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DUAL RECOVERIES FROM SMOKING AND ALCOHOL PROBLEMS AMONG NATURALLY RECOVERED ALCOHOL ABUSERS

M.B. Sobell and L.C. Sobell

Interviews were conducted on two occasions separated by 5 years with alcohol abusers who at the first interview had recovered without treatment (Group R, N=120) or who had an active and untreated problem (Group NR, N=62) (Sobell *et al.,* 1992, 1993). When this report was prepared, second interviews had been conducted with 109 subjects in Group R and 35 in Group NR. Only 3 of the 35 Group NR subjects interviewed had recovered from their alcohol problem by the time of the second interview. 56.6% of subjects who had ever smoked (n=129) had quit smoking by the first interview, and this rose to 61.4% by the second interview. The recovery rate for Group R (67.7) exceeded that for Group NR (45.5%). Relapse rates at Interview 2 for subjects recovered at Interview 1 were 12.8% for drinking and 8.7% for smoking. 85.8% of subjects had a consistent smoking status across interviews. Only 9.9% had never smoked. By Interview 2, 25.0% of smokers at Interview 1 had quit smoking, while 8.2% of quitters had relapsed to smoking. Disregarding subjects who never smoked, subjects who were recovered from an alcohol problem at Interview 1 were significantly (Chi-square = 7.2, $p<.03$) more likely to have relapsed to drinking by Interview 2 if they were still smoking at Interview 1 than if they'd quit smoking by Interview 1. Subjects with a dual recovery at Interview 1 had a greater likelihood of relapse to drinking if they relapsed to smoking, and only a small likelihood of relapse to drinking if they stayed recovered from smoking. Dually recovered subjects rated recovering from smoking to have been more difficult than recovering from drinking. Subjects who had quit smoking by Interview 2 were a bit older than other subjects and had been somewhat heavier smokers; aside from heaviness of smoking, recovery from smoking was not significantly related to severity of dependence on tobacco or alcohol.

While causal inferences are not possible from these data, the findings suggest a possible relationship between smoking and drinking problems in that recovered alcohol abusers who were still smoking at Interview 1 had nearly four times greater likelihood of relapsing by Interview 2 than did those who had quit smoking by Interview 1. These findings provide no support for the notion that it would be detrimental for persons to attempt to deal with smoking and drinking problems simultaneously.

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ACKNOWLEDGEMENTS:

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AFFILIATION:

Addiction Research Foundation and University of Toronto

CONDITIONING FACTORS AND CUE EXPOSURE TREATMENT IN DRUG DEPENDENCE: THE ROLE OF EMERGENT EQUIVALENCE RELATIONS

R. J. DeGrandpre, W. K. Bickel, A. J. Mortensen, S. Higgins

Historically, the idea that non-drug stimuli can exert control over drug-taking and drug-withdrawal has been conceptualized in terms of a classical conditioning (CC). One such approach is that environmental stimuli paired with drug withdrawal can become conditioned stimuli, thus producing a conditioned-withdrawal response; another CC paradigm proposes that the stimuli paired with the drug's stimulus effects become conditioned stimuli that increase the likelihood of drug administration. Based on these approaches, several strategies for reducing the eliciting effects of environmental cues have been proposed (e.g., cue exposure treatment). Although these CC phenomena are common in the lore of drug treatment and have been verified in experimental settings, a recent review of 20 years of research on the role of CC in relapse argued, however, that this research has failed to demonstrate a relationship between conditioned responses (to drug-related stimuli) and relapse in drug or alcohol dependence (Drummond *et al.,* 1990). Also, this review argued that evidence of the effectiveness of extinction treatment is lacking. Based on these findings, another model of conditioning is presented that stems from operant research on discriminative-stimulus control, viz. stimulus equivalence. In the study presented, using a matching-to-sample procedure, relations between arbitrary stimuli and between arbitrary stimuli and three activities (acquisition of cigarette puffs, money, or prizes) were trained to examine whether stimuli never paired with drug use can, via stimulus equivalence, set the occasion for drug-taking. Results supported the notion that novel stimuli can exert control over drug-taking via shared membership in an equivalence class. These findings and their implications to previous research on cue reactivity and drug treatment will be discussed.

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ENHANCED CONTINUITY OF CARE AND DESIPRAMINE IN CRACK COCAINE ABUSERS

S. M. Hall, S. Tunis, P. Banys, D. Tusel, H. W. Clark, D. Presti, and P. Stewart

We report data from a trial of enhanced continuity of care and drug treatment for crack cocaine abuse (N = 94). The study focused on increasing entrance into outpatient treatment after brief inpatient treatment for crack cocaine abuse, and enhancing retention, and therefore abstinence. In a random assignment, 2x2 design, we compared enhanced continuity of care vs. standard treatment, and desipramine (200 mg) vs. placebo. In the enhanced continuity condition, subjects had the same counselor in inpatient and outpatient treatment. They began attending groups on the outpatient unit while inpatient. Under the standard treatment structure, subjects had different counselors during inpatient and outpatient treatment and no contact with the outpatient clinic until the end of inpatient treatment. Drug administration began during the first week of the 3-week inpatient stay and continued for five weeks of outpatient treatment (eight weeks total). Subjects were assessed at Weeks 3, 8, 12, and 26. We hypothesized that subiects assigned to the desipramine-continuity condition will be more likely to (1) be abstinent from cocaine at all assessments, and (2) attend more outpatient treatment sessions. We have found enhanced continuity (1) decreases cocaine use (self-report verified by urine toxicology) at Week 3, and (2) increases attendance at individual treatment sessions. Desipramine increased days in treatment if therapeutic levels were attained, but did not affect drug use. The desipramine data support and expand those recently reported from cocaine-abusing methadone patients. The data also suggest that psychological intervention may play an important role in the treatment of cocaine dependence.

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RETENTION OF COCAINE ABUSING WOMEN IN RESIDENTIAL TREATMENT

P.H. Hughes, S.D. Coletti, R.L. Neri, C.F. Urmann, D.M. Sicilian, S.S. Stahl, and J.C. Anthony

This NIDA "Perinatal 20" demonstration research project randomly assigned 53 cocaine abusing women to two treatment conditions in a therapeutic community (Coletti *et al.* 1992). Women in both conditions received the same TC treatment. However, "TC^{+}" women (n=31) were permitted to bring one or two of their children (up to 10 years old) to live with them during the 18-month residential program, while "standard TC" women (n=22) were advised to place their children with the best available caretaker or in foster care. The study tested the hypothesis that providing on-site child care accommodations would have a positive impact on retention for women with children.

The mean age of the women was 27.3 years, 81% were African-American, and 79% had prior treatment. Preliminary findings support the hypothesis. TC^{+} women had a significantly longer mean length of stay (281 days) than TC women (131 days), $t = 2.80$, $p < .05$. Survival analysis showed their retention curves differed significantly from each other, L (n=53, 1)=8.86, $p < .005$. By the third month, 71% of women in the TC^{+} condition remained in residential treatment, compared to 32% of standard TC women. By the sixth month, 58% of TC^{+} women remained in residence, compared to 18% of standard TC women. By the end of 12 months, 26% of TC^{+} women remained, compared to 5% of standard TC women. Additional time will be required before post-treatment comparisons are possible.

Because the study group status of all women was known to clinicians, evaluators, and to subjects themselves, we were concerned about possible bias in retention findings. Yet no differences were found when retention rates of standard TC women were compared with those of non-study women admitted during the same years.

These preliminary results suggest cocaine abusing women will have greater retention in therapeutic communities if they can enter with one or two of their children.

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INCENTIVES IMPROVE TREATMENT RETENTION, COCAINE ABSTINENCE AND PSYCHIATRIC SYMPTOMATOLOGY IN AMBULATORY COCAINE-DEPENDENT PATIENTS

S. T. Higgins, A. J. Budney, W. K. Bickel, F. E. Foerg, R. Donham, and G. J. Badger

This study was conducted to assess the efficacy of an incentive program during outpatient, behavioral treatment for cocaine dependence. Forty cocaine-dependent adults were randomly assigned to one of two treatment groups: 24 weeks of behavioral treatment with or without an added incentive program. The behavioral treatment was based on the Community Reinforcement Approach and was provided to both groups. Subjects in the group with incentives received vouchers exchangeable for retail items contingent on submitting cocaine-free urine specimens during weeks 1-12 of treatment, while the group without incentives received no vouchers during that period. The two groups were treated the same during weeks 13-24.

Seventy-five percent of patients in the group with vouchers completed 24 weeks of treatment vs. 40% in the group without vouchers ($p=0.03$). Average duration of continuous cocaine abstinence during weeks 1-24 of treatment were 11.7 ± 2.0 weeks in the group with vouchers vs. 6.0 ± 1.5 in the group without vouchers ($p=.03$). At 24 weeks after treatment entry, the voucher group evidenced significantly greater improvement than the no-voucher group on the drug scale of the Addiction Severity Index (ASI), and only the voucher group showed significant improvement on the ASI psychiatric scale.

Incentives delivered contingent on submitting cocaine-free urine specimens represent an effective intervention for increasing treatment retention and cocaine abstinence and reducing psychiatric symptomatology during outpatient treatment for cocaine dependence.

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CONTINGENCY CONTRACTING IN METHADONE MAINTENANCE

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

The effectiveness of methadone maintenance differs among clinics. In this study the conditions of treatment are varied to determine the effectiveness of six models. In a 3 (level of services) by 2 (contingency contracting) factorial design, 353 new admissions to methadone maintenance were randomly assigned to one of six cells. Levels of services were: (1) "medication only", (limited to one 15 minute counseling session per month); (2) "standard " counseling, (weekly counseling in first 90 days, at least monthly thereafter, assisted referral to community agencies, on-site psychiatric services available); (3) "enhanced" services: (same as standard, plus attended weekly skill building and/or process groups, marital counseling available). The contingency contracting conditions were: (1) no contingencies (NC); (2) contingency contracting (CC). All subjects were notified in writing of each positive urinalysis result. After a 60 day "stabilization" period and an additional 90 day "warning and assistance" period, negative contingencies of dose reduction of response to each positive UA and eventual discharge were implemented for CCs. The sample is 62.7% male; 37.6% African-American, 3.9% Hispanic, and 56.8% white; mean age, 38.2, 73% unemployed; and 37.3% with less than high school education. Subjects are assessed initially and at 6, 12, 18, and 24 months post admission via a structured interview. Presented here are the 12 month outcomes for treatment retention and weekly urinalysis. Level of services and contingency contracting groups were compared separately on treatment retention by survival analysis. CC subjects were discharged at a greater rate than the NC group (Lee-Desu = 6.8, $p < .01$). However, CC subjects were re-admitted at a faster rate (Lee-Desu = 5.2, $p < .05$). There were no treatment retention differences based on level of services. Since there was differential treatment retention between contingency groups, endpoint methodology was used to extrapolate missing urinalysis data points for subjects discharged from treatment prior to the 12 month follow-up. Urinalysis data were then analyzed using a 3X2 ANCOVA with age and preadmission drug use as covariates. NC subjects provided more urines positive for any illicit drug ($m = 28.4$, $d = 12.1$) than did CC subjects $b = 24.1$, $d = 12.3$, ($F = 9.9$, $p < .01$). For opiate positives a significant level of services by contingency contracting interaction was found ($F = 3.8$, $p < .05$). Post hoc analysis indicated the interaction was due to medication only/CC subjects obtaining fewer opiate positives ($m = 20.5$, $sd = 13.1$, $Q = 3.7$, $p < .01$). The groups did not differ on number of cocaine positive urines. In settings where minimum services are being provided as part of methadone maintenance, contingency contracting may assist in producing outcomes similar to those associated with providing standard counseling services during the first year of treatment. The contingency contracting system studied produced less illicit drug use by methadone clients as predicted, but also led to poorer treatment retention. Future studies of contingency management systems within methadone clinics should focus on systems that would lead to reduced illicit drug use without adversely affecting treatment retention.

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THE EFFECTIVENESS OF COGNITIVE-BEHAVIORAL TREATMENT FOR COCAINE-USING METHADONE PATIENTS

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

Preliminary outcome evaluation results are reported for an innovative cocaine abuse treatment model adapted for cocaine-using methadone patients. Ninety-four patients were randomly assigned to six months of high intensity ("neurobehavioral") or low intensity ("control") therapy for cocaine dependence. Intensive treatment consisted of three to five individual and group sessions a week. Controls received once a week groups. Forty-three methadone patients entered intensive cocaine treatment, 19 entered the control group and 32 eligibles did not enter treatment. At intake 40% were sniffing cocaine, 60% were using crack and 38% were injecting drugs (multiple routes possible). Demographic characteristics were 53% female, 47% male; 62% Hispanic, 31% black and 7% white; mean age was 36. Therapy was completed by 49% of neurobehavioral and 53% of control patients. Patients who dropped out during study intake were more likely than treated patients also to drop out of the methadone clinic within six months. In paired comparisons between intake and six-month follow-up, neurobehavioral patients, but not controls or study intake drop-outs, showed significant declines in cocaine and other drug use (measured by urinalysis and self-reports), as well as significant improvement in psychological status (as measured by the Brief Symptom Inventory and the Profile of Mood States). The findings suggest that specialized cocaine abuse treatment can benefit methadone patients; intake to the study is continuing.

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CONTINGENT REINFORCEMENT OF GROUP PARTICIPATION VS. DRUG FREE URINES IN A METHADONE MAINTENANCE PROGRAM

M. Y. Iguchi, R J. Lamb, and J. J. Platt

Numerous studies demonstrate that take-home (TH) incentive programs based on urinalysis results can reduce illicit drug use among methadone maintenance clients. This studv examines the use of TH medications to reinforce either the provision of urines free of illicit substances (UA group) or participation in groups providing Training in Interpersonal Problem Solving (TIPS group). Subjects are randomly assigned to either the UA or TIPS condition after a three month baseline. In the UA condition, subjects earn 1 TH/week if they provide 2 consecutive weeks of urines free of illicit substances (x3/week testing; EMIT), with 1 more TH provided for each additional 2-week period of drug-free urines. A maximum of 4 THs per week may be earned. THs are reduced by 1 TH for each urine testing positive for illicit substances. In the TIPS condition, subjects earn a single TH for use the next week if they attend the first TIPS session. Subjects then earn 1 TH/week for the remainder of the six month treatment period if they attend the second TIPS session. Additional THs are earned at the rate of 1 TH/week for every 2 TIPS sessions attended, up to a maximum of 4. Contingencies are in effect for six months.

To date, 45 subjects have completed the nine month protocol. Preliminary analysis of urine data indicate a significant treatment effect ($F(1,43)=5.54$, $p<.05$) as well as a significant group x treatment interaction ($F(1,43)=5.55$, $p<.05$). Table 1 shows an increase in the percentage of urines testing negative for illicit substances in the UA group, with a corresponding decrease in the percentage of urines testing negative for illicit substances in the TIPS group.

TABLE 1: Percentage of Urines Testing Negative for Illicit Substances

Group	Baseline (mos 1-3)	Treatment (mos 4-6)	Treatment (mos 7-9)
UA	25%	37%	49%
TIPS	45%	42%	38%

In a second analysis, subjects were classified as demonstrating clinically significantly behavior change from baseline if they: 1) submitted >10% more urine samples testing negative for illicit substances and had at least one continuous month of verified abstinence during the intervention phase; or, 2) submitted >10% fewer drug negative urines testing negative for illicit substances during the intervention phase. In the UA condition, 11 of 26 subjects (42%) met criterion for significant clinical improvement while three subjects (12%) were classified as getting worse. In the TIPS condition, 4 of 19 subjects (21%) met the criterion for significant clinical improvement, while nine subjects (43%) were classified as getting worse.

The preliminary analyses indicate that the UA intervention was significantly more effective in reducing illicit drug use in methadone maintenance clients than the TIPS intervention. Program staff reported that the TIPS sessions were well liked and that participants were frequently observed making use of the skills in their daily lives. In the absence of explicit contingencies for reducing illicit substance use however, TIPS subjects were more likely than UA subjects to increase their use of illicit drugs.

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A COMPARISON OF FUNCTIONAL AND STRUCTURAL SOCIAL SUPPORT: ROLE IN RELAPSE PREVENTION

L. Goehl and E. Nunes

The relative effects of functional social support (quality and diversity of the supportive functions of the social network) and structural social support (quantity and density of the social network) on mood and abstinence were examined in a study of methadone maintenance treatment patients (N=70). Structural social support was expected to have a direct impact on both mood and illicit drug use by the subject, whereas functional social support was expected to improve mood and abstinence by buffering the impact of stress. Subjects were given baseline measures of functional social support, structural social support, mood, stress, and drug use in the network and followed prospectively for three months with weekly urine drug screens. With demographic variables controlled, structural social support was not significantly correlated with either positive affect (r = .19, NS) or negative affect (r = -.02, NS). Conversely, functional social support was significantly correlated with both positive affect (r = .59, p< .001), and negative affect (r =-.40, p< .01). Stress level was also significantly correlated with both positive affect (r = -.38. p< .01), and neaative affect (r = .46. p< .001). Using a multiple regression analysis, with functional social support and stress entered as predictors of affect, functional social support accounted for 35% of the variance in positive affect (DF =l, Std Error = 0.08, t = 5.79. p< .001) and 11% of the variance in negative affect (DF =1, Std Error = 0.09. t = -3.31; p< .001). Stress accounted for 8% of the variance in positive affect (DF =1, Std Error = 0.26. t = -3.06. p< .01) and 21% of the variance in negative affect (DF =1, Std Error = 0.31, t = 3.92, p < .001). No measures of social support, affect or stress correlated with the proportion of drug positive urines. Additionally, neither measure of social support showed significant stress buffering effects for mood outcome, although the stress buffering effects of functional social support on drug use outcome approached significance (p = .07) in those subjects with drug users in their close social network. This study highlights the importance of the quality, rather than the quantity, of the social network in relapse prevention.

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ONE TRIAL CONDITIONED EFFECT OF AMPHETAMINE IN NIGRAL RATS

P. B. Silverman

In rats with a unilateral 6-hydroxydopamine lesion of substantia nigra, direct-acting dopamine agonists induce an acute episode of contralateral circling. Dopamine agonists with Dl activity, but not selective D_2 dopamine agonists, also result in a remarkable conditioned rotation. That is, weeks or months after limited administration of agonist, mere m-introduction of the rat into the drug-associated environment results in a brief, intense burst of contralateral circling (Silverman and Ho 1981; Silverman 1992). Indirect agonists, able to promote release and/or block reuptake of dopamine only on the intact side, ordinarily induce acute ipsilateral rotation. Despite large acute effect they do not result in (ipsilaterallv directed) conditioned circling comparable to that which follows direct D_1 or D_1/D_2 agonists. When an indirect agonist which acts through the newly synthesized dopamine pool (e.g., amphetamine) is administered shortly after an animal has been lesioned, acute circling is directed contralaterally (Oberlander *et al.* 1979). Here, 1 to 5 mg/kg amphetamine was administered one day after rats were lesioned in order to determine if amphetamine, in this circumstance acting preferentially on the lesioned side, resulted in both acute and conditioned contralateral rotation. When rats that had been treated with amphetamine one day after they were lesioned were placed in the rotation environment two weeks later, they exhibited a brief rapid burst of stereotyped contralateral circling like that which typically follows administration of direct dopamine agonists with Dl activity. This conditioned contralateral circling was still significant six weeks after one amphetamine treatment. The results show that failure of indirect agonists to induce conditioned rotation in chronically lesioned rats is not attributable to interference by drug stimulus effects, and suggest that the extraordinary conditioning seen in this preparation depends upon drug activity in the denervated, supersensitive hemisphere.

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INTRAVENOUS SELF-INJECTION OF METHCATHINONE IN THE BABOON

B. J. Kaminski and R.R. Griffiths

Methcathinone is a phenylisopropylamine derivative that has been produced by clandestine laboratories and identified in illicit drug traffic. Methcathinone has been reported to be a locomotor stimulant and to occasion amphetamine-lever responding in a drug discrimination study with rats (Glennon *et al.,* 1987). The present study evaluated the intravenous self-administration of methcathinone in three baboons using a cocaine substitution procedure. Self-injections were available 24 h/day according to a fixed-ratio (FR) schedule and with a 3 h timeout following each injection. Doses of racemic methcathinone HCl (0.01 - 1.0 mg/kg/injection) and its vehicle were substituted for cocaine for 15 or more days. A concurrent FR schedule of food pellet delivery allowed evaluation of any changes in food intake. Self-injection of methcathinone was dose dependent. The lower doses of methcathinone, 0.01 and 0.032, maintained low and intermediate rates of self-injection, respectively. Several doses of methcathinone (0.1, 0.32, 1.0) maintained rates of self-injection comparable to cocaine. Food pellet intake was suppressed slightly during substitution of 1.0 mg/kg/injection methcathinone. Acute administration of 3.2 mg/kg in two baboons produced signs of psychomotor stimulant toxicity that included stereotypic movements, behavioral agitation, tremors, and tracking of non-existent visual objects (suggesting hallucinations). The present data indicate that methcathinone functions as a positive reinforcer in baboons and suggests that it may have significant abuse potential.

