ sensitive in the range of 60-360 mM; and 6) the amount of specific binding (defined with 30 μM cocaine) was 4-8% of the amount in the striatum (about as predicted).

A distinct, cocaine-displaceable binding pattern was discernible in both species. In the amygdala, the bassolateral nucleus was labeled, while the denate molecular layer, CA4 and CA3 pyramidal layers, and the stratum radiatum throughout the cornu ammonis were labeled in the hippocampus. Binding in the temporal cortex was more variable and inconsistent. These experiments demonstrate that hippocampal and amygdalar DAT sites can be visualized and quantitated in human post mortem brain employing [^{125}I]RTI-121.

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COCAINE INCREASES EXTRACELLULAR ASPARTATE AND GLUTAMATE IN RAT NUCLEUS ACCUMBENS (N. ACC.)

S. E. Robinson, H. Guo, J, R. Maher, J. A. Smith, M, J. Wallace, D. T. Otey, and P. M. Kunko

Several laboratories have suggested involvement of excitatory amino acids in certain behavioral effects of stimulants. The effects of cocaine HCl were studied on extracellular concentration of the excitatory amino acids aspartate and glutamate using intracerebral microdialysis of the N. Acc. of male Sprague-Dawley rats (225-350g). Five days prior to microdialysis. rats under Equithesin anesthesia were implanted stereotactically with guide cannulas aimed at the N. Acc.. On the day of the cxpcrimcnt. a CMA/12 concentric microdialysis probe (dimensions of exposed dialysis membrunc = 0.5 mm x 2 mm) was inserted through the guide cannula into the N. Acc.. Probe buffer was pumped at a flow rate of 2 µl/min.. Data were analyzed by analysis of variance. After an equilibration time of three hours, samples were collected in ten minute fractions for an additional two hours to establish baseline values in the awake, freely moving rat. Cocaine (7.5, 15, or 30 mg/kg) or saline was injected i.p., and samples were collected for an additional two hours. Cocaine produced increases in aspartate concentration in the microdialysate (effect of treatment on maximum increase, $F_{3,15} = 10.359$, $p < 0.0001$). An initial slight decrease, followed by an increase (effect of treatment on maximum incrcasc, $F_{3,15} = 5.745$, $p < 0.01$) in the microdialysate concentration of glutamate were observed after cocaine injection. Saline injection had no significant effect on the concentrations of either of these two excitatory amino acids. Perfusion of the probe with "Ca++-free" probe buffer (0.2 mM EGTA and no added Ca++) reduced the responses of extracellular aspartate and glutamate to cocaine in rats injected with 15 or 30 mg/kg, i.p., cocaine (effect of treatment on maximum aspartate increase, $F_{2,8} = 1.508$, $p > 0.05$; effect of treatment on maximum glutamate increase, $F_{2,8} = 1.262$, $p > 0.05$). Thus, cocaine appears to activate the excitatory amino acid innervation of the N. Acc.

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AN EVALUTION OF THE NOVEL PSYCHOSTIMULANT DRUG, MODAFINIL, IN RHESUS MONKEY SELF-ADMINISTRATION AND RAT DRUG DISCRIMINATION PARADIGMS

L. H. Gold and R. L. Balster

Modafinil has been evaluated to treat narcolepsy and idiopathic hypersomnia. This drug has been shown to stimulate locomotor activity in mice and to increase wakefulness in rats and cats and nocturnal awakening in monkeys. Interestingly, many of the behaviors produced by modafinil are reversed by the $alpha_1$-adrenergic receptor antagonist, prazosin, but not by antagonists acting at $alpha_2$ or dopamine receptor subtypes, leading to speculation that modafinil functions as a central $alpha_1$-adrenergic agonist. In the present study, modafinil was evaluated for its discriminative stimulus properties and to determine whether it could serve as a reinforcer for laboratory animals. The effects of modafinil were compared with those of d-amphetamine, a prototypical psychostimulant drug, and l-ephedrine, a widely available, weak stimulant sold without prescription in the U.S.. The ability of prazosin to antagonize modafinil's effects was also examined. Modafinil was self-administered by cocaine-experienced rhesus monkeys when tested in a substitution paradigm. The rates and patterns of responding resembled those of the baseline stimulant, cocaine. In two additional respects, responding for modafinil resembled responding when cocaine was available, and was dissimilar to responding when saline or vehicle was available. First, the within-session time course for modafinil resembled cocaine in that the infusions were evenly distributed throughout the session. This is in contrast to the negatively accelerated pattern of infusions observed within saline and vehicle sessions, which suggests responding is being extinguished. Secondly, the number of daily infusions usually remained stable or increased during a modafinil substitution. This pattern differs from the decreasing trend in the number of daily infusions obtained from the first to the last day when an ineffective reinforcer, like vehicle or saline, was substituted. Limited substitution tests with d-amphetamine and l-ephedrine also provided evidence for reinforcing effects. Modafinil substituted for cocaine in five of six rats trained to discriminate 10 mg/kg cocaine from saline. Like modafinil, ephedrine also substituted for cocaine in the rat drug discrimination procedure. The reinforcing and discriminative stimulus effects required very high doses of modafinil; it was much less potent than d-amphetamine and even less potent than l-ephedrine. Little evidence was obtained that these effects of modafinil were produced by $alpha_1$-adrenergic stimulation, based on experiments performed in combination with prazosin. In conclusion, modafinil has some stimulant-like discriminative stimulus and reinforcing properties, but it is very impotent for these effects and its efficacy may be qualitatively no greater than is observed with l-ephedrine.

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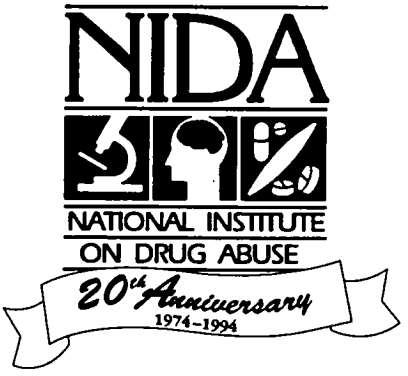

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