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THE EFFECTS OF GBR 12909 ON RESPONDING OF RHESUS MONKEYS MAINTAINED UNDER SCHEDULES OF COCAINE- AND FOOD-DELIVERY

J. R. Glowa, F. H. Wojnicki, B. de Costa, D. Matecka, K. C. Rice, and R. B. Rothman

Responding of 6-10 kg male rhesus monkeys was maintained under multiple FR 30-response schedules of food and cocaine delivery. With saline high rates of responding were maintained in the food component and low rates of responding (extinction) occurred in the drug component. Low doses (3-10 µg/kg/injection) of cocaine maintained maximal rates of responding in both drug and food delivery components, while doses higher than 10 @kg/injection resulted in progressively decreased rates of responding in both components. With responding maintained by 25 µg/kg/injection, pretreatment with 1 mg/kg GBR 12909 (i.v. bolus) selectively decreased cocaine-maintained responding. Pretreatment with lower doses (0.3 mg/kg) of GBR had no effect and higher doses decreased responding in both components. With responding maintained by 10 µg/kg/injection, pretreatment with slow-infusion (15 min i.v. drip) of GBR 12909 in doses up to 3 mg/kg produced selective effects (i.e. up to 100% decrease) on cocaine-maintained responding without producing an effect on food-maintained responding. The time course for these effects was short (1-2 hr). By 3-4 hrs the effects of GBR had diminished. These results suggest that GBR 12909 can selectively decrease cocaine-maintained responding, at doses without effects on alternative behaviors. In addition, self-administration of doses GBR 12909 of 3-30 µg/kg/injection was not obtained in cocaine-naive monkeys. These results suggest that GBR-based agents may be useful in the development of drugs to modify cocaine self-administration.

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CHRONIC HALOPERIDOL ENHANCES COCAINE CONDITIONED PLACE PREFERENCE

T. A. Kosten, M. J. D. Miserendino, D. W. Marby, and E. J. Nestler

The rewarding and other behavioral effects of cocaine (COC) are believed to be mediated, in part, through dopamine (DA). Accordingly, DA antagonists have been proposed as pharmacological "blocking" agents for COC abuse. Acute pretreatment with the DA antagonist, haloperidol (HAL), alters COC's behavioral effects in many paradigms (e.g.. Colpaert, *et al.,* 1978; Roberts and Vickers 1984), although a previous study (Spyraki, *et al.,* 1982) failed to find an effect of HAL on COC conditioned place preference (CPP). In contrast to these acute effects, chronic DA receptor blockade with DA antagonists can lead to receptor supersensitivity (Seeger, *et al.,* 1982) which may enhance COC's behavioral effects. The present study compared acute vs chronic HAL treatments on COC CPP.

For the acute study, separate groups of rats (n's=6-8) were maintained on HAL or vehicle (VEH) given in the drinking solution (about 1.2 mg/day) during COC (0, 7.5, 15, or 30 mg/kg) CPP training. Acute HAL blocked the acquisition of COC CPP as demonstrated by a significantly lower time shift to the COC-paired side (Baseline - test times, both 30 min sessions), $F(1, 49)=4.5$; $p<0.05$. The effect was particularly strong at the 15 mg/kg dose, where the VEH rats showed the greatest COC CPP. For the chronic study, rats were maintained on HAL or VEH for 30 days prior to and then during COC (0, 5, 7.5, or 15 mg/kg) CPP training. Chronic HAL treated rats showed enhanced COC CPP, particularly at the low doses which did not support CPP in VEH rats, $F(1, 48)=12.3$; $p<0.001$.

Using a full COC dose-response function, we demonstrated that acute HAL does block COC CPP. contrary to a previous study (Spyraki, *et al.,* 1982) which only used one COC dose. Thus, our results are consistent with the effects of acute HAL on other COC-mediated behaviors. In contrast, chronic HAL treatment leads to behavioral supersensitivity, lowering the threshold of the COC dose that supports CPP. The latter finding is consistent with studies that show that chronic HAL leads to receptor supersensitivity and to enhanced locomotor responsivity to COC (LeDuc and Mittleman 1993). These results suggest that using HAL or other DA antagonists would be contraindicated as treatments for COC abuse as they may lead to enhanced abuse potential. Moreover, the phenomenon of COC abuse in schizophrenics may be due, in part, to chronic neuroleptic treatments leading to an enhancement of COC's effects.

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EFFECTS OF ADRENALECTOMY ON INTRAVENOUS COCAINE SELF-ADMINISTRATION IN RATS

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Previous data from our laboratories have demonstrated an effect of cocaine on benzodiazepine and corticotropin-releasing factor binding in the rat brain, especially in regions associated with the mesocorticolimbic dopaminergic system. We have also reported that benzodiazepines (*e.g.,* alprazolam, chlordiazepoxide) decrease cocaine self-administration in rats in a dose-related manner. Most recently, we reported that rats exposed to non-contingent electric footshock 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, suggesting the involvement of stress in the etiology of cocaine self-administration. Since rates of self-administration were significantly correlated with stress-induced changes in plasma corticosterone, the following experiment was designed to further investigate the role of the hypothalamo-pituitary-adrenal axis in cocaine reinforcement by comparing the acquisition of self-administration in adrenalectomized and sham-treated controls. Each rat was implanted with a chronic indwelling jugular catheter and was allowed to recover for a minimum of four days. The rats were then trained to respond under a fixed-ratio 1 schedule of food reinforcement. When responding stabilized, the rats were allowed access to intravenous injections of cocaine by pressing a second lever located in the experimental chamber. Very low doses of cocaine were initially tested (i.e., 0.031 mg/kg/infusion), and the concentration was doubled each week (range 0.031 to 1.0 mg/kg/infusion). Each Monday, the rats were tested under the food reinforcement schedule to ensure that they could still meet the response requirement, and cocaine was made available Tuesday through Friday of each week. Adrenalectomy significantly reduced plasma corticosterone (72.4 ± 8.1 ng/ml, sham vs 7.2 ± 4.3 ng/ml, adrenalectomized). Sham-treated control rats exhibited a typical inverted "U" shaped dose-response acquisition of cocaine self-administration, with response rates similar to those seen during saline substitutions at every dose of cocaine tested. These data further suggest a role for the hypothalamo-pituitary-adrenal axis in cocaine reinforcement.

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ATTENUATION OF COCAINE SELF-ADMINISTRATION IN RATS BY IBOGAINE

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Ibogaine, an indole alkaloid, has recently received attention as a potential agent in treating drug abuse. This compound interacts with a number of brain systems thought to be involved in drug reinforcement mechanisms, and can modulate the behavioral and neurochemical effects of morphine and amphetamine. In two experiments, the effects of ibogaine on cocaine or heroin self-administration were evaluated in rats. Responding was maintained on an FR 10 schedule by i.v. drug infusion (0.33 mg/inf of cocaine or 0.018 mg/inf of heroin). Sessions of 3 hour (cocaine) or 4 hour (heroin) duration were conducted five days per week. Pretreatment with ibogaine (40.0 or 80.0 mg/kg, i.p.) 1 hr before the session dose-dependently decreased drug intake, with greater reductions occurring in heroin self-administration. When 80.0 mg/kg was given 90 minute prior to the session, cocaine infusions decreased further, but no effect was observed when the pretreatment was 24 hours. In a third experiment, food reinforcement on an FR 10 schedule with a 6 minute timeout after each reinforcer resulted in rates and patterns of responding and food intake over the 2 hour session that were similar to those observed when cocaine was the reinforcer. With a 1 hour pretreatment, 40.0 mg/kg of ibogaine had very little effect on food-maintained responding, but 80.0 mg/kg severely decreased responding, and this effect persisted during the next day's session. In all experiments, casual observation of the rats during pretreatment period revealed tremors, shaking, and profound disruptions of locomotor activity. Thus although ibogaine does appear to successfully decrease drug self-administration, its effects may not be specific to drug reinforcers and may include some undesirable side effects.

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GENETIC FACTORS IN ACUTE COCAINE-INDUCED LOCOMOTOR ACTIVITY AND CONTEXT-SPECIFIC CONDITIONED SENSITIZATION

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Repeated administration of cocaine leads to an increased response to the drug that is specific to the dose, administration schedule and context of administration. The purpose of the current series of experiments was first to establish the degree of genetic variation in the locomotor activating effects of cocaine and second to establish a mouse model of context-specific behavioral sensitization to cocaine in a number of inbred strains.

First, cocaine's dose-response curves for locomotor activity were determined in six inbred strains of mice (AKR/J, C57BL/6J, DBA/2J, C3H/HeJ, BALB/ByJ and CBA/J) Large differences in the potency and efficacy were found as a function of genotype. The ED_{50} and efficacy of cocaine's locomotor stimulant effect differed by 2.9 and 4.5-fold, respectively. Cocaine was most efficacious in the CBA/J mice and had no significant effect in the DBA/2J or BALB/ByJ mice.

Second, conditioned sensitization in each genotype was determined by administering the ED_{50} dose for each strain in the locomotor activity monitor or the home colony for 1, 2, or 3 days and testing for context-specific sensitization to the ED_{25} dose the following day in the locomotor activity monitor. Large differences in the degree and context-specific nature of sensitization were found as a function of genotype. Sensitization to cocaine's locomotor effects differed both quantitatively and qualitatively in the number of injections required to show sensitization and context specificity. For example, C57BL/6J mice showed context specific sensitization following one administration whereas DBA failed to show any form of sensitization following three injections.

Thus, genotype significantly affects the acute and chronic effects of cocaine as well as the context-specific nature of conditioned sensitization.

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DNQX IN THE NUCLEUS ACCUMBENS INHIBITS CONDITIONED PLACE PREFERENCE INDUCED BY AMPHETAMINE OR COCAINE

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The nucleus accumbens receives dopaminergic and glutamatergic projections, and dopaminergic activity in this area is associated with many drugs that have rewarding effects. This study deals with the possibility that glutamatergic activity is also associated with these drugs. Such an idea derives from ovservations that injection into the nucleus accumbens of agonists for the AMPA subclass of glutamatergic receptors elicits increases locomotor activity in rats (Arnt 1981; Donzanti and Uretsky 1983) similar to that stimulated by amphetamine or cocaine. Additional studies imply that action of both glutamatergic and dopaminergic receptors in the nucleus accumbins is required to elicit a locomotor response (Arnt 1981; Boldry *et al.,* 1991; Willins *et al.,* 1992). For psychostimulant drugs, stimulation of locomotor activity is correlated with ability to elicit reward (Wise 1987). which suggests that activation of AMPA receptors in the nucleus accumbens may contribute to drug-induced reward. This hypothesis was tested using a conditioned place preference paradigm. Rats were allowed to freely move between the white and black compartments of the apparatus during a pre-training test in which all rats preferred the black environment. On training days one, three, five, and seven, rats were given 1 mg/kg amphetamine, 20 mg/kg cocaine, or 10 mg/kg morphine and confined to the white side. On days two, four, six, and eight, rats were given saline and confined to the black side. On day nine, rats were allowed to freely move between the compartments. After training with drugs, preference was shifted to the white compartment. For acquisition experiments, 1 µg DNQX, an antagonist at AMPA receptors or vehicle was injected into the nucleus accumbens just prior to systemic administration of rewarding drug on training days, and animals were drug-free during testing. DNQX treatment inhibited the acquisition of place preference elicited by amphetamine or cocaine but not that elicited by morphine. In expression experiments, training was done in the absence of antagonist drugs. and a single intracranial injection was-made just prior to testing on day nine. In these experiments, DNOX treatment inhibited the expression of place preference elicited by all three rewarding drugs. Our data suggest that activation of AMPA receptors in the nucleus accumbens is required for the development or acquisition of rewarding effects of psychostimulant drugs but not opiates. Furthermore, activation of AMPA receptors may be involved in the expression of behaviors previously linked to reward elicited by both psychostimulants and morphine.

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DOES ACCUMBENS ACETYLCHOLINE PLAY A ROLE IN ADDICTION

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Recent evidence suggest that drug withdrawal involves a decrease in dopamine (DA) release in the nucleus accumbens (NAC) which implies that animals might re-initiate drug-taking to restore DA (Pothos *et al.* 1991). Our new evidence points to acetylcholine (ACh) as having a complimentary role in the NAC. ACh sampled by microdialysis was decreased by morphine (20 mg/kg), and then increased during naloxone-precipitated withdrawal (Rada *et al.* 1991). Local methylnaloxonium (100μM via dialysis in the NAC) was sufficient to increase ACh in normal animals, and this effect was potentiated in morphine dependent rats. To see if elevated ACh was a result or a cause of an aversive state, we did experiments with results which suggest both cause and effect relationships aversion. ACh increased when rats experienced a taste (CS) which reminded them of nausea (US). When ACh was raised experimentally in the NAC with local neostigmine (US) in association with a taste, it caused a conditioned taste aversion. Together the results suggest that ACh in the NAC might play a role in an aversive state that reinforces behavior to escape that state, e.g. drug relapse. Thus we raise the possibility that ACh in the NAC mediates part of a negative reinforcement process and that this process might play a role in addiction.

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ORAL AND IP CAFFEINE EXPOSURE AS DETERMINANTS OF LOCOMOTOR ACTIVITY AND TOLERANCE

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Adult, male rats were maintained at 80% body weights. Locomotor activity was measured in daily, 1-hour sessions. Acute i.p. caffeine injections (2.5-40 mg/kg) produced dose-related activity-rate (counts/min) increases up to 20 mg/kg, but at 40 mg/kg activity was between the levels observed at 5 and 10 mg/kg doses, and was still elevated 4 h after 20 mg/kg. No activity effects remained after 8 hours. With daily, 20 mg/kg injections tolerance developed by the 5th day, but even after 21 days of injection tolerance was not complete.

Caffeine solutions were self-administered orally by exposing rats to a schedule-induced polydipsia procedure in which food pellets were delivered 1/min in daily, 3-hour sessions. Dose was varied by manipulating caffeine concentration and vehicle composition. After each polydipsia session, rats were then evaluated for activity as before. There was a dose-related (9.3-36.5 mg/kg) increase in locomotor activity, and increases remained evident even after 8 hours. At the highest caffeine intake, tolerance developed after about two weeks of exposure, but again tolerance remained incomplete.

Caffeine and metabolite (theobromine, paraxanthine, theophylline) pharmacokinetics were followed for 24 hours after dose initiation for i.p. and oral self-administration. For similar doses, caffeine AUCs were larger for the i.p. route, but were linear functions of dose for both routes. The elimination rate for the smallest oral dose (8.8 mg/kg) was less than the rate for the two larger doses (19.4, 37.9 mg/kg). Ratios of the three metabolite levels to caffeine were 2-3 times greater for the oral than for the i.p. route.

A plot of 4-hour serum caffeine AUCs against activity-rate AUCs showed that oral caffeine was about twice as effective as i.p. caffeine in producing activity increases. For oral caffeine, assuming 1st-order, 1-compartment, open-model kinetics, activity rate was linearly related to serum caffeine concentration, and the predicted activity rate at zero serum caffeine agreed precisely with the value observed.

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MARIJUANA SMOKING INCREASES PLASMA COCAINE LEVELS AND SUBJECTIVE REPORTS OF EUPHORIA IN MALE VOLUNTEERS

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The combined use of smoked marijuana followed by intranasal cocaine is a popular combination among drug abusers. The reason why individuals use this particular combination is not entirely clear, however, it has been speculated that marijuana potentiates cocaine's subjective effects. Five healthy adult male recreational drug users provided informed consent and volunteered to participate in this study. Subjects were prepared with an i.v. catheter for continuous blood withdrawal and sat in an isolated chamber. On three different occasions, separated by at least one week, each subject smoked a marijuana cigarette containing either 0.004% (placebo), 1.24% or 2.64% Δ^9-THC. Thirty minutes after smoking, they received an intranasal dose of cocaine (0.9 mg/kg). Subjects continuously reported changes in their mood state via an instrumental joystick device and on visual analog scales. Peak plasma cocaine levels were 138.2 ± 18.9 ng/ml after placebo marijuana, but pretreatment with the high-dose marijuana resulted in a significant increase in peak cocaine levels to 242.5 ± 22.1 ng/ml. The duration of all marijuana- and cocaine-related subjective effects was unchanged after both drugs, but marijuana pretreatment reduced the mean latency to detection of cocaine effects from 1.9 to 0.75 minutes and caused a moderate increase in the number of euphoric events from 14.5 ± 6.5 to 43.1 ± 18.7. Since marijuana smoking does not appear to alter plasma cocaine levels after the i.v. route, these data suggest that the effects observed in the present study may be due to an increase in cocaine absorption secondary to marijuana-induced vasodilation of the capillaries in the nasal mucosa. Thus, concomitant use of cocaine and marijuana may be based on significant pharmacodynamic interactions between the two drugs.

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BEHAVIORAL EFFECTS OF ALPRAZOLAM IN HUMANS

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The effects of acute doses of alprazolam on task performance, including DSST, time estimation (DRL schedule of point presentation), repeated acquisition of response sequences, number recognition and repeated acquisition of task sequences, and drug ratings were examined. Six subjects participated in daily 4 hr sessions. Alprazolam (0, 0.25, 0.5 or 1.0 mg) was administered thirty minutes after consumption of a fixed breakfast. Task performance was continuous over a 3-hr interval beginning 30 min after drug administration. Drug ratings were obtained immediately following task performance. Acquisition of task sequences was maintained by monetary contingencies; no contingencies were associated with performance of other tasks or drug ratings. Pronounced dose-related changes in performance were associated with alprazolam administration. DSST trial rate was decreased, but no changes in accuracy were observed. Increases in inter-response times on the DRL task were observed. Rates of incorrect responses were increased during the repeated acquisition of response sequences task, and learning efficiency was decreased. Reaction time and discrimination accuracy during number recognition were both decreased. In contrast, alprazolam produced no changes in visual-analog scale ratings of drug effects, including "Stimulated, "Sedated," "Potency," "Anxious," or "Liking," and no changes in the acquisition of task sequences, maintained by monetary contingencies, were observed. This profile of effects was distinct from those obtained using a similar protocol with other drugs of abuse, including diazepam and alcohol.

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PREFERENCE FOR ETHANOL AND DIAZEPAM IN LIGHT AND MODERATE DRINKERS: A WITHIN-SUBJECTS STUDY

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The goals of this study were: i) to examine preference for ethanol (EtOH) and diazepam (DZP) in light drinkers vs moderate drinkers, and ii) to examine the relationship between subjects' responses to the two drugs. Fourteen light drinkers (LD; average 2.2 drinks/week) and 13 moderate drinkers (MD; average 11.2 drinks/week) participated in two 7-session choice experiments, assessing preference for EtOH (0.5 g/kg) or DZP (20 mg) vs placebo. Half of the subjects participated in the EtOH experiment first, half in the DZP experiment first. Sessions were conducted in groups of four subjects during the evening in a comfortable laboratory environment. A double-blind preference procedure was used in which subjects first sampled drug and placebo (four sessions) and then chose the substance they preferred (three sessions). The number of times subjects chose drug over placebo was the primary measure of preference. At regular intervals during the sessions, subjects completed self-report questionnaires assessing their mood and drug effects (*e.g.*, magnitude and liking of effects, measures of euphoria, sedation, and psychomotor impairment).

In the EtOH experiment, both groups chose EtOH more often than placebo (66% drug choice for LD group and 80% drug choice for MD group; difference ns). Both groups reported typical EtOH-like subjective effects after EtOH administration. In the DZP experiment, the MD group chose the drug significantly mom often than the LD group (73% for MD vs 40% for LD; t-test $p<.05$). and reported liking the drug significantly more than the LD group. LD subjects reported more sedation, confusion and dysphoria after DZP than the MD group. In sum, although preference for EtOH was similar in the two groups, the heavier drinkers showed a greater preference for DZP. Greater preference for DZP among individuals with heavier alcohol consumers may be indicative of a higher likelihood of non-therapeutic use of this drug.

Individual subjects' choice of EtOH was positively correlated with their choice of DZP ($r=0.56$), and ratings of liking of the two drugs were positively correlated ($r=0.66$). The subjective effects of the two drugs were positively correlated on several scales of the Addiction Research Center Inventory, including "euphoria" (MBG; $r=0.59$) and "dysphoria" (LSD; $r=0.55$) scales. Correlations were observed even when the effects of habitual alcohol consumption were removed using ANCOVA (drinks/week as covariate). Thus, individual differences in behavioral and subjective responses to EtOH and DZP are correlated in ways that are partly, but not completely, accounted for by differences in habitual alcohol consumption.

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DISCRIMINABILITY OF SUBTHERAPEUTIC DOSES OF DIAZEPAM AND BUSPIRONE IN HUMANS

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The discriminative stimulus effects of therapeutic and subtherapeutic doses of diazepam (DZ) and buspirone (BUS) were assessed in healthy, drug-free, paid volunteers (N=18). The study was conducted in three phases. During the training phase, drug and placebo, identified by letter codes (e.g., drug A or B). were administered in a mixed order across sessions and subjects were instructed to attempt to discriminate between the two drugs. Approximately 2 hours after drug administration, subjects reported their drug identification by telephone. One group (N=10) was trained to discriminate DZ (10 mg) from placebo, while a second group (N=8) was trained to discriminate BUS (15 mg) from placebo. Correct discriminations earned $10. All subjects showed reliable discrimination (≥80%). The subsequent phase was identical to the training phase except half the sessions were training sessions and the other half were test sessions. Each test dose was tested at least 4 times and subjects were paid $10 for correct or incorrect discriminations during test sessions. Placebo, 2.5, 5 and 10 mg of DZ occasioned 12.6. 17.2. 61.0, and 92.1% DZ responding, respectively, in the DZ-trained group. In the BUS-trained group, placebo, 3.75, 7.5 and 15 mg of BUS occasioned 3.3, 6.6, 33.0, and 93.0% BUS responding, respectively. In the final phase, the lowest discriminable dose of the training drug was determined by training subjects to discriminate progressively lower doses of drug from placebo for at least 20 sessions at each dose. The lowest discriminable dose of DZ was 1.25, 2.5 or 5.0 mg in 1, 4 and 2 subjects, respectively. The lowest discriminable dose of BUS was 3.75, 7.5 or 15 mg in one, two and one subjects, respectively. These findings extend previous human research on the discriminative stimulus effects of DZ and BUS, and suggest subtherapeutic doses of these drugs are behaviorally active. DZ is approximately three times more potent than BUS in this regard.

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COMPARATIVE ABUSE LIABILITY OF SERTRALINE, ALPRAZOLAM AND DEXTRO-AMPHETAMINE IN DRUG NON-ABUSERS

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Sertraline, an antidepressant acting as a highly selective and specific 5-HT reuptake inhibitor (Heym and Koe 1988) may also be effective in diminishing alcohol consumption (Gill *et al.,* 1988). We tested the abuse liability of sertraline in 20 healthy males (mean age 27, range 18-46) who were recreational users of CNS depressants but did not meet DSM-III-R criteria for alcohol or psychoactive substance use disorder. Subjects were first screened for their ability to distinguish a CNS depressant (Secobarbital 150 mg) from placebo and report pleasant effects of the drug. In a double-blind, randomized, cross-over, placebo-controlled study, sertraline 100 and 200 mg, dextro-amphetamine 10 mg, alprazolam 1 mg and placebo were administered to each subject at weekly intervals. Subjects completed a battery of objective tests (*e.g.* psychomotor performance) and subjective questionnaires including the Profile of Mood States (POMS), the Addiction Research Center Inventory including Cole subscales (ARCI and Cole/ARCI), and a Drug Performance and Preference Profile (DPPP) to measure drug effects. An observer rated questionnaire was also included.

Alprazolam but not δ-amphetamine or sertraline significantly impaired psychomotor performance (measured by a manual tracking task) compared to placebo ($p = 0.0001$). Subjective effects showed that δ-amphetamine and alprazolam both had higher peak responses than at least one dose of sertraline and placebo on the POMS Elation, ARCI MBG (Euphoria) and the Cole/ARCI Stimulation Euphoria and Abuse Potential Scales ($p < 0.001$). In contrast, the Cole/ARCI Unpleasantness-Physical scale and showed a peak response higher for 200 mg sertraline than for all other drug conditions ($p = 0.007$). On the DPPP 7-point 'liking' scales, alprazolam and δ-amphetamine exceeded sertraline and placebo in peak pleasant effects on the mind and body ($p = 0.0001$ for both). However, overall drug 'liking' was highest for &amphetamine than for all other drug conditions ($p < 0.05$). These data suggest a very low abuse potential for sertraline compared to alprazolam and &amphetamine and a comparable abuse potential for alprazolam and δ-amphetamine at the doses tested. This study also demonstrates the sensitivity and reliability of drug non-abusers to report pleasant subjective effects of therapeutic doses of psychoactive drugs and to distinguish these drug effects from placebo.

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INDEPENDENCE OF CRAVING SELF-REPORTS AND PHYSIOLOGICAL REACTIVITY TO COCAINE CUES IN COCAINE ABUSE PATIENTS

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Ninety-three cocaine abuse patients were exposed to cocaine-related cues while changes in physiological reactivity and reported craving were assessed. Cues consisted of audiotapes of "drug talk", videotapes depicting simulated drug use, and drug paraphernalia which the patients were asked to handle. Subjects react to these cues with decreases in skin temperature and skin resistance and increases in heart rate and in reported craving. The purpose of the present analyses was to determine whether physiological reactivity and reported craving are related. First, correlations between each of the physiological indices and craving reports were calculated. The correlations ranged between -.13 and .08, revealing no relationship between the measures. Next, subjects were split into two groups; group 1 subjects reported no change or a decrease in craving while group 2 subjects reported an increase in craving. Five of six t-tests revealed no significant group differences in physiological reactivity. Finally, a discriminant analysis was performed to predict membership in the two craving level groups based on levels of physiological responding. The overall level of accuracy was just 8% above chance. These findings are consistent with earlier work demonstrating that reported craving and physiological reactivity are independent. These results discourage the use of physiological measures as surrogates for craving reports. Possible explanations for this asynchrony between self-reports of craving and autonomic reactivity will be discussed.

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NALTREXONE INTERACTIONS WITH COCAINE, HYDROMORPHONE, AND A "SPEEDBALL" COMBINATION IN SUBSTANCE ABUSERS

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Mesolimbic dopamine pathways mediate, in part, the reinforcing effects of both opiates and cocaine, and preclinical data suggest a functional interaction between the opiate and dopamine systems. Several preclinical studies have shown a modulation of the reinforcing effects of cocaine following administration of opioid antagonists. This study was designed to evaluate the interaction between naltrexone, an opioid antagonist, and cocaine in human substance abusers. In addition, because heroin and cocaine are commonly abused intravenously in a combination known as a "speedball," the interaction between naltrexone and a laboratory speedball combination was also assessed.

This double-blind, placebo-controlled, crossover study was conducted while subjects resided for seven weeks on a closed research unit. Capsules were given each morning, containing either placebo (weeks 1, 6 and 7) or ascending doses of naltrexone (3.125, 12.5, 50, and 200 mg) during weeks 2, 3, 4, and 5, respectively. In thrice-weekly experimental sessions, subjects received intravenous injections of either hydromorphone, cocaine, or the speedball combination of hydromorphone and cocaine. Three ascending doses of the challenge drug were given one hour apart, and the doses were as follows: cocaine (0, 20 and 40 mg), hydromorphone (0, 1.5, and 3.0 mg) or speedball (0, 20 mg cocaine and 1.5 mg hydromorphone and 40 mg cocaine 3.0 mg hydromorphone). The order of the drug challenge sessions was randomized across weeks. Subjects were monitored on physiological and subjective measures before and for one hour after each injection.

Hydromorphone, cocaine, and the speedball combination produced distinct subjective and physiological profiles. The magnitude of drug effect produced by the speedball combination was greater than that produced by either hydromorphone or cocaine alone. Naltrexone produced dose-related blockade of the subjective and physiological effects of hydromorphone. All active doses of naltrexone produced partial attenuation of the speedball effects, which appeared to be attributable to the selective blockade of the opioid component of the combination. Naltrexone had no effect on any of the physiological or subjective effects of cocaine. These data suggest that naltrexone has no therapeutic utility for the treatment of cocaine abuse in this dose range.

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EFFECTS OF AGONIST/ANTAGONIST OPIOIDS IN HUMAN VOLUNTEERS TRAINED TO DISCRIMINATE AMONG HYDROMORPHONE 0, 1, AND 4 MG

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This study is one in a series using drug discrimination methods in human volunteers to evaluate and characterize the clinical pharmacology of, and to differentiate among, opioid mixed agonist/antagonists. These studies are relevant to characterizing both the pharmacological bases for similarities and differences among opioids as well as the behavioral-procedural factors that influence expression of these similarities and differences. In a residential laboratory and after passing medical and psychiatric screening, six non-physically-dependent, current-sporadic-opioid-abuser, paid volunteers were trained in a three-choice procedure to discriminate among i.m. administration of saline placebo, and 1 mg, and 4 mg hydromorphone (a morphine-like opioid mu-agonist). The discrimination was readily learned. After training, test sessions were conducted to assess the effects of a range of doses of the training drug (hydromorphone 0.375 - 4 mg) and of four opioid mixed agonist/antagonists (pentazocine 7.5 - 60 mg; butorphanol 0.75 - 6 mg; nalbuphine 3 - 24 mg; and buprenorphine 0.075 - 0.6 mg). Maximum doses for each drug were approximately 2-3 times typical therapeutic doses for analgesia. Behavioral discrimination performance and subjective effect indices were concurrently assessed in all sessions.

All five test drugs were discriminated as hydromorphone 1 mg-like at one or mom dose levels. Hydromorphone showed an inverted-U shaped dose effect function on discrimination as hydromorphone 1 mg-like. All five drugs showed increasing discrimination as hydromorphone 4 mg-like as dose increased. Only hydromorphone itself met our discriminative cross-generalization criterion (75% or more drug-appropriate responding) for discrimination as hydromorphone 4 mg-like. Subjective effect indices showed clearer differentiation among the test drugs than did drug discrimination performance. Pentazocine, butorphanol, and nalbuphine produced subjective effects different from those produced by hydromorphone and buprenorphine. Hydromorphone's and buprenorphine's subjective effects were similar to one another and indicated greater liking and good effects than with the other mixed agonist/antagonists. In other experiments, in which we have tested these same drugs after training a different discrimination (e.g.. hydromorphone 3 mg vs. butorphanol 6 mg vs. placebo), drug discrimination performance differentiated among the drugs as well as did subjective effect indices.

We conclude that the concurrent assessment of subjective and discriminative drug effects can be an effective tool for detecting and characterizing subtle differences between opioids, that the sensitivity of drug discrimination performance to between-drug differences depends upon the specific discrimination that has been trained, and that the relationship between subjective and discriminative measures also depends upon the specific discrimination that has been trained.

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DIFFERENTIAL CUE REACTIVITY IN HEAVY AND LIGHT SMOKERS

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An influential model of conditioned drug responses holds that exposure to drug cues will elicit compensatory physiological responding, enhanced urges/desires for drug use and contribute to tolerance. However, studies of cue reactivity in a variety of substance abusers have often failed observe such reactions. In other studies, appetitive-type physiological responding has been seen. The varied pattern of cue reactivity could be due to factors such as level of dependence, type of cue and the response system measured. Heavy and light smokers (each n=30) were each exposed to both "distal" and "proximal" type cigarette cues, and in another session, a neutral control cue. Dependent measures included urge to smoke, heart rate (HR), and T-wave amplitude, an index of sympathetic cardiac activity. After exposure to Cue and to Control, subjects smoked a 50 mm portion of a cigarette (0.8 mg nicotine) *ad lib*. Both light and heavy smokers experienced significant changes in urge, with light smokers reporting greater urge to smoke in response to the distal cue. Only heavy smokers experienced physiological cue reactivity. Each of the two cues elicited compensatory responses in HR (quadratic function of time). Reactivity of the T-wave amplitude was differential for the two cue types, with the distal cue eliciting an appetitive response, and the proximal cue a compensatory response. Physiological reactivity was related to the sympathomimetic agonist effects of nicotine. Furthermore, heavy smokers smoked faster after exposure to the smoking Cue, compared with the Control condition [$t(29) = 2.36$, $p = .025$]; an effect which was not observed in the light smokers [$t(29) = 1.38$ $p > .05$]. The effect of nicotine on HR was assessed after cue exposure. Although exposure to smoking Cue did not result in reduced HR compared to Control, the unconditioned HR effect of nicotine was influenced by the effect of cue reactivity. Regression analysis revealed a significant relationship between magnitude of HR reactivity to the proximal cue and change in HR after smoking. The results demonstrate behaviourally-relevant cue reactivity, and suggest that cue reactivity is influenced by the level of drug use, the type of cue and the pharmacologic action of the substance. Although the present observations are consistent with a learning model of cue reactivity, the conditioned compensatory response model is only partially supported. Further models for cue reactivity should attempt to explore relationships between these variables.

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A TEST OF CAFFEINE SELF-ADMINISTRATION IN ADOLESCENTS

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Although almost all children ingest caffeine-containing beverages and foods daily, whether some children self-administer caffeine has not been directly tested. Eighteen children (ages 11-15) who were in the 90th percentile of caffeine use, underwent six independent, randomized, double-blind, placebo-controlled trials. (Results for the first nine subjects were previously reported at the 1992 ISGIDAR meeting. We now present the results of the full sample). In each trial, subjects first sampled a non-caffeinated soda and a non-caffeinated soda to which 50 mg/12 oz of caffeine was added in a double-blind, crossover procedure. Caffeine self-administration was then tested by giving subjects concurrent access to the same two sodas. Only one out of 18 (6%) subjects met our two criteria for reliable caffeine self-administration (repeatability criterion defined by self-administration of caffeinated soda greater than non-caffeinated soda on five out of six trials and a statistical criterion). One other subject met the repeatability criterion but not the statistical criterion. Preliminary analyses indicated that on sampling days in which subjects received only non-caffeinated soda little, if any, withdrawal symptoms were observed. These generally negative results differ from our prior studies in which 33% of adult soda drinkers and 31% of the coffee drinkers showed reliable caffeine self-administration and withdrawal.

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VISUAL HABITUATION PERFORMANCE IN THREE-MONTH-OLD INFANTS EXPOSED PRENATALLY TO COCAINE

L. C. Mayes, M. H. Bornstein, K. Chawarska, and R. H. Granger

This study investigates relations between prenatal cocaine exposure and infant habituation performance at three months of age. The habituation response in infants is involved with attention, learning, memory and early habituation performance is predictive of later information processing capacities. Given the effects of cocaine on central dopamine function, links between the dopaminergic system and attentional mechanisms that are likely to involve the habituation process make it plausible to hypothesize that prenatal cocaine exposure could affect habituation performance in early infancy. In the present study, 69 infants (40 cocaine exposed and 29 non-cocaine exposed all from the same socio-economic class) participated at three months of age in an infant-control habituation procedure administered by experiments blind to the exposure to cocaine were significantly more likely to fail to complete the habituation procedure. Twenty-six of the 69 infants were unable to begin the habituation phase due to irritability (47.5% vs. 24%; $X^2=3.91, \underline{p}=0.05$). After presentation of the habituation stimulus, and additional ten infants, eight of whom were cocaine exposed, were sufficiently irritable and a significantly greater proportion of these were from the cocaine exposed group (67.5% vs. 31%; $X^2=8.96$, $\underline{p}=0.003$). Among infants who reached habituation criterion, there were no significant differences for drug exposure status on habituation performance as measured by the length of longest or peak look, accumulated looking time, or the recovery of attention to novel stimulus. For both groups, the proportion of recovery of attention to a novel stimulus was significantly different from chance, an indication that both cocaine exposed and non-cocaine exposed infants attended to the novel stimulus and that salient aspects of the habituation stimulus had been processed by both. Thus, in the present study, cocaine exposed infants were more labile and reactive to novel stimuli but if the infant was able to attend, there was no difference in measures of habituation performance. It may be that cocaine exposure does not specifically affect early information processing or attention regulation but does influence capacities for the organization of states of arousal and reactivity. Infants with such difficulties may be at increased risk for later problems in attention and difficulties in responding to novel situations as opposed to information processing *per se.* Conversely, the lack of differences in habituation performance for those infants reaching habituation criterion neither predicts nor precludes cocaine-related effects either on later measures of information processing or on other concurrent measures of attentional regulation.

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THE CLINICAL NEUROLOGICAL EXAMINATION IN CHRONIC COCAINE ABUSERS: PRELIMINARY FINDINGS

J. L. Cadet, T. Gendron, W. R. Lange, J. E. Henningfield, and R. B. Rothman

The acute and chronic use of cocaine is associated with medical and neuropsychiatric abnormalities. The neuropsychiatric disorders include seizure, psychosis, subarachnoid hemorrhage, and thromboembolic phenomena. Subarachnoid hemorrhages and thromboembolic infarctions are associated with clinical neurological signs consistent with those diagnoses. Most of these abnormalities occur in the acute setting of cocaine use. However, we are aware of no studies which used the detailed classical neurological examination in order to classify possible effects of the drugs on the central (CNS) and peripheral (PNS) nervous system. As a first step towards the elucidation of cocaine effects on the nervous system, we have thus started to carry out thorough neurological examination in subjects who are chronic cocaine abusers and who are seronegative for HIV. The seropositive subjects were excluded because of the known presence of neuropsychiatric abnormalities in that population of patients. Subjects with a long history of cocaine abuse receive a complete medical and neurological examination. In addition, blood tests including folate and vitamin B12 levels, antinuclear antibodies, rheumatoid factors, and protein electrophoresis were done in order to exclude other possible causes of neurological dysfunction. The results of these examinations have shown some consistent findings. A total of twenty subjects were evaluated. Four subjects were dropped because of positive autoantibodies. The abnormal findings on the neurological examination included horizontal nystagmus (40%), abnormal eye pursuit (65%), abnormal saccades (70%). decreased reflexes (83%), and increased jaw jerk (29%), vibration (44%) and position (44%) senses were also abnormal. The presence of nystagmus and increased jaw jerk in these subjects may be related to cocaine effects on brainstem pathways. The reflex and sensory abnormalities appear to correspond to a bilateral symmetric neuropathy. When taken together, these results suggest that cocaine may cause deleterious effects on the nervous system by causing constriction of the vasa nervorum which supply the PNS. In addition to providing preliminary documentation of the damage done to the PNS by cocaine, these findings suggest a new line of investigation which will focus on the clinical neurological consequences of cocaine abuse. These studies will help to determine if cocaine can cause axonal degeneration or a demyelinating neuropathy.

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DIFFERENTIAL REGULATION OF THE DOPAMINE TRANSPORTER IN COCAINE OVERDOSE DEATHS

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Metropolitan Dade County has one of the highest frequencies of cocaine-related emergency room episodes and cocaine overdose deaths in the United States. Based on a retrospective case control analysis of the toxicology reports, scene descriptions, supplemental background information, and autopsy findings, we define a cocaine overdose death as a death attributed to the toxic effects of cocaine. One of the most serious psychiatric sequelae of cocaine abuse is excited delirium, which is associated with hyperthermia and sudden death. The dopamine transporter is a primary recognition site for cocaine, that is related to substance abuse. Our hypothesis is that alterations in the affinity, density or allosteric regulation of cocaine recognition sites on the dopamine transporter may contribute to the behavioral, physiological and toxic effects of cocaine. We have used the potent cocaine congeners [^{125}I]RTI-55 and [^{3}H]WIN 35,428 to map and characterize cocaine recognition sites post mortem in the human brain from cocaine overdose deaths. Using quantitative *in vitro* autoradiography. we have observed an apparent 2-fold elevation in the density of RTI-55 binding sites within particular sectors of the striatum from cocaine overdose deaths. However, no increase in the density of high affinity RTI-55 binding sites was seen in the anterior striatum for the excited delirium subgroup. Equilibrium-saturation binding analysis of [^{125}I]RTI-55 and [^{3}H]WIN 35,428 isotherms demonstrated multiple binding sites in the putamen in agreement with previous studies in the rodent and primate brain (Boja *et al.,* 1992; Madras *et al.,* 1989). Computer-generated curve fits of the saturation binding data demonstrated no significant change in the affinity of the two binding sites in the cocaine overdose deaths or in the excited delirium subgroup as compared to control values. Analysis of the saturation values for WIN 35,428 binding in the anterior sectors of the putamen demonstrated a significant increase in the apparent density of high affinity sites on the dopamine transporter in cocaine overdose deaths as compared with control values ($p < 0.05$). Taken together, these observations suggest that chronic cocaine use may lead to a compensatory increase in the density of high affinity sites on the dopamine transporter. Saturation analysis of [^{125}I]RTI-55 and [^{3}H]WIN 35,428 binding demonstrated a significant overall decrease in the binding site densities for the excited delirium subgroup as compared to control values ($N = 8$; $p < 0.001$). This lack of an elevation of the high affinity cocaine recognition site for the excited delirium subgroup may indicate a diminished capacity for dopamine reuptake during a cocaine challenge or short term 'binge' use. Since the concentration of dopamine in the synapse is controlled by reuptake mechanism(s), we suggest that the lack of an 'upregulation' in the cocaine recognition site may explain the cocaine psychosis.

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QUANTITATIVE EEG ANALYSES IN COCAINE ABSTINENT SUBJECTS

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

We report quantitative electroencephalographic (QEEG) observations in a sample of 25 (mean age 34.6, 5 female) subjects recovering from polysubstance abuse who preferentially used cocaine. The major QEEG effects were significant decreases of absolute power in the delta and theta frequency bands. These values were significantly lower than normal all 21 leads in delta and 14 of 21 leads in theta bands. In normal subjects of this age group, the low amplitude delta and theta activity each comprise between 10-15% of the resting occipital EEG activity when quantitatively analyzed; frontally, delta activity represents from 25-30% and theta represents about 20% of the resting EEG. Reduced power in the lower frequency bands appeared to be related to both, duration of marijuana abuse and with the amount of cocaine used. This represents an independent confirmation of hypofrontal low frequency EEG activity in abstinent cocaine abusers reported by Alper *et al.* (1991).

Delta waves are thought to be generated by dipoles between superficial cortical layers and layer V that reflect sequences of excitatory and inhibitory processes of cortical neurons (Steriade *et al.* 1990). Extrathalamic afferent projections to the cortex include those of noradrenergic, dopaminergic and serotonergic systems (Foote and Morrison 1986). Activity in such systems is thought to be altered by chronic substance abuse; particularly cocaine (Jaffe 1990). Cortical neurons have been found to change firing patterns from rhythmic burst firing in the delta frequencies to tonic single spike activity by tonic depolarization. That is, changes in tonic depolarization switch the tiring pattern of a neuron from burst firing to single spike firing and vice-versa. These burst firing cells are thought to be pyramidal cells found predominantly in layer V whose apical dendrites ascend superficially into layer I. Several neurotransmitters, serotonin, norepinephrine, histamine, and acetylcholine, have been shown to switch burst-firing cells to tonic firing via such depolarization when applied to the neurons (McCormick 1992).

This could provide a substrate for the reduced delta activity seen in subjects recovering from chronic substance abuse. An hypothesized up-regulation of these neurotransmitters or neuromodulators, particularly early in abstinence, could lead to a change in tonic depolarization and thus a decrease in burst firing rates of cortical neurons. This would be reflected in a decrease in low amplitude low frequency EEG activity.

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DIFFERENTIAL COCAINE-INDUCED PHYSIOLOGICAL AND PATHOLOGICAL ALTERATIONS IN RATS ARE RELATED

C. A. Branch, V. W. Fischer, Q. Gan, and M. M. Knuepfer

A subset of conscious rats are more sensitive to the cardiovascular effects of cocaine, *i.e.* approximately one-half of rats respond consistently with acute decreases in cardiac output (CO); in the remainder CO is relatively unaffected or increased (Branch and Knuepfer, 1993). The decrease in CO is associated with sympathoexcitation (Knuepfer *et al.,* 1993). This study was conducted to determine if there was a relationship between cocaine-induced CO responses and ultrastructural myocardial damage. To address this question, four groups of rats were examined. Two groups were given cocaine for 14 days (5 mg/kg, i.v., twice daily) and either had a pulsed Doppler flow probe on the ascending aorta for CO measurement (group 1, n=19) or did not (group 2, n=8). Group 3 had flow probes for CO but received saline for 2 weeks (n=6) and group 4 were naive controls (n=4). Following the last treatment, left ventricular and septal tissue were fixed with glutaraldehyde (3%) in Sorensens's phosphate buffer at pH 7.2 and routinely processed for electron microscopic examination. Myocardial tissues were analyzed in a blind fashion.

In group 1. cocaine produced an average decrease in CO (>10%) in 11 of 19 rats. Myocardia from the 11 rats in which CO decreased exhibited a higher incidence and greater severity of lesions than in the remaining rats. Lesions were focal, intramyocytic and diffusely distributed, and included dilated sarcoplasmic reticulum, early signs of mitochondrial alterations, myofibrillar derangement and foci of myocardial fibrosis. Sarcoplasmic dilatations were best correlated with the CO response. Similarly, group 2 displayed wide variability in the degree of myocardial damage between individual rats. Control groups 3 and 4 (saline treated) had few or no identifiable lesions. These data suggest that functional depression of CO is correlated with myocardial ultrastructural pathology in rats. The individual variability resembles that described in humans.

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EVALUATION OF THE EFFECTS OF NIFEDIPINE ON COCAINE INTOXICATION IN MICE

T. -A. Ansah and D. C. Shockley

A number of studies have evaluated the calcium channel entry blockers (CCEBs) for their potential as either pharmacotherapeutical agents in cocaine abuse or as antidotes to cocaine-induced lethalities. Isradipine and nimodipine have been shown to attenuate cocaine-induced discriminative stimulus, intravenous self-administration, reinforcing properties and spontaneous locomotor activity. It was also shown that nifedipine, diltiazem and flunarizine were effective in antagonizing cocaine-induced conditioned place preference. When cocaine-using volunteers were pretreated with oral nifedipine, they observed a decrease in some subjective effects resulting from the intravenous administration of cocaine. The effectiveness of the CCEBs as antidote to acute cocaine toxicity is unclear. Beneficial, potentiation or no effect have been reported. We have previously shown that whereas nimodipine and diltiazem would block cocaine-induced locomotor activity in rats, the CCEBs offered no protection against the lethal effects of cocaine. Instead, the toxicity was enhanced. The present studies were undertaken to develop a mode1 for evaluating the effects of CCEBs on cocaine-induced toxicity. Male Swiss-Webster or ICR mice (20-30 g) were injected intraperitoneally with vehicle or CCEBs. After 30 min, they were administered cocaine and observed for lethalities over a 24-hour period. Nifedipine produced a dose-dependent increase in the number of lethalities caused by 80 mg/kg cocaine in ICR mice. At 30 mg/kg nifedipine, the number of lethalities increased from 40% to 50%. At 40 mg/kg, the number of lethalities increased to 80%. In the presence of 40 mg/kg nifedipine, the LD_{50} for cocaine in ICR mice decreased from 83 mg/kg to 66 mg/kg. Diltiazem (50 mg/kg) produced effects similar to that of nifedipine (40 mg/kg). Verapamil (40 mg/kg) had no effect on cocaine-induced lethalities. Doses higher than 40 mg/kg were toxic. potentiation of cocaine-induced toxicities by nifedipiie was also observed in Swiss-Webster mice. Studies are underway to determine the mechanisms involved in the potentiation of cocaine-induced toxicity by CCEBs.

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NITRIC OXIDE (NO) SYNTHASE INHIBITORS ABOLISH SENSITIZATION TO REPEATED COCAINE ADMINISTRATION

Y. Itzhak and K. M. Kantak

Recent studies imply the involvement of the glutamatergic system in the effects of cocaine. Particularly, the role of the N-methyl-D-aspartate (NMDA) type of glutamate receptors in the development of sensitization to the neurotoxic effects of cocaine is supported by both, behavioral and *in vitro* receptor binding experiments *(e.g.,* Itzhak and Stein. *J. Pharmacol. Exp. Ther.* 262:464-470, 1992). Since activation of the NMDA receptor results in an increase in the synthesis of NO, and blockade of the enzyme NO synthase (NOS) provides protection against NMDA-mediated glutamate neurotoxicity, the present study was undertaken to investigate the effects of NOS inhibitors on cocaine-induced sensitization.

Repeated administration of cocaine (45 mg/kg/day; i.p.; for 7 days) to Swiss Webster mice produced sensitization to the kindling response typified by a progressive increase in the duration of the convulsive reaction and an increase in the number of animals that seized. This treatment also resulted in an increase in lethality rate after the 4th day of treatment. Pretreatment of animals with NOS inhibitors, N^g-nitro-L-arginine (NO_2Arg; 25 mg/kg/day, i.p.) or N^g-nitro-L-arginine methyl ester (L-NAME; 100 mg/kg/day, i.p.) abolished completely the development of sensitization to the convulsive and lethal responses to cocaine. To investigate whether the effect of the drug treatment is associated with the modulation of the NMDA receptor, the binding parameters of the competitive NMDA receptor antagonist, [^{3}H]CGP39653, were determined in cortical membranes of saline, cocaine, L-NAME/cocaine and L-NAME treated mice. A significant up-regulation of the NMDA receptor was detected in membranes derived from cocaine treated animals (Bmax = 149±80 vs. 1080±53 fmole/mg protein for cocaine and saline groups, respectively). However, no significant change in the Bmax of [^{3}H]CGP39653 was observed in membranes derived from L-NAME/cocaine (Bmax = 1190±45 fmole/mg protein) and L-NAME (Bmax = 1140±63 fmole/mg protein) treated animals.

Taken together, these results indicate that NOS inhibitors abolish the development of sensitization to cocaine-induced toxicities. In addition, it appears that the increase in the kindling response to cocaine is associated with the up-regulation of cortical NMDA receptors, and NOS inhibitors prevent the development of this phenomenon. The present data further sustains the involvement of the NMDA receptor in cocaine-induced toxicities, and also supports the role of NO in NMDA-mediated glutamatergic neurotransmission.

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ATTENUATION OF HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL RESPONSE IN ABSTINENT ALCOHOLICS

N. C. Bernardy, A. C. King, W. R. Lovallo, and O. A. Parsons

Alterations in the hypothalamic-pituitary-adrenocortical (HPAC) axis have been seen in alcoholics as an attenuated cortisol response to pharmacological agonists. Recent data have shown abstinent alcoholics exhibit a decreased adrenocortical response to psychological and physical stressors. It is uncertain whether these changes are due to acute disruption of the HPAC axis, or if they reflect long-term system changes. This study investigated urinary cortisol levels during behavioral stress in 21-day abstinent alcoholics (n=42) and non-alcoholic controls (n=14). Subjects engaged in two demanding, moderately aversive tasks, mental arithmetic (10 min) and isometric handgrip exercise (5 min; 20% max grip strength). Two urines samples were collected: a pm-stress baseline (collected 8:00 to 8:30 a.m.) and post stress (collected from 8:30 a.m. to 30 min post task at 11:30 a.m.). Subjects reported activation and distress on subjective mood questionnaires before and after each task. Dependent variables included baseline and post stress cortisol values, subjective mood subscale scores, nicotine use. admission liver enzyme values, various drinking parameters, Beck Depression Inventory and Spielberger State Anxiety Inventory. Cortisol concentrations were elevated in early morning samples of both groups compared to the post stress sample, suggesting normal diurnal variations. Compared to controls, alcoholics showed significantly lower post stress cortisol concentrations ($p<.001$), indicating an attenuated task response. The cortisol levels among alcoholics do not appear to be a function of group differences in task perception since the alcoholics and controls described similar distress and activation levels. Additionally, although alcoholics showed more anxiety and depression symptoms than controls and used significantly more nicotine ($p<.001$), these did not correlate with their cortisol levels. Alcoholics who reported the greatest number of withdrawal symptoms had the lowest post stress cortisol values (r=-.41, $p<.05$). independent of any admission liver dysfunction. Results suggest there is a subset of alcoholics who have ethanol-induced HPAC axis injury, resulting in an attenuated cortisol response to stress.

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GENETICS AND SMOKING

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Genetic factors have been reported to have an important influence on smoking by men (Cannelli *et al.,* 1992). We have analysed self-report data on smoking habits obtained from 2967 Australian twin pairs (including 1608 female like-sex pairs) and found evidence for familial influence on risk of starting to smoke (twin correlations in females: MZ=.85, DZ=.55; males: MZ=.79, DZ=.45) and on whether one quits or persists in smoking (correlations in females: MZ=.56, DZ=.43; in males: MZ=.73, DZ=.16). When genetic models were fitted to these data, genetic effects appeared to be as important in women as in men, accounting for 83% of the variance in smoking initiation and 62% in smoking persistence. However, a strong association was found between twin pair concordance for becoming smokers, and the degree to which twins reported playing together as children (which is higher in MZ than DZ pairs). Thus non-genetic explanations for twin pair concordances for smoking initiation could not be excluded. However, no effects from social interaction were found to explain genetic influence on smoking persistence.

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IMPACT OF PARENT MONITORING ON DRUG SAMPLING THROUGH LATE CHILDHOOD

J. C. Anthony and H. D. Chilcoat

Recent evidence indicates that higher levels of monitoring and supervision of children by parents signals reduced risk of drug sampling in elementary school children. We followed an epidemiologic sample of 926 urban-dwelling 8-10 year olds from 1989 to 1992. Individual interviews were conducted annually to assess drug use, monitoring by parents, peer drug use, and other suspected risk factors. Survival analytic strategies were employed to compare the cumulative incidence of drug sampling across levels of patent monitoring measured in 1989. Drug sampling was defined as use of any of the following at least once: tobacco, alcohol without parents' permission, marijuana, cocaine, or inhalants. Kaplan-Meier curves indicated that children in the lowest quartile of parent monitoring initiated drug use at earlier ages, and the risk of drug sampling was greater for these children than for those reporting higher levels of parent monitoring, across all ages in the follow-up sample (log rank test = 16.3, df = 3, p = 0.001). The difference in risk of initiating drug use between levels of parent monitoring was greatest for ages younger than 11 years old. After age 11, "survival" *(i.e.,* probability of not initiating drug use) for children with the highest level of parent monitoring was comparable to that of children in the lowest quartile of parent monitoring who were two years younger. This two year lag persists through age 14, which is the oldest age in the follow-up sample. A similar analysis was conducted in which the outcome was redefined to reflect more "deviant" drug use, *i.e.* inhalant, marijuana or cocaine use. There was significantly lower survival, in terms of use of these drugs, for children reporting lower levels of parent monitoring at baseline than those with higher levels (Log rank test = 13.3, df = 3, p = 0.004). The difference in survival increased as children grew older. These findings indicate that high levels of parent monitoring might prevent initiation of any drug use before age eleven and delay onset of drug use through late childhood and early adolescence. In addition, these results suggest that effective parent monitoring might prevent more serious forms of drug use, such as inhalant, marijuana, or cocaine use from occurring early in adolescence and possibly delay or prevent onset of use of these drugs through the adolescent years.

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PHYSICAL TRAUMA AMONG FEMALE DUI DRIVERS

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Several recent studies show that female alcoholics experience high rates of both physical and sexual abuse and injuries. Coping with abuse in current romantic relationships and with memories of past physical trauma have become major treatment issues for women. As the public has become aware of the connection between alcoholism and victimization, a tendency to exaggerate and stereotype has appeared. It is important that the incidence of these problems be accurately understood. This study investigates rates of physical and sexual abuse and serious physical injury and associated characteristics among a population of alcoholic women incarcerated for serious drunk driving offenses. All subjects were inmates of the Longwood Treatment Center in Boston. The Longwood Treatment Center is a 125-bed alcoholism treatment facility within the Massachusetts Department of Correction that receives male and female offenders with serious DUI offenses. This sample consists of 52 women interviewed between May 1991 and November 1992. In this paper the term "abuse" is limited to physical or sexual abuse. Subjects completed several standardized questionnaires and semistructured interviews. A total of 49 women met DSM-III-R criteria for alcohol dependence, and three women met criteria for alcohol abuse. Of the 52 women, 88.5% reported experiencing physical or sexual abuse or serious injury during their lifetime. Physical or sexual abuse, reported by 75%, was more common than serious injury, reported by 44.2%, but 30.8% had experienced both. All serious injuries occurred after the age of 16, but 38.5% of subjects reported abuse incidents occurring before age 16. An unexpected finding was that only 41% (16/39) of the women who had been victims of abuse had suffered serious injuries. In contrast 53.9% (7/13) of the women who had never been victims of abuse had suffered serious injuries. Of the twenty women (38.5%) who reported episodes of abuse during childhood, 16 (30.8% of the total sample) had been sexually abused. Brothers were the most frequently mentioned perpetrators Eleven women (21.2% of the total sample) had been physically abused during childhood. Seven women (13.5%) had suffered both sexual and physical abuse during childhood. As adults 57.7% of the subjects reported having been battered, while 28.8% reported having been raped. Seventy percent of the victims of childhood abuse were also victims of violence during adulthood. Surprisingly, almost 60% of the women not victimized in childhood became victims of violence in adulthood. Also surprising was the finding that serious injury during adulthood occurred more than twice as often among woman not victimized during childhood than among those who were (56.2% vs. 25%). History of injury and abuse were associated with psychiatric characteristics. Women who had suffered trauma showed significantly higher rates of history of non-alcoholic substance abuse or dependence (76.1% vs. 16.7%. p=.003). Women who experienced both forms of child abuse had a mean age of onset of alcohol dependence almost eight years younger than those who had not (16.3 years vs 24 years, p=.0028). Almost 60% of women who had experienced both forms of child abuse manifested ASPD, compared to 13.3% of the other women in the sample (p=.0005). Seventy live percent of victims of childhood sexual abuse manifested borderline personality disorder, compared to 36.1% in the rest of the sample (p=.0189). Almost all victims of childhood sexual abuse (93.3%) reported frequent painful menstrual cramps, compared to less than half (45.7%) of the rest of the sample (p=.0016). The data from this study suggest that there are clinically significant subgroups with distinct histories of trauma among women incarcerated for serious drunk driving offenses and that these histories may require a variety of treatment approaches.

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HEROIN CESSATION AND OTHER SUBSTANCE USE

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This paper examines long-term patterns of tobacco, alcohol, and marijuana use among 354 male narcotics addicts who were first admitted to the California Civil Addicts Program in 1962/64 and were followed for over 20 years (Hser *et al.,* 1993). These subjects were classified into four groups according to their narcotics use pattern, criminal activity, and incarceration status during the 3-year period prior to the interview. Fifty-nine subjects (16.7%) are considered "Winners" who had ceased illicit drug use and criminal activity for over 3 years. Forty-six "Recovering Addicts" (13.0%) had not been involved with narcotics and crime for at least one year (but less than 3 years). The other two groups are considered "Losers," including 146 "Continuing Addicts" (41.2%), who had not ceased narcotics use but had avoided being incarcerated in the year prior to interview, and 103 "Incarcerated Addicts" (29.1%) who had been incarcerated at some point within the prior year.

Almost all subjects reported using tobacco at some time in their lives. Recovering Addicts reported the longest time using alcohol heavily (131.4 months) and marijuana daily (48.1 months). Incarcerated Addicts reported the least time using alcohol and marijuana (81.3 and 23.3 months, respectively); however, they also were incarcerated for the longest period of time (129.0 months, compared to 84.8 for Continuing Addicts, 66.1 for Recovering Addicts and 55.8 for Winners) which limited their access. As for current use, Winners reported the lowest rates of tobacco use (52.5%), alcohol use (45.8%), and marijuana use (6.8%). Tobacco use was not different among the other three groups (between 76.1 to 79.6%). Recovering Addicts continued to report the highest rates of current alcohol use (80.4%) and marijuana use (32.6%). Continuing Addicts and Incarcerated Addicts also reported cocaine use (6.2 and 10.7%) prior to their last incarcerated period.

These analyses suggest that eventual cessation of narcotics addiction is not common among addicts and often involves a change of lifestyle such as termination of criminal career and cessation of other substance use, sometimes including tobacco, alcohol, and marijuana. A more common pattern is a predilection for a drug-using lifestyle involving multiple substances.

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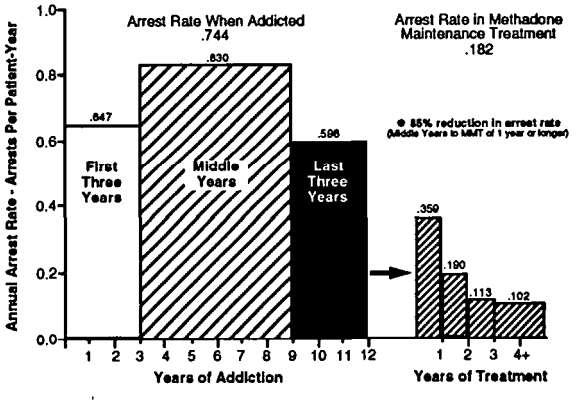
LIFETIME ARREST RATES OF HEROIN ADDICTS IN BALTIMORE

J.C. Ball and S.B. Greberman



Lifetime arrest rates of 151 male addict patients were derived from official records. These intravenous heroin users had 11.4 mean years of opiate dependence prior to their present admission to methadone maintenance treatment. Thus far, (at age 37), these 151 addicts had experienced a total of 1,503 arrests, or 10 arrests per person.

During their eleven years of opiate addiction, these 151 addicts had an annual arrest rate per person of .744. Thus, they committed crime with a frequency sufficient to accumulate 74.4 arrests per year per 100 persons throughout their addiction years.

Their annual arrest rates when addicted had the following trends: (1) a marked increase in arrests occurred after onset of addiction; (2) this early increase was evident during the first 3 years of addiction (see graph); (3) arrest reached a high-level during the "middle years" (*i.e.*, 83.0 arrests per year per 100 addicts); and the rate was somewhat lower during the three years preceding admission to treatment (probably due to the effect of prior drug abuse treatment).

There was a marked reduction in arrest rates after admission to methadone maintenance treatment (MMT) and this decline continued if patients remained in treatment Overall, the annual arrest rate during MMT (18.2 arrest per year per 100 patients) was a 75.5% reduction of the rate when addicted (74.4 arrests per year per 100 addicts). After the first year of treatment - a transition year for many - there was a 85% reduction in the arrest rate from the addiction years.

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A METHOD FOR ESTIMATING THE LOCAL POPULATION OF DRUG ABUSERS: AN APPLICATION OF CAPTURE-RECAPTURE MODELS

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Information about the local population size of drug abusers is critical in assessing the magnitude of drug problems and in planning interventions, as well as for determining the feasibility for conducting a study. However, accurate estimation is difficult to obtain because drug abusers are hard to identify using standard enumeration techniques, which assume that the population size is *a* priori known. Capture-recapture models have been used by biologists to estimate wildlife population, but have been of limited use to epidemiologists in part due to the requirement of at least two independent observation sources. When data are available from a single source over an extended period of time, however, finite periods of time can be used as substitutes for multiple independent observations. We applied a capture-recapture method to estimate the population size of drug abusers in a target area of St. Louis. We utilized intake admission data obtained from HealthStreet, a community-based triage center for a city-wide research demonstration project designed to reduce the spread of AIDS through community outreach (DA06163). A total of 609 drug users were recruited to HealthStreet between July 1990 and June 1992 through street outreach, which covered a geographic area represented by six zipcodes. Of them, 44 (7.2%) were identified as "duplicates" who came to HealthStreet at least twice, based on matching first and last names, social security numbers and demographic characteristics such as gender, age, race. The percentage of duplicates each month increased from 0% to 20% over-time, indicating either positive learning effects or increasing population saturation. We estimated the population size using three models: first using the fixed time interval of four months without weights; the second, based on the same fixed interval of four months with weights computed from duplicates; and, the third, the time interval varied to be the shortest monthly period until at least one duplicate is found, while weighting by the proportion of captures within an interval over of the sample. The first model tends to overestimate the population, whereas the second tends to provide a conservative estimate. The results suggest that the total population of drug abusers in the target area is between 12 to 26 times as large as the study sample. Efficiency is a primary advantage of our capture-recapture method, although it has the same limitations associated with multiple sources data, such as the assumptions of random drawing, independent sampling, and population equilibrium. Only data from one site is needed, and the formula can be applied quickly. The results can be generalized to the local target area.

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NEIGHBORHOOD ENVIRONMENT AND OPPORTUNITY TO USE COCAINE

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INTRODUCTION: Recent epidemiologic evidence highlights a need to search for modifiable neighborhood characteristics that signal increased risk of drug-related behavior, especially cocaine use. By extension, we hypothesized that neighborhood deterioration might be an index of "exposure opportunity," the intermediate step on a path toward starting to use cocaine. In contrast, we anticipated substantially weaker or no relationships for more ubiquitous drugs, such as tobacco and alcohol.

METHODS: To test this hypothesis, we have analyzed self-report data gathered in Spring 1992 by means of confidential interviews with 1416 urban-dwelling middle-school participants in a longitudinal field study. "Exposure opportunity" was assessed for tobacco, alcohol, marijuana, inhalants, and cocaine, using standardized pre-coded interview questions. After about 10 minutes of interviewing on other topics, an 18-item neighborhood scale was administered to ask about safe streets; boarded-up windows on neighbors' houses; and other characteristics.

RESULTS: Within this epidemiologic sample, 50 youths said that someone actively had offered them a chance to take cocaine or smoke crack; tobacco had been offered to 395 youths, alcohol to 429 youths. Using multiple logistic regression to hold constant grade, sex, minority status, and peer drug use, we found a strong association between neighborhood deterioration and exposure to cocaine: youths living in neighborhoods with the most deterioration (highest tettile) were an estimated 3.0 times more likely to have been offered cocaine, as compared to those in relatively undeteriorated neighborhoods (p=0.03). By comparison, there were weaker but statistically significant associations involving tobacco exposure opportunity (relative odds, RO=1.45, p=0.05) and alcohol exposure opportunity (RO=l.44, p=0.05).

CONCLUSION: Though subject to confirmation in more definitive research, these epidemiologic findings point toward specific neighborhood characteristics that are modifiable. In theory, the process of modifying these characteristics also might yield a reduced risk of early-onset use of drugs, especially cocaine.

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RACIAL/ETHNIC DIFFERENCES IN CRACK USE WITHIN NEIGHBORHOODS

H. D. Chilcoat and C. D. Schutz

Summary overviews of crack use in the U.S. indicate that the lifetime prevalence of crack use for African Americans is 2-3 times that of White Americans. However, a recent study that used interview data from the 1988 National Household Survey of Drug Abuse (NHSDA) found no racial/ethnic differences, once neighborhood was held constant (Lillie-Blanton *et al.* 1993). In light of an observed increase in crack use among African Americans since 1988, we set out to determine whether differences existed between race/ethnicities, using data from the 1990 NHSDA. Employing a post-stratification procedure, we found no overall differences in lifetime prevalence of crack use for African Americans relative to White Americans (RO = 1.37, 95% CI = 0.82 - 2.29) but found that Hispanic Americans had lower odds than whites (RO = 0.52, 95% CI = 0.28 - 0.96). However, stratification by age group indicated that African Americans 30 - 34 years old had significantly higher odds of lifetime crack use than White Americans in the same age strata when neighborhood is held constant (RO = 2.51, 95% CI = 1.10 - 5.74). Crack use in the year prior to interview was common among African American crack users in this age group (63%). whereas it was unlikely among similarly aged White or Hispanic Americans with a lifetime history of crack use (14% and 0%, respectively). Generalized Additive Models (GAMs) were used to examine trends in the age-specific prevalence of lifetime crack use between 1988 and 1990 by race/ethnicity. The overall increase in lifetime crack use among African Americans is explained by an increase in prevalence for African Americans who are approximately 30 years old - from 5% in 1988 to 8% in 1990. No change was observed for African Americans of other ages: These findings point to the importance of race/ethnicity as a marker for socio-economic risk factors.

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NOVEL TIPP ANALOGS WITH SUBNANOMOLAR δ OPIOID ANTAGONIST POTENCY AND EXTRAORDINARY δ SELECTIVITY

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Recently, we reported the discovery of a new class of opioid peptide-derived δ antagonists that contain a tetrahydroisoquinoline 3-carboxylic acid (Tic) residue in the 2-position of the peptide sequence (Schiller *et al.* 1992). The two prototype antagonists were the tetrapeptide H-Tyr-Tic-Phe-Phe-OH (TIPP) and the tripeptide H-Tyr-Tic-Phe-OH (TIP). TIPP showed high antagonist potency against various δ agonists in the mouse vas deferens (MVD) assay (K_e = 3-5 nM), and high δ affinity (Ki^{δ} = 1.22 nM) and extraordinary δ selectivity (Ki^{μ}/Ki^{δ} = 1410) in the rat brain membrane binding assays. Furthermore, TIPP displayed no μ or κ antagonist properties in the guinea pig ileum (GPI) assay at concentrations as high as 10 μM. The compound was recently prepared in tritiated form and [^{3}H]TLPP was shown to be an excellent new radioligand for the study of δ opioid receptor interactions. Analogs of TIPP containing tryptophan, 2-naphthylalanine or homophenylalanine in place of Phe^3, or p-nitrophenylalanine in place of Phe^4 showed a 1.5 - 2.5-fold increase in δ antagonist potency and 3-5-fold enhanced δ receptor selectivity. Substitution of N$^{\alpha}$-methyltyrosine or 2,6-dimethyltyrosine (Dmt) for Tyr^1 produced a further increase in antagonist potency. The peptide Dmt-Tic-Phe-Phe-OH (DIPP) showed K_e values (0.13-0.17 nM) against δ agonists in the MVD assay that were about five times lower than those of naltrindole and thus represents the most potent δ antagonist known. TIPP and TIPP analogs am stable in the aqueous buffer solution (pH 7.7) used for biological testing for periods up to six months. However, these peptides were found to undergo slow spontaneous Tyr-Tic diketopiperazine formation with concomitant cleavage of the Tic-Phe peptide bond in certain organic solvents. This observation prompted the design of corresponding peptides containing a reduced peptide bond between the Tic^2 and Phe^3 residues, since this structural modification altogether eliminates the possibility of diketopiperazine formation. The resulting TIPP pseudopeptide analog, H-Tyr-Ticψ[CH_2-NH]Phe-Phe-OH(TIPP[ψ]), also retained high δ antagonist potency (K_e~2.5 nM) in the MVD assay and showed unprecedented δ selectivity (K_i^{μ}/K_i^{δ} = 10500, being 500 times more selective than naltrindole. In contrast to naltrindole, TIPP[ψ] again showed no i.t or κ antagonist effects. Furthermore, TIPP[ψ] showed excellent stability against enzymatic degradation for extended periods of time. TIPP, TIPP[ψ] and their analogs are likely to find wide use as pharmacological tools in opioid research and may also have potential as therapeutic agents for applications in analgesia and immunosuppression.

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MET-CAMO AND N-CPM-MET-CAMO ARE MU-SELECTIVE IRREVERSIBLE OPIOID ANTAGONISTS DEVOID OF AGONISTIC PROPERTIES

J. M. Bidlack, Q. Jiang, A. Sebastian, and S. Archer

5ß-Methyl-14ß-(p-nitrocinnamoylamino)-7,8-dihydromorphinone (MET-CAMO) (Jiang *et al.* 1993) and the corresponding N-cyclopropylmethyl analog, N-CPM-MET-CAMO, were studied both in opioid receptor binding assays and in mouse tail-flick assays, to measure analgesia. In the receptor binding assays, incubating bovine striatal membranes with either MET-CAMO or N-CPM-MET-CAMO produced a wash-resistant and concentration-dependent inhibition of opioid binding of the μ-selective ligand, [^{3}HJ[D-Ala^2,(Me)Phe^4,Gly(ol)^5]enkephalin (DAMGO), but did not inhibit the binding of the δ- or κ-selective ligands, [^{3}H][D-Pen^2,4-p-C1-phenylalanine, D-Pen^5]enkephalin or [^{3}H]U69,593, respectively. In addition, the inhibition of [^{3}H]DAMGO binding by MET-CAMO and N-CPM-MET-CAMO was blocked by preincubation with the μ opioids, morphine and naloxone but not by δ- or κ-selective opioids. Preincubation of membranes with MET-CAMO or N-CPM-MET-CAMO decreased the ^{B}max values of [^{3}H]DAMGO binding without changing the K_d values. Neither MET-CAMO nor N-CPM-MET-CAMO produced any antinociception in the mouse tail-flick assay when administered intracerebroventricularly at doses up to 100 nmol. However, a single 1-nmol i.c.v. dose of either affinity ligand from 8 to 72 hr before testing suppressed morphine-induced antinociception, but had no effect on antinociception medicated by δ or κ opioid receptors. MET-CAMO is the first N-methylated morphine derivative which shows such long-lasting μ-selective opioid antagonism with no agonistic properties. Likewise, the N-CPM-MET-CAMO did not produce opioid-mediated antinociception. These data indicate that both MET-CAMO and N-CPM-MET-CAMO are μ-selective irreversible opioid antagonists.

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MORPHINE-LIKE AND NON-MORPHINE-LIKE STRUCTURES OF OPIOID 4-PHENYLPIPERIDINES

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For symmetrically substituted 4-phenylpiperidines, it has been proposed that the low energy form consists of a pair of mirror image conformers. Using a previously developed model for opioid receptor ligands, one of these is morphine-like and should have morphine-like structure-activity relationships whereas the other appears to be associated with opioid antagonist activity. To test this hypothesis, 3-demethyl-, α-, and ß-prodine with and without a phenyl meta hydroxyl were synthesized. The racemates were resolved using a chiral column. Resolution of the enantiomers also separates the morphine-like and non-morphine-like structures, particularly for ß-prodine which is conformationally homogeneous.

The synthesized compounds were screened on receptor binding assays specific for μ1, μ2, δ, κ1 and κ3 opioid receptors and found to predominantly have affinity for μ1 and μ2 receptors. Consistent with the reduced *in vivo* activity of the hydroxylated achiral and racemic compounds, there was a drop in affinity upon hydroxylation. However, this only occurred for the (+)-enantiomers for which the affinities dropped 10-50 fold. For the (-)-enantiomers, there tended to be small increases in affinity for all five receptor subtypes. The (+)-enantiomers of the non-hydroxylated compounds, which are more potent *in vivo*. are known to have the non-morphine-like structure whereas the (-)-enantiomers have the morphine-like structure. Since hydroxylation only causes small changes in the optical rotations, this suggests that the absolute configurations are the same as for the non-hydroxylated compounds. We are attempting to confirm the absolute configurations. With this assumption, it appears that the effect of hydroxylation on the morphine-like structure is a morphine-like increase in receptor affinity while there is a large drop in affinity for the non-morphine-like structures.

As the racemate of hydroxylated ß-prodine has been reported to be a pure opioid antagonist, its enantiomers were tested for agonist and antagonist activity in the guinea pig ileum and mouse vas deferens assays. The only opioid activity that was found was that both enantiomers were weak antagonists in the guinea pig ileum assay with the (-)-enantiomer being about three times as potent as the (+)-enantiomer.

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INDOLO-5-ARYLMORPHANS AS POTENTIAL SELECTIVE OPIOID RECEPTOR PROBES

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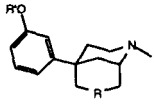
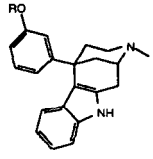
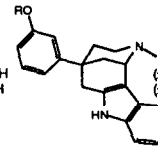
The study of the opioid receptors (μ, δ, and κ) and their subtypes necessitates the development of compounds with high selectivity for these receptors. One approach involves the modification of known potent opioid compounds guided by the "message-address" concept of Schwyzer (1977) as interpreted by Portoghese *et al.* (1990). This strategy has been applied to the phenyl-axial 4,5-epoxymorphinans and produced highly selective antagonists(δ) ssuch as naltrindole (Sofuoglu *et al.,* 1991). It was of interest to apply this method to phenyl-equatorial 5-arylmorphans in an attempt to increase receptor selectivity. Racemic 5-(3-hydroxyphenyl)morphan ((±)-1a) is as potent an analgesic as morphine (May and Murphy, 1955) and upon resolution, both enantiomers exhibit significant opioid activity, in clear contrast to the 4,5-epoxymorphinans, of which only the levo isomers arc active as analgesics or narcotic antagonists. Whereas (+)-la is four-fold more potent than morphine, the levo isomer (-)-la is equipotent to morphine as an antinociceptive, has antagonist properties. and displays low physical dependence (May and Takeda, 1970). The addition of a phenyl moiety (possible address) to the 5-arylmorphan



(±)-**1a**, R=CH_2, R'=H
(+)-1S, 5R-**1a**, R=CH_2, R'=H
(-)-1R, 5S-**1a**, R=CH_2, R'=H
(±)-**2a**, R=CO, R'=Me
(±)-**2b**, R=CO, R'=H
(+)-1S, 5S-**2b**, R=CO, R'=H
(-)-1R, 5R-**2b**, R=CO, R'=H



(±)-**3a**, R=Me
(±)-**3b**, R=H
(+)-1R, 5S-**3b**, R=H
(-)-1S, 5R-**3b**, R=H



(±)-**4a**, R=Me
(±)-**4b**, R=H

nucleus was accomplished by the Fischer indole reaction of phenylhydrazine with the 7-ketone (±)-2a prepared by the method of Bonjoch *et al.* (1988). The structures of the major (±)-3a and minor isomer (±)-4a were confirmed by single-crystal X-ray diffraction. These racemates could be demethylated to the phenolic compounds (±)-3b and (±)-4b. Compound (±)-4b displaced [^{3}H]DAMGO from the μ opioid receptor with half the affinity of either of the parent compounds (+)- or (-)-la and had low affinity for δ and κ]1 receptors labeled with [^{3}H]DADLE and [^{3}H]U69,593, respectively.

	IC$_{50}$ (nM±SD)		
Compd.	[^{3}H]DAMGO(μ)	[^{3}H]DADLE(δ)	[^{3}H]U59,593(κ1)
(+)-1a	21.4±2.40	>1000	910.5±50.6
(-)-1a	20.8±1.67	>1000	818.6±96.2
(±)-3b	26.55±1.54	8.53±0.63	>1000
(±)-4b	43.9±4.0	>1000	798.3±86.4
(+)-3b	21.4±1.39	660.1±160.2	
(-)-3b	14.24±1.01	5.56±1.51	

Enantiomerically pure (+)-3b bound predominantly to μ receptors and (-)-3b bound to both μ and δ receptors in about the same ratio as (±)-3b. Therefore, the introduction of the δ address to the parent 5-(3-hydroxyphenyl)morphan as in (-)-3b has increased interaction with the δ 1 receptor > 180 fold. Interestingly, although both (+)- and (-)-3b were only a little different in their interaction with the μ receptor, and (+)-3b interacted only slightly with δ receptors, (-)-3b was found to be >119 fold stereoselective for δ receptors and appears to be one of the most potent known phenylmorphan based ligands for the δ 1receptor.

REFERENCES: Available upon request.

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DERIVATIVES OF OCTAHYDROBENZO[F]QUINOLINES WITH HIGH AFFINITY FOR DOPAMINERGIC RECEPTORS

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Derivatives of octahydrobenzo[f]quinolines have been synthesized and assayed for DA activity. Synthesized compounds include the cis and trans isomers with either a 7-OH or 7,8-diOH groups and an N-phenethyl group. The compounds were screened for affinity for DA receptors in rat brain, primate *(Macaca fascicularis)* brain, and cloned receptors. In rat brain, the compounds were moderately selective for D2 receptors relative to D1 receptors. The trans isomers had affinities for D2 receptors that were among the highest for known compounds. The cis isomers had surprisingly high affinities (several-fold weaker than the trans compounds) for D2 receptors considering that cis compounds have previously been reported to be very weakly active at best. At D1 and D2 receptors in primate brain, the trans- and cis-diOH compounds bound to two sites with different affinities which is characteristic of DA agonists. Again, the trans compounds had affinities that were among the highest for D2 receptors. Similar results were obtained on cloned D2, D3, and D4 receptors with the major difference being that the cis isomers had slightly higher affinities than the trans compounds. There did not appear to be any significant subtype selectivity for these three pharmacologically similar DA receptors. In preliminary results, the trans compounds reduced the forskolin induced increase of cyclic AMP consistent with D2 agonist activity. The cis compounds appeared to be less efficacious on this assay. Past reports of the low activity of cis compounds may be due to their being partial agonists or mixed agonists/antagonists.

The trans- and cis-7,8-diOH compounds were submitted to the NIDA Cocaine Treatment Discovery Program. Receptor binding results for DA were similar to those described above. For 5HT receptors, only the trans compound had high affinity for 5HT1a receptors while both compounds had low affinities for 5HT1c and 5HT2 receptors. Both compounds had low affinities for DA and 5HT reuptake sites and low potencies for blocking reuptake sites for DA, NE, and 5HT in rat brain synaptosomes. Both compounds reduced the locomotor activity induced in mice by 20 mg/kg of cocaine. However, both compounds reduced the locomotor activity with similar potencies in the absence of cocaine. The ED_{50} for reduction of locomotor activity by the trans compound (in the absence of cocaine) was a very low 0.038 mg/kg.

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SPECIFICITY OF NOVEL TROPANE ANALOGS AT DOPAMINE AND 5-HT TRANSPORT SITES

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Tropane analogs of cocaine are often synthesized using cocaine itself as a precursor. A novel route of tropane synthesis has recently been developed using vinylcarbenoid precursors, and a series of cocaine analogs have been synthesized and tested for specificity at dopamine (DA) and serotonin (5-HT) transport sites in rat brain preparations. Binding studies assayed displacement of [^{125}I]RTI-55 binding to striatal membranes for DA sites, and of [^{3}H]paroxetine binding to frontal cortex membranes for 5-HT sites. Analogs were also tested for inhibition of [^{3}H]DA and [^{3}H]5-HT uptake into synaptosomes from rat striatum and frontal cortex, respectively. This synthetic strategy produced racemic compounds, two of which have been separated into enantiomers using chiral HPLC columns. In all of these analogs, the aryl group at the 3 position was directly bound to the tropane ring (as in WIN-35,428). and methyl or ethyl ketone moieties were present at the 2 position instead of the typical ester group. This series of 35 analogs provided an extremely wide range of potencies at both DA and 5-HT transporters, with IC_{50} values ranging from <0.1 nM to >50 μM. In general, there was an excellent correlation between the potencies of these analogs in inhibiting uptake and in binding assays, with correlation coefficients of 0.96 and 0.92 between binding and uptake assays for DA and 5-HT transporters, respectively. The replacement of the ester at the 2-position with either methyl or ethyl ketones had little effect on potencies at either DA or 5-HT transport sites. However, the substituent at the 3-position had a major effect on both potencies and selectivities. Replacement of the aryl group at the 3 position with a 2-naphthyl group produced the most potent analogs, with IC_{50} values < 0.1 nM vs. [^{125}I]RTI-55 and [^{3}H]paroxetine. One analog, WF-23 (containing an unsubstituted 2-naphthyl moiety) was the most potent tropane yet reported at DA transport sites, with an IC_{50} value of approx. 0.03 nM for the active stereoisomer in both binding and DA uptake assays. This compound was relatively non-selective at DA and 5-HT transporters, since its K_i value at 5-HT sites was 0.06 nM. Therefore, several of these 2-naphthyl analogs paralleled the low specificity of cocaine, but with much greater potencies than cocaine. However, other compounds were relatively selective at DA transporters. The active enantiomer of PTT, a toluyl analog with an IC_{50} value of 4 nM at DA sites, was approx. 20 times more potent at DA sites than 5-HT sites. Other analogs were relatively selective for 5-HT sites. For example, although WF-9 (an ethyl phenyl analog) was only slightly more potent at 5-HT transport sites than DA sites in binding assays, it was approx. 50 times more potent in inhibiting [^{3}H]5-HT uptake than [^{3}H]DA uptake. These analogs represent the first report of 5-HT-selective tropanes, and confirm that this synthetic strategy can be an effective way of producing selective probes for the cocaine pharmacophore.

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SOCIAL RELATIONSHIPS AND ABSTINENCE FROM COCAINE USE

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A sample of 104 treated cocaine users, abstinent at the end of treatment, participated in a study of predictors of relapse. A major focus of the study was to examine links between social relationship variables and outcomes. Subjects were followed for 6 months after treatment completion. There were 12 weekly posttreatment assessments and a final assessment at 6 months. Social relationship variables included social integration, perceived social support, (emotional and instrumental), and social-network cocaine use. Subjects' self-reports of abstinence were confirmed by urine assays.

There were 54 Caucasian and 50 African-American subjects, 28 women and 76 men, who were recruited from one intensive outpatient and four inpatient treatment programs. Most subjects, 48.1%, smoked crack/freebase, 33.7% used cocaine intranasally, 12.5% snorted and smoked, and 5.8% injected.

In the 12 weekly and the 6-month assessments, effects of social integration on abstinence were observed in Caucasians only. The proportion of abstinent Caucasians increased with higher levels of social integration. Effects of perceived emotional support were also conditional on race, with the benefit limited to Caucasians. The effects, however, were limited to the first 12 weeks. Instrumental support had no effect on abstinence at any point in the study. Social network drug-use data for 12 weeks and 6 months showed race differences consistent with those noted above: For Caucasians only, the absence of current cocaine users and the presence of former users in social networks predicted abstinence.

Results suggest that aspects of social relationships may act as protective factors in Caucasian cocaine patients, findings consistent with literature on social support and health outcomes. The data do not provide explanations for the lack of effects of these variables on outcomes for African-Americans. Future research should address how social relationships are linked to abstinence outcomes and should test interventions to assist clients in obtaining protective levels of support. Such research should be sensitive to possible differences among racial and ethnic groups.

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AXIS II DISORDERS AND ASSOCIATED FEATURES IN COCAINE-DEPENDENT INPATIENTS

H. R. Kranzler and S. Satel

Previous research has shown a high prevalence of co-morbid personality disorders among individuals seeking treatment for cocaine dependence. We studied Axis II disorders (using the SCID II) in 51 patients (80.4% male; 57% black; mean age = 30.4 yr) admitted to one of two inpatient rehabilitation programs. All patients met lifetime criteria for cocaine dependence and reported having used cocaine during the month prior to admission. Mean cocaine use during this month was 23.6 g. The predominant route of administration was smoking (80.4%). Fifty-seven percent of patients reported having ever experienced cocaine-induced paranoia. Seventy-one percent of patients met criteria for at least one Axis II diagnosis; the mean number of Axis II diagnosis among these patients was 2.6. The most common Axis II diagnosis was borderline (35% of all patients), followed by ASP (28%), narcissistic (8%), avoidant (24%), paranoid (22%), obsessive-compulsive (18%). and dependent (12%). Patients were divided into two groups based on work by Pettinati et al. (1991): 1. Low Risk (i.e., those with no Axis II diagnosis and those with a cluster C disorder only, N=22) and 2. High Risk *(i.e.,* those with a cluster A or B disorder, N=29). High Risk patients reported a longer mean duration of intravenous cocaine use, but other measures of cocaine use (including mean duration of intranasal and freebase use), other substance use and family history of alcohol or drug abuse did not differ by group. Significant group differences (High Risk > Low Risk) were observed for the number of Axis II symptoms and diagnoses, a measure of psychosis proneness *(i.e.,* the Per-Mag scale of the Wisconsin Scales of Psychosis Proneness), the prevalence of comorbid anxiety and depressive disorders and the proportion of first- and second- degree family members with a history of psychiatric disorder. In addition, the proportion of patients who reported having experienced cocaine-induced paranoia was greater for the High Risk group. These findings replicate earlier work by Satel and Edell (1991) and suggest that subgroups of cocaine-dependent patients can be differentiated by comorbid psychopathology. These findings may have relevance for patient-treatment matching.

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CLINICAL IMPLICATIONS OF CO-MORBID DEPRESSION IN SUBSTANCE-DEPENDENT DELINQUENTS

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Should co-morbid depression raise clinical concerns for adolescent boys referred for treatment of substance use and behavioral problems? Ninety-nine such boys (ages 13-19) were evaluated in a residential treatment facility with the Diagnostic Interview Schedule for Children (DISC), Comprehensive Addiction Severity Index-Adolescents (CASI-A), Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), Carroll Rating Scale for Depression (CRS), Children's Depression Rating Scale (CDRS), and Child Behavior Checklist (CBCL). All boys had Conduct Disorder and 96.5% had Substance Dependence diagnoses. Depression scores from instruments relying largely on self-report--CRS, CDRS, DISC--correlated significantly with the staff-rated CBCL. Twenty-one of the 99 boys were diagnosed with Major Depression and/or Dysthymia by DISC. Depressed boys had significantly more drug dependence diagnoses ($p<.01$) and were more likely to have co-morbid ADHD ($p<.05$) as well as PTSD ($p<.05$) and other anxiety disorders ($p<.01$), than the non-depressed. The depressed boys developed their first symptom of Conduct Disorder at an earlier age than the non-depressed ($p<.05$). CRS depression scores were significantly higher in the depressed boys ($p<.05$) and intake CRS scores for both depressed and non-depressed boys did not change significantly when CRS was repeated after four weeks.

Conclusions--Depressed delinquents appear to have more substance dependence diagnoses than non-depressed. Depressed boys begin to have behavioral problems at an earlier age, have increased anxiety and attentional problems, and have been more severely affected by trauma than the non-depressed. Depression in this group may not be related to substance abuse, as it does not appear to remit after four weeks of abstinence. These findings may have specific implications for a combined psychiatric and substance abuse treatment program in this population.

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PARENTAL RELATIONSHIPS AMONG METHADONE PATIENTS: THE IMPACT ON LEVELS OF PSYCHOLOGICAL SYMPTOMATOLOGY

M. Rutherford and D. Metzger

The relationship between parental substance use problems and quality of parental relationships with levels of psychological symptomatology, as measured by the SCL-90 and Beck Depression Inventory (BDI), is examined in 155 women and 324 male heroin addicts enrolled in methadone maintenance treatment. In addition to the SCL-90 and BDI, all subjects were given the Treatment Effectiveness Questionnaire which consists of questions regarding demographics; employment history; drug and alcohol use/treatment history: illegal involvement; physical and emotional health: high risk behaviors for HIV infection; family social relationships; and substance use in relatives. Of the 479 who completed the questionnaire, 168 subjects were randomly selected to do an Addiction Severity Index (ASI) interview.

Data analysis revealed that, in general, parental substance use problems were associated with greater levels of psychological symptomatology and higher ASI social and medical composite scores. Positive parental relationships were associated with significantly lower levels of psychological symptomatology on the SCL-90 and BDI, but no differences on any ASI composite scores were found. Subjects reporting positive paternal relationships, however, had significantly lower ASI psychological composite scores than subjects with poor paternal relationships. Conversely, ASI family/social composite scores were significantly higher in subjects reporting poor paternal relationships compared to those reporting positive paternal relationships.

To ascertain the relative importance of parental relationships and parental substance use, as well as the degree to which these variables contribute information regarding levels of psychological symptomatology, forward stepwise multiple regression analyses were performed controlling for gender and race. Maternal relationship had the strongest association with subject SCL-90 scores, but the amount of variance accounted for was small. BDI scores had the strongest association with parental SUPs and maternal relationship, but again the variance accounted for was small. Significant regression equations were generated for the ASI social and medical CS only. Parental substance use accounted for a small but, significant percentage of the variance in the ASI medical CS. The combination of current paternal relationship and whether one's father was living, accounted for 11% of the variance in the ASI family/social CS.

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THE ADDICTION PROBLEM SURVEY (APS): A VALID, SELF-REPORT MEASURE OF ADDICTION PROBLEM SEVERITY

D. DePhilippis, D. S. Metzger, and H. A. Navaline

This study presents data concerning the validity of a self-report questionnaire (APS) measuring problem severity in the following areas: medical, employment, drug and alcohol use, legal involvements, and family/social functioning. As part of a study investigating the relationship between methadone treatment services and patient outcome, 167 patients from four methadone maintenance (MMT) clinics in the Philadelphia metropolitan area were assessed with the APS, Addiction Severity Index (ASI), urine toxicology reports, and counselor ratings of patient functioning. Data was analyzed to determine the concordance between the APS and the established assessment modalities. With respect to content validity, APS items measuring drug use (heroin, cocaine, alcohol, amphetamines, marijuana, and sedatives) in the past 30 days had a mean exact agreement of 84% (range: 78% to 97%) with corresponding ASI items, and the mean kappa coefficient was .68 (range: 55 to .94). As an index of predictive validity, the APS composite score for drug use correlated higher than the ASI drug score (.54 versus .26) with the mean percentage of drug-positive urine screens for the subsequent six month period. Corresponding problem area composite scores for the APS and ASI manifested the strongest intercorrelations – an indication of convergent and discriminant validity. APS composite scores also manifested higher correlations with counselor ratings than did the ASI in all but one problem area – medical. One loses the opportunity to probe for greater clarity and specificity when using self-report measures versus interviews. Data loss due to missed items also is greater with questionnaires. Nevertheless, in the absence of ASI-trained staff and/or when one needs to assess groups of patients, the APS permits efficient measurement of addiction problem areas with validity comparable to the ASI. Further studies of the APS are necessary to determine the reliability of the aforementioned findings, its test-retest reliability, its validity in non-MMT patient populations, and its utility when used clinically versus as a research instrument.

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A FACTOR ANALYTIC STUDY OF THE ASI

A. I. Alterman, L. S. Brown, Jr., D. C. Ajuluchukwu, and A. R. Zaballero

The Addiction Severity Index (ASI) is probably the most widely used substance abuse assessment instrument. In each of its seven areas, two summary indices are provided – the interviewer severity rating (ISR) and the composite score (CS). A systematic factor analysis of the content of each area has not been performed. We separately factor analyzed each ASI scale using a verimax rotation. The ASI baseline evaluations of 729 newly admitted methadone maintenance patients provided the data. All of the ASI items were used in each area. Items loading <.40 were removed from the model. The drug area yielded five interpretable factors, the alcohol and employment area yielded four factors, the medical, family/social and psychiatric areas each yielded three factors; while the legal area yielded two interpretable factors. The factor content and item loadings of these factors are described and the implications and limitations of the findings discussed.

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RETROSPECTIVE REPORTS OF DRUG USE OVER SIX MONTHS BY METHADONE PATIENTS ARE RELIABLE AND VALID

R.N. Ehrman, S. J. Robbins, and G. Stephens

Research on drug abuse often makes use of retrospective self-reports of drug use. One popular technique, the time-line follow back (TLF) interview, requires subjects to report at one time daily drug use over a period of months. Previous TLF studies have looked exclusively at alcoholics. The present study had two primary purposes: 1) to expand the study of TLF reports to heroin and cocaine users, and 2) to validate TLF reports for the first time against a biological marker (urine samples) collected throughout the reporting interval. Fifty-nine methadone-maintained heroin abusers reported daily use of heroin and cocaine over a six-month period during two TLF interviews given six weeks apart These reports were compared against weekly urine samples taken throughout the six month interval. Self-reports were highly reliable across the two interviews. Furthermore, TLF estimates of drug use frequency were significantly correlated with the frequencies detected by urinalysis, demonstrating the validity of the technique. Although reports of drug use frequency were reliable and valid, subjects failed to accurately identify on which particular days drug use occured. In general, these results encourage the use of TLF reports in research projects aimed at measuring long-term drug use frequency; however. they do not support using the TLF interview to identify specific episodes of drug use. Future studies need to extend the generality of these findings to other clinical populations and settings.

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RISK CHARACTERISTICS OF FEMALE IDUS

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Using data from our NIDA-funded, longitudinal study of injection drug users (Risk Assessment Project), we examined whether the HIV risk behaviors of females in this sample are substantially different from the males, thereby requiring gender-specific interventions. The 255 study subjects included 152 randomly selected methadone-maintained IDUs and 103 out-of-treatment opiate-abusing IDUs. Three year retention rate was 90%. Data was collected at 6 month intervals on demographics, drug use and risk behaviors via self-administered questionnaires and personal interviews (ASI and modified versions of the AIDS Initial and Follow-up Assessments). HIV testing was accompanied by pre- and post-test counseling. Analyses – chi-square and t-tests – were considered significant at p-value equal to or less than .05.

RESULTS:

Demographics: Twenty-four percent (n=62) of the sample was female. There were no significant gender differences in reported age (F: 38 ± 8, M: 39 ± 8). The groups did differ significantly in their ethnic composition (F: 53% African-American, 40% Caucasian, 5% Hispanic; M: 71% African-American, 20% Caucasian, 8% Hispanic).

Drug Use: Females reported onset of drug use at significantly later ages (alcohol: 16 ± 4 vs 14 ± 4; heroin: 21 ± 6 vs 19 ± 6; cocaine: 29 ± 9 vs 26 ± 9). While both sexes reported high rates of drug use during the month preceding baseline, significantly fewer females reported iv cocaine use (43% vs 63%) and daily alcohol use (12% vs 30%).

Risk Behaviors By Gender: Close to one-half of females and males reported sharing needles. However, significantly more of the females sharing needles reported that their sharing partner was also a sexual partner (53% vs 29%). Females reported significantly fewer sex partners than did males (2 ± 5 vs 3 ± 6), and were less likely to report (12% vs 43%) unprotected sex with multiple partners. However, significantly more females (60% vs 42%) reported unprotected sex with a single partner, and of these, significantly more females than males (70% vs 32%) identified that partner as an IDU.

Behaviors Over Time By Serostatus: Of females retained through 24 months (n=56), a greater proportion of seropositive (n=8) than seronegative subjects (n=48) reported needle-sharing (71% vs 35%, ns) at baseline. By 24 months, prevalence of needle-sharing had dropped to 13% among the negative women and 0% among the positive women. Unsafe sexual activity was reported by a smaller proportion of positive than negative females (29% vs 59%, ns) at baseline. This trend continued as 38% of the seropositive and 49% of the seronegative women reported unsafe sex at 24 months.

CONCLUSIONS: Although self-reported risk behavior has been found to predict HIV conversion in this sample, subjects' tendency to report socially desirable behaviors may have adversely affected the validity of these self-reports. While reported rates of needle sharing among females in this sample have decreased over time, unsafe sex continues to be reported at high rates. The data suggests that monogamous female IDUs with injection drug using partners may be a group requiring specially designed interventions.

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OUTCOME OF A PSYCHOEDUCATION INTERVENTION FOR HIV PREVENTION IN SUBSTANCE ABUSING AFRICAN-AMERICAN MALES

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Our objectives were to evaluate mediating variables associated with change in HIV risk behavior based on the AIDS Risk Reduction Model (ARRM) and to assess the effects of a culturally-sensitive Psychoeducational (PE) approach to these variables. Consecutive admissions to a VA drug dependence inpatient drug treatment program (n=140) were randomly assigned to a PE or standard information (INFO) condition. PE involved a 6-hour small group intervention designed to improve knowledge and attitudes regarding HIV prevention, to develop skills in condom use, needle sterilization, and negotiation of safer sexual and injection practices, and to modify sexual and drug-related HIV high risk behaviors. The INFO condition consisted of audio-visual and printed HIV prevention materials with similar content.

Both HIV prevention interventions produced short-term increases in several ARRM variables associated with change to the following safer behaviors: increased knowledge, response efficacy, self-efficacy, communication skills, and condom use skills among the recovering substance abusers in our sample. Relative to the INFO group, PE subjects showed significantly decreased sexual HIV risk behaviors. However, the groups appeared to adopt different strategies to reduce risk behaviors with the PE group being more likely to report switching to monogamous relationships and the INFO group reporting increased condom use. Hypotheses derived from the ARRM regarding relationships among variables associated with stages of the model and the process of change were supported by regression analyses which indicated that positive changes in mediating variables were related to risk behavior reductions three months post-intervention.

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PATHOGENESIS OF AIDS ENCEPHALITIS IN DRUG ABUSERS

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Our goal is to determine the contributions of HIV-1-infected macrophages and cytokines (produced as part of local inflammation) to the pathogenesis of HIV encephalitis in drug abusers. For HIV-1 detection and characterization of infected and uninfected cells. we use explant culture, *in situ* hybridization (ISH) and immunohistochemical techniques (IHC) (Shapshak *et al.,* 1992). We demonstrated that HIV is predominantly associated with ferritin or KP-1 reactive microglia (Yoshioka *et al.,* 1992). Recently, we have commenced using polymerase chain reaction (PCR), nested PCR, cloning, and DNA sequencing to characterize HIV directly from brain. Cocaine and cocaethylene (C & CE) may contribute to immune decline and stimulate HIV replication. We are studying the mechanism of C & CE stimulation of HIV-1 replication *in vitro* and *in vivo* since cocaine is a major drug abused in South Florida. C & CE stimulated HIV replication 1.8-2.1x in normal donor peripheral lymphocytes and neural cells at 6-15 days post-treatment as measured by reverse transcripate assay. By chloramphenicol acetyl transferase (CAT) assay of HIV-infected transgenic (LTR-CAT)-containing cell lines, the degree of stimulation is 16 fold 1 day after treatment. The effects of virus strain, cell type, and cytokines are under investigation.

We are examining the central and peripheral nervous systems of drug abusers who died with AIDS. Pathogenesis in AIDS brain is associated with local immune activation including TNF-alpha production by macrophages and Il-6 production in endothelial cells. Drug abusers exhibit increased inflammation in brain compared to other risk groups. Up to 15% of AIDS patients experience peripheral neuropathy. Dorsal root ganglia (DRG) offer a simpler model of cell infection and pathogenesis than brain. We find a relation of cytokines with neuronal death in nodules of Nageotte in DRGs. We found 2x more Nodules of Nageotte, 1.2x more macrophages, 7x more CD8 cells in AIDS DRGs than in normal DRGs; however, IL-6 positive cells occurred only in AIDS tissue. We detected HIV RNA by ISH in 3/12 AIDS DRGs and by PCR in 4/5 AIDS DRGs. Immune activation, HIV infection, and cytokine production appear to be associated with pathology in brain and DRGs; however the mechanism may not be the same in these tissues since inflammatory profiles may differ.

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SEROPREVALENCE OF VIRAL HEPATITIS B,C,D IN HIV-INFECTED INTRAVENOUS DRUG USERS

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BACKGROUND: Intravenous drug users (IDU) have an increased incidence of hepatic dysfunction and chronic liver disease, most commonly caused by viral infections. Prevalence of hepatitis B, C, and D and HIV infections has been reported to be up to 90%, 85%, 20%, and 60% respectively, on heroin addicts in drug treatment. Both hepatitis B and C infections have been reported to be more frequent in HIV-infected patients. In New Haven, CT, in a blinded study of clients in drug treatment, the seroprevalence of HIV and hepatitis C infections were reported to be 28% and 81% respectively.

PURPOSE: The purpose of this pilot study was to identify the prevalence of hepatic dysfunction as marked by serum liver function tests (SGOT, SGPT, GGPT), and to identify the seroprevalence of hepatitis B, C, and D infections and co-infections in a group of known HIV-infected IDU. The association of risk factors (sex, race, sharing injection equipment, concomitant cocaine and alcohol use) with liver disease was investigated.

METHODS: Medical and drug use history, and serum blood tests (SGOT, SGPT, GGPT, HBsAg, HBsAb, HBcAb, HCAb, HDAb, T-cells) were obtained from a group of 38 HIV-infected patients in methadone treatment in New Haven, CT.

RESULTS: 58% male, 50% white, mean age 37 years, mean length of opiate use 18 years, 92% on methadone maintenance dose, 8% initiated methadone treatment, 47% shared injection equipment in the past year, 95% used cocaine, 29% had alcoholism. Only 21% of the patients had normal liver function study. 92% had serological evidence of hepatitis B infection (92% with HBcAb, 40% with HBsAb, 3% with HBsAg), 89% had HCAb, 0% had HDAB. 82% showed antibodies for both hepatitis B and C infections. All patients had either HBcAb or HCAb. Risk factors evaluation was not statistically useful.

CONCLUSION: In this HIV-infected IDU in drug treatment population, this study showed: 1) high prevalence of liver dysfunction, 2) high prevalence of hepatitis B, C infections and co-infection with HIV disease, 3) common prevalence of only HBcAb without HBsAb. 4) low prevalence of HBsAg and HDAb. Risk factors evaluation was not statistically useful due to the high prevalence of the disease and small sample size.

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A TWO YEAR STUDY OF CAGE BEHAVIOR OF MONKEYS MADE DEPENDENT ON MORPHINE AND INFECTED WITH SIMIAN IMMUNODEFICIENCY VIRUS

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INTRODUCTION:

Behavioral and general comportment was measured as an integral part of a study of the possible modulatory effects of opioids on the immune system of rhesus monkeys before and after simian immunodeficiency virus (SIV) infection. Four treatment groups were investigated: 1) saline, 2) saline treatment followed by infection with SIV, 3) opioid treatment and, 4) opioid treatment followed by infection with SIV.

METHODS:

Rhesus monkeys *(macaca mulatta)* were housed singly with visual and auditory contact with others of the species and were exposed to general events in the holding area. All animals were subjected to the same daily routine. The monkeys received water ad libitum; were hand-fed biscuits twice a day at reasonably precise time intervals; were injected three times per day, seven days a week; and were weighed every three days. Two daily sessions to record cage behavior were held five out of seven days on a random basis. Within each day, the first session occurred after the second feeding and before the second injection. The second session followed the second injection. The cage behavior of the rhesus monkeys was annotated using bar codes to describe as many aspects of the behavior of the monkeys as possible. The observer was prompted by a program on a notebook computer. The observer selected the appropriate bar code and stroked the code with the input wand.

RESULTS:

Initially, the animals established consummatory patterns. Opioid administration altered the consummatory behavior on a short lived basis but the animals re-established a consistent pattern. The slope of weight gain, however, was depressed throughout the project period. Post-injection of SIV produced an interruption in consummatory patterns in all animals. Some recovery appeared as the viremia progressed. As the immune functions exhibited alterations, chronic diarrhea appeared intermittently and then persistently in all animals; the persistent diarrhea was non-responsive to usual anti-diarrheal treatment even in the face of chronic opioid administration. A gradual and overall progression of behavioral depression was noted with the infected animals. The opioid dependent animals exhibited symptoms and signs of SIV infection earlier than the infected animals treated only with saline. In the terminal stages, animals from all the infected groups, except one saline-treated animal, were equally affected.

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ADHERENCE TO ZIDOVUDINE (AZT) AMONG PATIENTS IN A METHADONE MAINTENANCE PROGRAM: ON-SITE DISPENSING COMPARED TO USUAL CARE

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Substance abuse treatment programs faced with the AIDS epidemic have been expanded to include HIV-related medical services. Substance Abuse Services of San Francisco General Hospital, for example, specializes in the treatment of opiate dependent patients who have HIV infection. The methadone maintenance program provides primary medical care including routine monitoring, treatment for acute HIV-related illness, and prophylactic medication regimens such as zidovudine (AZT). AZT is an effective treatment in the secondary prevention of HIV-related morbidity. Successful treatment, however, requires adhering to the drug. Injection drug users have been shown to be less adherent to AZT than other patient groups. This random assignment study evaluated the effect of an intervention on adherence to AZT among methadone maintenance patients. Twenty-five subjects were randomly assigned to one of two groups. One group (n=13) received an eight-week intervention that involved on-site dispensing and monitoring of AZT adherence by a registered nurse. The other group (n=12) received the clinic's usual care, i.e., monthly AZT prescriptions, occasional inquiry about medication, and regularly scheduled blood draws. Assessments of adherence occurred at weeks four and eight, and one month following the intervention. Measures of adherence included self-report, mean corpuscular volume-(MCV) of erythrocytes, percentage of Medication Event Monitoring System (MEMS) events, and pill counts. At weeks four and eight, subjects in the intervention group, compared to usual care subjects, demonstrated higher rates of AZT adherence on all four measures. There was a statistically significant difference ($p<.05$) in change in MCV (a side effect and indirect biological marker of AZT treatment) between the groups. At the one month follow-up, there were no significant group differences. This intervention was effective in improving adherence to AZT, but did not produce any long term effects when it was drawn. Results suggest change in MCV is a relatively reliable and valid measure of AZT adherence and should therefore be monitored by health care providers as an indicator of patients' adherence. Further research is needed to establish cost effectiveness, longer lasting effects, and the efficacy of this approach over other potentially effective adherence interventions.

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KNOWLEDGE OF AZT AND PENTAMIDINE AS EARLY INTERVENTION MEDICATIONS FOR HIV INFECTION AMONG INJECTION DRUG USERS AND SEX PARTNERS

V. Lidz, B. Brown, and M. Y. Iguchi

In October 1989, the State of New Jersey started a publicly supported Early Intervention Program for medically indigent HIV-infected persons. EIP supports continuing outpatient care for patients who cannot obtain treatment from private physicians, clinics, or health centers. A study to assess the preparation of inner-city IDUs and sex partners of IDUs to participate in EIP was conducted by the AIDS Community Outreach Demonstration Projects of Newark and Jersey City. A brief questionnaire was administered to 2000 subjects in Newark and 1492 subjects in Jersey City to determine: 1) knowledge of AZT and pentamidine; 2) awareness of the availability of these medications; and 3) awareness of need for these medications. Approximately 35% of the IDU subjects and 15% of SP subjects proved on testing to be HIV infected. Eight hundred and ninety-five subjects in Newark and 719 subjects in Jersey City were reinterviewed at 6-month follow-up. Follow-up subjects had received HIV counseling since the first administration of the questionnaire, including information on AZT and pentamidine and on agencies providing medical care for HIV-related conditions.

At baseline interviews, 40% of subjects said they had heard of AZT, 34% could explain its use in common sense terms, 3.3% indicated that they had a need for AZT, and 2.2% reported ever having taken AZT, with 1.4% currently taking it. Knowledge of pentamidine was strikingly lower. Only 3.5% of subjects reported having heard of pentamidine, with respectively 1.7% able to explain its use. Less than 1% of subjects indicated a need for pentamidine, ever trying it, or currently taking it.

At follow-up, there was improved knowledge of AZT. Yet, fewer than 50% could explain the use of AZT at follow-up, despite the HIV counseling received six months previously. The percentages of subjects who acknowledged a need for AZT, indicated having tried it, or reported taking it were doubled from baseline, yet remained small. Follow-up results for pentamidine showed small increases in recognition of the term and knowledge of its use. Subjects indicating a need for, ever trying, or currently taking pentamidine remained < 1%.

Results from the AZT/Pentamidine questionnaire were linked to results on the AIDS Initial Assessment for 1500 subjects, producing the following statistically significant findings: individuals who can explain the use of AZT have served more weeks in jail during the past 5 years, had more years of schooling, and comprised larger percentages of white subjects than blacks subjects and black subjects than Hispanic subjects. They reported more years of drug use, more years of injection drug use, more frequent use of crack, and were more likely to use speedball. They also believed themselves to have greater likelihoods of developing AIDS and believed HIV infection to be more widespread in their communities.

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HIV DISEASE PROGRESSION AND SURVIVAL: A COMPARISON OF INJECTION DRUG USERS (IDUs) AND NON-IDUs

L. S. Brown, Jr., J. Neaton, D. Wentworth, and R. Sherer

In a nationwide, multisite study, the Community Programs for Clinical Research on AIDS (CPCRA) sponsored by the National Institute of Allergy and Infectious Diseases, an observational study began in September, 1990. Seventeen community-based agencies participated in conducting HIV clinical research and have enrolled 4.826 patients, 37% of whom-are IDUs. Follow-up is completed for 85% of IDUs and 94% of non-IDUs and losses to follow-up are censored. Survival and disease progression are summarized with proportional hazards regression with covariates corresponding to various factors (CD4, race, etc.). Compared to non-IDUs, IDUs had higher CD4+ levels (246 vs 169 mm3), a higher percent of females (30% vs 13%), and a lower crude death rate (8.8 vs 14.9 per 100 person years). While IDUs were more likely to have TB or bacterial pneumonia at baseline and during the period of observation, however, no statistical differences in clinical disease progression were evident. The risk of death (lDU/non-IDU) adjusted for covariates mentioned previously was 0.78 ($p=0.03$); however, for CD4+$\geq$300/mm3, the adjusted relative risk was 3.2 ($p=0.02$). This finding suggests causes of death, among HIV-infected IDUs possibly unrelated to HIV disease.

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FAILURE OF 5-HT_3 ANTAGONISTS AND OTHER DRUGS TO BLOCK THE NICOTINE DISCRIMINATIVE STIMLUS

I. P. Stolerman and H. S. Garcha

Drugs from diverse classes have been reported to block behavioural or physiological effects of nicotinic agonists in various test systems (Albuquerque *et al.,* 1983; Carboni *et al.,* 1989). Some of these substances have been examined in rats (n=6–8) trained to discriminate (-)-nicotine (0.1 mg/kg) from saline in a two-bar drug discrimination procedure (food reinforcement). There was no generalization from nicotine to the 5-HT3 antagonists ondansetron (0.1–10.0 mg/kg) or MDL 72,222 (7.5 µg/kg – 1 mg/kg); these doses of the 5-HT_3 antagonists also failed to attenuate the response to nicotine (0.1 mg/kg) or to alter response rates themselves, although large doses of either drug in combination with nicotine slightly reduced response rates. Phencyclidine (PCP, 1–2 mg/kg) and bupivacaine (5–28 mg/kg) reduced overall rates of responding but did not generalize with or shift the dose-response curve for nicotine. Buspirone (0.125–1.5 mg/kg) also reduced the overall rate of responding but did not generalize with or block the discriminative effect of nicotine (0.1 mg/kg). The reported effects of 5-HT_3 antagonists on place preferences conditioned with nicotine cannot be explained easily by a general weakening of sensitivity to nicotine. Bupivacaine and PCP, that can block ion channels of some nicotinic receptors *in vitro,* may not attain large enough concentrations for parallel effects *in vivo.*

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A RAT MODEL OF NICOTINE ABSTINENCE SYNDROME

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Few animal models of the recognized clinical problem of nicotine dependence and abstinence are currently in use. Our laboratory has introduced a rapid and convenient model using the rat (Malin *et al.,* 1992). Dependence was induced by 7 days of continuous s.c. infusion with nicotine tartrate (3 or 9 mg/kg/day). Sixteen hours after infusion ended, rats displayed behavioral signs generally similar to those seen in the opiate abstinence syndrome. Rats previously infused with nicotine displayed more signs than saline controls. The number of signs seen during a 15 minute observation was elevated relative to baseline and infusion periods and reached maximum 16 hours after nicotine removal. The frequency of symptoms began to decline 24 hours post-nicotine removal, and had returned to baseline levels by 40 hours post-nicotine. The number of signs depended on the rate of nicotine infusion, and the syndrome was promptly alleviated by s.c. injection of 0.4 mg/kg nicotine tartrate. Abstinence signs could be rapidly precipitated by an injection of the non-competitive nicotinic antagonist mecamylamine (1 mg/kg s.c.). Marked, temporary decreases in locomotor activity and increases in weight gain concomitant with the behavioral withdrawal signs provided confirming evidence of an abstinence syndrome.

Similarities between the behavioral signs seen in nicotine and morphine abstinence syndromes prompted an investigation of a possible relationship between nicotine and opiate dependence (Malin *et al.,* 1993). Morphine sulfate (2 mg/kg s.c.) alleviated the spontaneous nicotine abstinence syndrome, while the opiate antagonist naloxone (3 and 4.5 mg/kg s.c.) precipitated abstinence signs in nicotine dependent rats. Exposure to nicotine stimulates enkephalin release (Pierzchala *et al.,* 1987), so chronic nicotine may chronically over-stimulate opioid production, leading to a state of endogenous opioid dependence. Withdrawal of the nicotine source may thus result in a state resembling opiate abstinence syndrome which contributes to the observed nicotine abstinence behaviors.

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EFFECTS OF PUNISHMENT ON A PHENCYCLIDINE DISCRIMINATION IN PIGEONS

S. H. Snodgrass and D. E. McMillan

Four pigeons were trained on a phencyclidine (1.0 mg/kg) vs. saline discrimination. The schedule of reinforcement was a multiple fixed interval-180 s fixed interval-180s punishment (0.6 mA of electric shock of 0.5 s duration) schedule. Incorrect responses during the limited hold under the first phase and the first incorrect response during the FI schedule under the second phase of the study were punished. Test sessions differed in that mixed grain was available for responding on either key and shock was omitted.

Under the first phase the PCP dose-response curves were continuous or "graded." There was little difference between the two FI dose-response curves. However, under control conditions the birds produced three times as many responses during the limited hold of the punishment FI than during the limited hold of the simple FI. Also, for three of the four birds all punished responses occurred after PCP administration. Under the second phase, the PCP dose-response curves were of an all-or-none pattern. Again, there was little difference between the two dose-response curves. However, under control conditions each bird made more incorrect responses under the simple FI than under the punishment FI. Also, more responses were punished after PCP than after saline administration. Under the second phase there were relatively few responses during the limited hold of either the punishment or simple FI schedules.

The results show that punishment can alter the pattern, or form, of the PCP dose-response curve dependent upon where in the FI schedule the punisher occurs. Also, punished behavior occurred to a much higher degree after PCP, than after saline, administration. This may be a factor in why the birds would respond more during the limited hold of phase 1, which produced the shock, than under phase 2.

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EFFECTS OF POSTNATAL PHENCYCLIDINE EXPOSURE ON PENTYLENETETERAZOL-INDUCED SEIZURE

R. Sircar

Phencyclidine (PCP) and PCP-like drugs (MK-801, Ketamine), non-competitive antagonists at the *N*-methyl-D-aspartate receptor, act as potent anticonvulsants in adult animals. NMDA receptor plays an important role in developmental plasticity - cell migration, synaptogenesis, establishment of neuronal circuitry. The developing brain is more prone to NMDA-induced seizures and NMDA-induced neurotoxicity than adult brain. Here we report the effect of chronic PCP treatment during development on seizure susceptibility in rats. Pups were treated postnatally with PCP (5mg/kg/day) for 11 days (postnatal days 5-15). Control pups received saline (1ml/kg). All rat pups were weaned on postnatal day 21. On postnatal days 21, 40, 60, 180, separate groups of saline and PCP-treated rats were injected with pentylenetetrazol (100mg/kg). The incidence and latency to reach each seizure stage-twitches, minimal (clonic) and maximal (generalized tonic-cloinic) seizures were measured. Also, PTZ-induced incidence of lethality were recorded. At all ages tested, the incidence of twitches and minimal seizures did not differ between PCP and saline-treated rats. The latency to reach minimal seizures on postnatal days 21 and 40 in PCP-treated rats was no different from saline-treated rats but on day 60, PCP-treated rats had longer latencies than controls. The differences in latencies to reach maximal seizures between normal and experimental groups were age-specific. At day 21 the latency was significantly reduced in the PCP-treated pups compared to saline-treated ones. At day 40, there was no difference between the two groups. In older rats (postnatal days 60 and 180) fewer PCP-treated rats compared to seven out of eleven in the saline-treated group. Even in the animals that did show maximal seizures, the latency was more than twice as long compared to saline-treated rats. There was higher incidence of lethality in PCP-treated older rats following pentylenetetrazol-treatment than saline-treated ones. These data indicate that postnatal PCP treatment produces age-related changes in pentylenetetrazol-induced seizures, proconvulsant effects in younger rats and anticonvulsant effects in older rats. The use of PCP-like drugs in children as antiepileptic or anesthetic/sedative agents needs reevaluation.

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ABECARNIL REVERSES ANXIETY-LIKE BEHAVIORS DURING ETHANOL WITHDRAWAL

H. Lal, C. J. Wallis, and S. M. Rezazadeh

Abecarnil (ABC), a novel-carboline derivative with high affinity for benzodiazepine (BZD) receptors has shown potent anxiolytic and anticonvulsant activity in rodents and humans (for references see Duka *et al.,* 1993). Pharmacologically, ABC has been characterized as a partial agonist at BZD receptors. Relative to classical BZDs, ABC produces little or no sedation and muscle relaxation in animals. Also, long-term treatment with ABC does not induce BZD-like dependence in mice (Steppuhn *et al.,* 1993). The purpose of this study was to investigate if ABC blocks ethanol withdrawal-induced anxiety and improves recovery from ethanol withdrawal (EW). The efficacy of ABC (0-0.64 mg/kg, ip, 1hr) to reduce anxiety-like behaviors displayed during EW was evaluated in the elevated plus-maze (EPM) and pentylenetetrazol (PTZ) discrimination model (Lal *et al.,* 1988). Male Long-Evans rats were fed a nutritionally complete liquid diet containing ethanol (4.5%) or isocaloric dextrin for either 7 d (PTZ) or 10 d (EPM). Rats were tested in the EPM 12-14 h after EW. EW significantly reduced both the number of entries to and time spent on the open arms of the EPM. EW also reduced the total number of entries made in the EPM. LBC treatment dose dependently increased the time spent in the open arms and the number of entries made to the open arms. But unlike diazepam, which reverses the effect of EW on both open arm activity and total number of entries, ABC does not increase the total arm entries. In animals trained to discriminate PTZ from saline, an EW-induced interoceptive stimulus generalized to PTZ (87-100% PTZ lever selection). ABC blocked the withdrawal-induced stimulus in a dose-related manner, with complete blockade at 0.32 mg/kg. To examine the efficacy of chronic treatment with ABC during protracted EW, a 2 mg/kg dose was injected tid for 6 days after EW. On day one, four, and six, rats were injected with flumazenil (40 mg/kg) and 15 minutes later were tested for PTZ lever selection. The results indicated that repeated doses of ABC during EW retarded the recovery as compared with untreated rats. Thus, ABC blocks anxiety-like behaviors due to EW in both the PTZ discrimination model and EPM, but does not mimic the complete activity of diazepam in the EPM.

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RITANSERIN AND OTHER 5-HT AGENTS ON ALCOHOL PREFERENCE AND ALCOHOL WITHDRAWAL IN RATS

T. F. Meert, H. Huysmans, W. Melis, and G. H. C. Clincke

Serotonin (5-HT) receptor subtypes have been implicated in alcohol abuse and alcohol withdrawal. In order to evaluate the role of some of these 5-HT receptor subtypes on alcohol consumption and alcohol withdrawal, we tested the effects of the 5-HT reuptake inhibitor fluoxetine, the 5-HT_{1A} agent buspirone, the 5-HT_2 antagonist ritanserin and the 5-HT_3 antagonist ondansetron on alcohol intake and alcohol withdrawal in rats.

Wistar rats can develop a high preference for 3% (v/v) alcohol after a period of forced alcohol exposure and two days of alcohol withdrawal. By selecting these animals at a medium ($\geq$ 60%) and a high ($\geq$ 85%) level of alcohol preference, it was possible to test the effects of the serotonergic compounds on alcohol intake and alcohol preference at two different levels of alcohol preference. Fluoxetine reduced alcohol intake and alcohol preference in both the medium and the high alcohol preference groups by means of a reduction in consummatory behaviour. The drug clearly affected total fluid intake and body weight gain. Buspirone reduced alcohol intake and alcohol preference in the group of medium alcohol preferring rats at doses between 0.0025 and 0.63 mg/kg. The drug did not change water drinking so that total fluid consumption diminished. At doses $\geq$ 2.50 mg/kg buspirone, alcohol consumption increased. Buspirone was almost without any effects on the high alcohol preferring rats. Ondansetron decreased alcohol intake in both the medium and the high alcohol preferring rats at doses between 0.01 and 0.16 mg/kg. Ondansetron had no effects on alcohol preference and water consumption. As a consequence, total fluid intake was sometimes reduced. Ritanserin reduced alcohol intake and alcohol preference in both the medium (0.04-2.50 mg/kg) and the high alcohol preferring rats (0.16-10 mg/kg). The decreases in alcohol intake were compensated by increases in water consumption, leaving total fluid intake unaffected.

In rats given a liquid diet containing 10% (v/v) alcohol, cessation of the alcohol intake resulted within 8 h in alcohol withdrawal reactions including a supersensitivity to harmine-induced tremor and an inhibition of exploratory behaviour in a neutral environment. Fluoxetine reversed the supersensitivity to 5 and 10 mg/kg harmine but was inactive against the alcohol withdrawal-induced inhibition of exploration in the open field test. Both buspirone and ondansetron had very limited effects on the alcohol withdrawal reactions. High doses of ritanserin could overcome the alcohol withdrawal-induced inhibition of exploratory behaviour in terms of the number of transits into the open field and the time spent in the open field. The same doses of ritanserin also reduced the tremor activity of 5 but not 10 mg/kg harmine. These data illustrate that the various 5-HT agents differentially act on alcohol intake, preference and withdrawal.

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CHLORDIAZEPOXIDE, BUT NOT BRETAZENIL, PRODUCES ACUTE DEPENDENCE, AS EVIDENCED BY DISRUPTIONS IN SCHEDULE-CONTROLLED BEHAVIOR

M. E. Bronson

The purpose of the present study was to determine whether the full benzodiazepine (BDZ) agonist, chlordiazepoxide (C), and the partial BDZ agonist, bretazenil (B), would produce acute dependence, as evidenced by disruptions in fixed interval responding during precipitated and/or abstinence withdrawal. Thirty male Long Evans hooded rats were trained on a fixed interval 1 minute limited hold 10 second procedure. In the precipitated withdrawal studies. doses of C and B administered acutelv were 10, 75 and 100 mg/kg. Cumulative doses of the BDZ antagonist flumazenil (range 1-100mg/kg) were administered 1, 2, 4 and 18 hours after a water injection and after all doses of B and the 10 mg/kg dose of C. Because animals were unable to respond in the operant chamber 1, 2 and 4 hours after the 75 and 100 mg/kg doses of C, flumazenil was only administered 18 hours after these C doses. During cumulative testing, each component was in effect until 5 reinforcers had been delivered, or in the case of no responding, for approximately 6 minutes. When cumulative doses of flumazenil were administered, the first component was always a water injection. This component served as a measure of the effects of pre-treatment with water, C or B. Withdrawal, defined as a significant decrease in fixed interval responding, was only seen when flumazenil was administered 18 hours after the highest, 100 mg/kg, dose of C. In the abstinence withdrawal studies, baseline responding was recorded at the usual run time, after which animals were fed and then 6 hours later injected with water or 32, 75 or 100 mg/kg of either C or B. Rates of responding were then monitored at the usual run time. i.e., 18, 42, 66 and 90 hours after the initial injection of water or BDZ. Water, B and the 32 mg/kg dose of C had no effect on responding on subsequent days. In contrast, the 75 mg/kg dose of C significantly decreased responding at 42 hours, with rates returning to baseline by 66 hours, while the 100 mg/kg dose of C did not decrease responding until 66 hours, returning to baseline rates at 90 hours. Thus both precipitated and abstinence withdrawal from C result in a decrease in operant responding. That only high doses of C produced acute dependence supports the findings of Boisse et al. (1986) who found that very high doses of C were required to produce physical signs of acute dependence. B did not produce acute physical dependence in the present study, thus supporting the findings of others (Martin *et al.* 1988, Moreau *et al.* 1990) that chronic administration of B does not result in physical dependence.

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SYSTEMIC ADMINISTRATION OF Δ^9-THC PRODUCES DEFICITS IN SPATIAL MEMORY IN RATS

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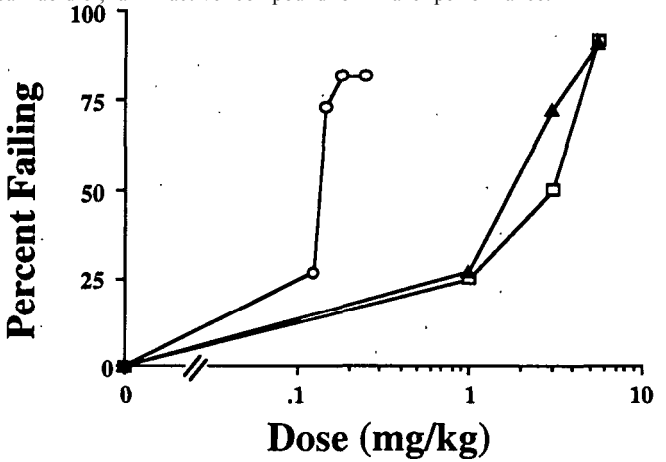
The purpose of this study was to examine the effect of cannabinoids on working memory as assessed in the eight arm radial maze. Twelve Sprague-Dawley rats were trained to obtain a food reinforcement in each arm of an eight arm radial maze with a maximum of 1 error (defined as revisiting an arm). Subjects committing more than 1 error or failing to visit all 8 arms during the 10 min test were scored as failing the task. We evaluated the effects of Δ^9-THC, CP-55,940, WIN-55.212-2, anandamide, the putative endogenous ligand, and cannabidiol, an inactive compound on maze performance.



The effects of Δ^9-THC (□), CP-55.940 (○), and WIN-55,212-2 (▲), on spatial memory as assessed in the eight arm radial maze. ED_{50} values for each respective drug were 2.1 mg/kg, 0.15 mg/kg, and 1.7 mg/kg.

The percent of subjects failing to reach criteria in the eight arm radial maze task increased in a dose-related manner after treatment with Δ^9-THC, CP-55,940, or WIN-55.212-2. Although the highest dose of each drug significantly increased the amount of time requited to complete the maze, doses corresponding to the ED_{50} values, failed to significantly increase completion time. In contrast, neither cannabidiol nor anandamide (10mg/kg or 30 mg/kg, for both) had any appearent impact on spatial memory. The apparent failure of anandamide to disrupt maze performance may be due to either its rapid metabolism or its inability to pass the blood-brain-barrier. These findings taken together are consistant with the notion that cannabinoids disrupt working memory through a cannabinoid receptor.

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RITANSERIN-INDUCED VARIATIONS IN DESIRE TO DRINK, ALCOHOL INTAKE AND ALCOHOL EFFECTS

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Ritanserin, a serotonin$_2$ receptor antagonist, decreased alcohol intake in some animal studies. We tested the effects of ritanserin in 39 (35 male, 4 female) heavy drinkers (consuming at least 28 drinks/week, 13.6 g alcohol/drink), aged 19-63 years, who were not requesting treatment. After an intake assessment, they received placebo for seven days in a single-blind baseline, and then were randomized, double-blind, to one of the following 14-day treatments: ritanserin 5 mg/day (n=12), ritanserin 10 mg/day (n=13), or placebo (n=14). Subjects monitored outpatient alcohol intake and rated desire, craving and liking for alcohol on a daily basis. Experimental bar sessions were conducted after baseline (EBS_1) and treatment (EBS_2); in each session subjects were offered up to 18 mini-drinks (total = 6 standard) and rated their desire to drink, intoxication and mood (POMS). Outpatient results: ritanserin 5 mg/day decreased desire and craving for alcohol (vs baseline, p's<0.05) but not alcohol intake. Liking of alcohol decreased from baseline with ritanserin 10 mg/day (p=0.0l) and placebo (p=0.05). Changes in alcohol intake from baseline with ritanserin 10 mg/day (increase, p>9.05) and placebo (decrease, p>9.05) were different (p<4.05). Alcohol intake correlated with desire, craving and liking (p's < .0.01). Low baseline liking was related to increased treatment response (% decrease from baseline in alcohol intake). EBS results: In EBS_2 desire ratings for the first three mini-drinks were lower after ritanserin 5 mg/day than after ritanserin 10 mg/day (p's <0.05). Changes in feelings of intoxication from EBS_1 to EBS_2 after ritanserin 10 mg/day (increase, p>0.05) and after placebo (decrease, p<0.05) were different (p<0.05). Consumption of alcohol during EBSs increased friendliness and decreased fatigue (p's<8.01 vs pre-alcohol). When compared with placebo, ritanserin 10 mg/day increased both the alcohol-induced increase in friendliness and the alcohol-induced decrease in fatigue (p's<0.05). Ritanserin 5 mg/day increased ethanols effect on fatigue only (p<0.05). Therefore, ritanserin had differential, dose-related and possibly model-dependent effects on alcohol intake, desire, craving and liking, intoxication and some of alcohol's effects on mood.

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Methamphetamine and Alcohol Interactions

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Cocaine and ethanol, when given simultaneously, produce enhanced cocaine-like psychophysiologic effects and a unique metabolite, cocaetbylene, which may mediate these effects. Methamphetamine and ethanol are often consumed simultaneously as well. To investigate the effects of methamphetamine and alcohol interactions, eight subjects received i.v. methamphetamine (30 mg) and ethanol (1 g/kg), in a double-blind, fully crossed, placebo-controlled study.

Significant methamphetamine-alcohol interactions were seen. Heart rate increased in the combination methamphetamine/ETOH when compared with the methamphetamine group alone ($p<0.01$) and remained significantly elevated for six hours following combination drug administration. Peak changes were 50±24 and 28±24 BPM, respectively. The usual rise in systolic blood pressure seen with methamphetamine was blunted in the combination drug condition. Intoxication ratings and amphetamine pharmacokinetics appeared unaffected by combination drug administration.

Methamphetamine and alcohol interactions share some of the same characteristics as cocaine and alcohol interactions. However, no unique metabolite has yet been identified which mediates these effects.

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URINARY EXCRETION OF METHAMPHETAMINE (ME) AND AMPHETAMINE (AM) AFTER ADMINISTRATION OF S(+)-METHAMPHETAMINE HYDROCHLORIDE BY ORAL, INTRAVENOUS AND SMOKING ROUTES

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In a series of studies of the pharmacokinetics of S(+)-methamphetamine hydrochloride, human male volunteers were given oral doses of the drug (0.125 and 0.250 mg/kg) both before and after daily dosing with Desoxyn (Cook *et al.,* 1992). intravenous doses of 0.19 mg/kg, and smoked doses of 0.26 mg/kg (Cook et al., 1993). Urine and plasma were analyzed for methamphetamine and amphetamine by gas chromatography/mass spectrometry or by gas chromatography with a nitrogen sensitive detector. Urine samples from these studies have been analyzed by enzyme-multiplied immunoassay (EMIT d.a.u.). Combining these data has now permitted us to (a) examine factors that influence the excretion of methamphetamine in urine, (b) examine the ratios of mehtamphetamine to amphetamine and (c) examine the effects of the above factors on the detection of methamphetamine use.

Since it is an organic base, the excretion of methamphetamine is influenced by urine pH (Beckett and Rowland 1965) and urine flow rate. The percentage of parent drug excreted in urine decreases with increasing dose, so that doubling the dose does not produce a two-fold increase in the amount excreted (or in the average concentration) in urine (Cook *et al.,* 1992-1993). This is also true when the bioavailable dose is used for calculations. We hypothesize that it is due to the presence of a saturable active secretion process for organic bases in the kidney (Rowland and Tozer 1989).

The ratio of methamphetamine to amphetamine in urine changes with time. Average ratios greater than 10 were found in urine samples collected three to six hours after dosing. High ratios could be an indicator of recent use. The low concentrations of amphetamine shortly after dosing could affect the ability to define a positive urine sample by the current NIDA guidelines. Of 114 samples containing the analytes, 68 were positive by EMIT at the NIDA guideline cutoff of 1000 ng/ml. All 68 had concentrations of 500 ng/ml of methamphetamine or greater as required for confirmation by the guidelines. However, 17 of these samples had amphetamine concentrations below the second confirmation guideline requirement of 200 ng/ml of this compound. Of these, 16 were taken at 0 to 3 or 3 to 6 hours after smoking or intravenous injection. Thus urine samples taken shortly after modest doses of methamphetamine are smoked or injected may not be confirmed. Methamphetamine concentrations above 500 ng/ml were found in samples below the immunoassay screening guideline cutoff (total of 28) shortly after administration (0 to 3 hours) or after 24 hours. Samples below the guideline screening cutoff, but with methamphetamine above 500 ng/ml and amphetamine above 200 ng/ml (total of 17) were found only in the later time periods. The applicability of these findings to the much higher (and often multiple) doses of abuse situations requites further study.

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REFERENCES: Available from senior author.

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EVALUATION OF SUBCUTANEOUSLY (SC) AND INTRAVENOUSLY (IV) GIVEN COCAINE (C)

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The sc route was felt to be more safe and convenient than the more widely used iv route for experimental studies. The subjective, behavioral, and physiologic effects of sc and iv C were tested in twelve subjects. Six of the twelve had venous plasma levels of C and benzylecognine after drug administration. Subjects were tested with saline sc and iv) m, C 15 and 50 mg iv, and C 50, 100 and 200 sc in randomized order under double blind, double dummy conditions. C sc had a slower onset and, longer duration of action but was approximately 4-6 times less potent than iv C. The profile of effects of sc C and iv C were similar. C sc produced greater plasma C levels than equi-effective iv doses for subjective, behavioral and physiologic measures. Hysteresis curves relating C plasma levels and CNS effect indicated that CNS effects ended even though plasma levels were maintained. This suggests that distribution and redistribution determine intensity and time course of CNS effects. The sc route is practical for experimental studies.

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OPIATE WITHDRAWAL SYMPTOMS AND COCAINE ABUSE: DIFFERENTIAL RESPONSE AT HIGH VS. LOW DOSE METHADONE OR BUPRENORPHINE MAINTENANCE

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In a six month randomized trial comparing 125 opiate dependent patients who were assigned to four treatment groups (2 mg or 6 mg of buprenorphine and 35 mg or 65 mg of methadone), we examined the effects of cocaine use on opiate withdrawal symptoms measured on a 75 point self report scale. For the methadone maintained patients receiving the relatively low dose (35 mg), weekly withdrawal symptoms-were highest when the urine toxicology for that week indicated no cocaine use (Fig. 1). Similar associations were found for buprenorphine (Fig. 2). Thus, when using cocaine, persistent opiate withdrawal symptoms were reduced which is consistent with previous naloxone precipitated withdrawal studies. Interestingly, with higher dose buprenorphine (6 mg) cocaine may have increased opiate withdrawal symptoms suggesting a possible mechanism for the reduction of illicit cocaine abuse also recently observed in patients treated with high dose (120 mg) methadone maintenance (Stine *et al.,* 1992).

Among the 125 patients 22 did not abuse cocaine during the trial, and among the 103 patients who abused cocaine 74 patients also had at least one week of cocaine-free urines. These 74 patients were comparable to the overall sample with respect to age, sex, race, days of cocaine use in the month preceding the study, and total years of cocaine use in lifetime. When the 74 intermittent cocaine abusers were separated into medication dosage groups, the difference in withdrawal symptom scores for cocaine-free vs. cocaine positive weeks significantly differed between the 36 high dose patients and the 38 low dose patients (Fig. 3). Thus, the high dose patients had higher opiate withdrawal scores when using cocaine, while the low dose patients had lower scores.

As discussed in this article withdrawal can be grouped into two components: 1) "Protracted withdrawal", a low level persistent discomfort which is higher at lower methadone or buprenorphine doses and, 2) "Precipitated withdrawal", a sensitivity to acute discomfort precipitated by pharmacological intervention *(e.g.,* by opiate antagonists or adrenergic agonists) which is higher at higher doses. This is consistent with the opposite direction of change seen in intermittent users.

These results support the clinical usefulness of higher buprenorphine maintenance dose in treatment of dually addicted patients. Future dose response studies need to examine higher doses with respect to cocaine abuse and opiate withdrawal symptoms.

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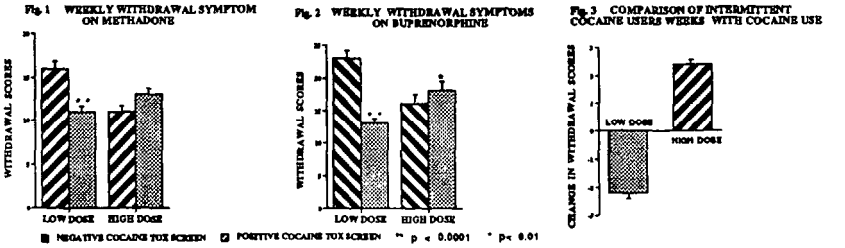

VERAPAMIL POTENTIATES MORPHINE ANALGESIA AND REDUCES EUPHORIA IN HUMAN SUBJECTS

D. B. Vaupel, W. R. Lange, and E. D. London

Organic Ca^{2+} channel antagonists enhance opiate-induced analgesia (Benedek and Szikszay 1984) and antagonize respiratory depression (Szikszay *et al.,* 1986) produced by morphine (M) in rodents. Preliminary data indicated verapamil (V) reduces the subjective effects of morphine in human subjects (Vaupel *et al.,* 1990). As these effects may have therapeutic utility, we assessed M-V interactions in 12 experienced male heroin users. Five treatments were tested: saline (S)+S; S+M (10 mg); V (10 mg)+S; V (2.5 or 10 mg)+M (10 mg). The first drug listed was infused i.v. over 2 minutes; i.v. infusion of the second drug was over 10 seconds and was initiated half-way through the 2-minute infusion. Effects were measured over 4 hours. Analgesia was measured using a finger pressure test and hand immersion in ice water. Respiration was measured using respiratory inductive plethysmography and transcutaneous CO_2 levels. The Addiction Research Center Inventory (ARCI) was used to measure the positive subjective effects of M on mood. Pain threshold, as determined with the finger pressure stimulus, was increased marginally by M ($p < .2$), but V was inactive. However, combinations of V (2.5 or 10 mg)+M (10 mg) significantly elevated pain threshold to produce analgesia. A similar trend was observed using the cold water stimulus. M produced euphorigenic effects based on the elevated scores ($p < .01$) on the MBG scale of the ARCI. V produced no subjective effects, but V (10 mg) antagonized elevation of MBG scores produced by M from the first through the third h after treatment ($p < .05$). The ability of V to antagonize euphorigenic effects of M and to potentiate its effect on pain threshold suggests that the neural circuits subserving these opioid actions may be differentiated using Ca^{2+} channel blockers, and may have therapeutic utility.

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A HIGHLY SENSITIVE METHOD FOR THE QUANTITATIVE ANALYSIS OF CODEINE AND MORPHINE IN HUMAN HAIR BY POSITIVE CHEMICAL IONIZATION MASS SPECTROMETRY AND ITS CLINICAL APPLICATIONS

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Studies of the disposition of drugs of abuse in human hair for pharmacokinetic and epidemiologic studies or in the evaluation of long-term compliance in drug treatment programs require a sensitive analytical method. A highly sensitive and specific method has been developed for the quantitative analysis of codeine and morphine in human hair. Hair samples collected from volunteers were cut into short. 1-2 cm segments and placed into flat-bottom glass vials. Ten mg of hair and 100 ng of deuterated codeine and morphine were digested overnight at 37°C in 500 µL of either 1M NaOH or Pronase E solution. Eleven calibration standards containing known concentrations of both codeine and morphine dried onto human hair were also prepared and digested. Digest solutions were extracted using a modified solid-phase procedure with Bond-Elute Certify® bonded silica extraction columns. The final eluate containing drug was evaporated to dryness at 50°C under nitrogen and the dried extracts were derivatized in TFAA for 30 minutes at 70°C, evaporated-to dryness under nitrogen at 50°C and reconstituted in 50 µL of ethyl acetate. Derivatized extracts were immediately analyzed by gas chromatography/mass spectrometry on a Finnigan ion trap mass spectrometer (ITS40™). Chromatographic separation was achieved with helium carrier gas and a DB5MS - 15M - 0.25 µ capillary column. Positive chemical ionization mode was utilized with acetone as reagent gas to enhance sensitivity and specificity. Regression analysis of the eleven-standard calibration curves indicated a linear range from 0.5 ng/mg to 75 ng/mg for both codeine and morphine (0.998 to 1.000). The assay is capable of quantitatively detecting as little as 10 pg of codeine and/or morphine on column. Intra-assay precision ranged from 8-22%. Accuracy was verified with control hair specimens of known concentration. This method is being used to quantitate codeine and morphine in dose-response disposition studies in human subjects.

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SAFETY AND PHARMACOKINETICS OF A NEW FORMULATION OF DEPOT NALTREXONE

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Naltrexone hydrochloride (Trexan) is an opioid antagonist, devoid of agonist activity, indicated in the maintenance of an opioid-free state in detoxified formerly opioid-dependent individuals. Typically, individuals are dosed with 50-150 mg of oral naltrexone every 24-72 hours. A major constraint on its utility as a treatment modality has been the lack of acceptance by clients, due in part to the frequency of dosing and incidence of adverse side effects.

The development of a depot formulation providing long-term opioid receptor blockade via sustained release of low levels of naltrexone may avoid these problems and thus improve treatment compliance. The purpose of this study was to evaluate the safety, pharmacokinetic, and pharmacodynamic profile of a newly developed form of depot naltrexone.

Four healthy nonsmokers, who reported no history of drug and alcohol dependence, participated in a placebo-controlled, double-blind, outpatient trial. On day one, subjects received two s.c. injections simultaneously, one in each upper arm (triceps area). Injections contained either naltrexone (52 mg) or placebo microcapsules. An assessment battery, consisting of dermatological, physiologic, subjective, and performance measures and blood samples for hematology, chemistry, and naltrexone concentration, was completed at pre-injection baseline and repeated at 4 and 8 hours postdrug and on days 2, 3, 5, 8, 11, 15, 22, 29, 36, 50, and 64.

Results indicated no tissue irritation or infection at the injection sites, and no adverse physical signs and symptoms. Laboratory results were normal. Mean maximal plasma naltrexone concentration of 0.93 ng/ml was observed at 24 hours post-naltrexone. Plasma levels declined to about 0.4 ng/ml at four days post-naltrexone and remained relatively stable through day 21.

Because the data suggest that this low dose (52 mg) of depot naltrexone is safe, testing will be conducted with higher doses to achieve a sustained naltrexone plasma concentration of 1-2 ng/ml.

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ACQUISITION AND EXTINCTION OF OPIOID-REINFORCED BEHAVIOR AS A FUNCTION OF GENOTYPE: RELATIONSHIPS TO LOCOMOTOR ACTIVITY, STRESS AND ACUTE OPIOID SENSITIVITY

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Operant drug-reinforced behavior in defined genotypes provides a unique paradigm to pursue questions related to biological or environmental factors important in drug-seeking behavior. Recent hypotheses regarding the predictive value of innate locomotor activity in the acquisition of drug-reinforced behavior are amenable to testing using this behavior genetics approach. The current series of studies investigated the relationship between drug-naive behaviors (locomotor activity/reaction to stress), drug-related behaviors (acute morphine-induced analgesia) and the rate of acquisition and extinction of opioid-reinforced behavior.

Genetic differences in locomotor activity in naive and stressed ACI, F344, Lewis and NBR rats were investigated as well as the locomotor activity of rats prepared for iv self-administration studies. Morphine-induced analgesia was determined via the hot-plate assay. Operant drug-reinforced behavior was examined in a 23 hr access paradigm in which rats received 1 mg/kg/inj of morphine on an FR 1:TO30" schedule of reinforcement. The results of these studies suggest large genetic differences in the rate of acquisition and extinction of morphine self-administration. For example, Lewis rats responded at high rates beginning in the first two days whereas the F344 rats responded at low rates and increased gradually over seven days. Drug maintained significantly greater amounts of behavior than vehicle in all strains. Across genotype, acquisition rate was marginally correlated with baseline locomotor activity but not with locomotor activity following restraint stress or sensitivity to morphine-induced analgesia. Within strain, there was no significant correlation between individual locomotor activity and the rate of drug self-administration behavior. This procedure provides an opportunity to explore genetic (across genotype) and environmental components (within genotype) of drug reinforced behavior.

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ANTAGONISM OF RESPIRATORY AND BEHAVIORAL EFFECTS OF LEVORPHANOL BY NALOXONAZINE

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Naloxonazine has been described as a μ_1-selective antagonist of opioid analgesia in rats with no effects on opioid-mediated respiratory depression. The present studies measured the effects of the μ-opioid agonist levorphanol on respiration and schedule-controlled behavior in rhesus monkeys alone and one or 24 hours after naloxonazine (1.0-3.0 mg/kg). In respiration experiments, awake seated monkeys breathed air or 5% CO_2 mixed in air. In behavioral experiments, monkeys responded under a fixed-ratio 30-response schedule of food presentation. Levorphanol (0.03-3.0 mg/kg) depressed CO_2-stimulated breathing and reduced rates of food-maintained responding in a dose-related fashion. When administered one hour before levorphanol, 3.0 mg/kg naloxonazine antagonized the effects of levorphanol by producing approximately 10- to 20-fold shifts to the right in behavioral and respiratory dose-effect functions in individual monkeys. When administered 24 hours before levorphanol, the effects of 3.0 mg/kg naloxonazine were diminished and the dose-effect functions'were shifted to the right approximately 3- to 6-fold in individual monkeys. These results indicate that the putative μ_1-selective antagonist naloxonazine, like naltrexone, may antagonize both rate-decreasing and respiratory depressant effects of opioids in monkeys.

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COMPARISON OF THE OPIOID ANTAGONISTS NALTREXONE AND 6-METHYLENE NALTREXONE (NALMEFENE) IN RHESUS MONKEYS

C. P. France and L. R. Gerak

The naltrexone (NTX) derivative nalmefene (NMF) is purported to be a long-acting, orally bio-available opioid antagonist which might be clinically superior to currently available opioid antagonists (*e.g.,* naloxone). Previous studies have demonstrated NMF to be an effective antagonist of morphine-like opioids under a wide variety of conditions and, like other opioid antagonists, NMF appears to have no potential for abuse. In the present study the opioid antagonists NTX and NMF were compared in rhesus monkeys for their discriminative stimulus effects and for their effects in antagonizing analgesic effects of receptor-selective opioid agonists. NTX and NMF had similar potency as discriminative stimuli in morphine-treated monkeys discriminating between 0.01 mg/kg NTX and saline. The onset of discriminative stimulus effects also was similar between NTX and NMF with a dose of 0.032 mg/kg of each compound producing >90% responding on the NTX lever 6-8 minutes after subcutaneous injection. NTX and NMF also had similar potency in: 1) antagonizing discriminative stimulus *(i.e.,* withdrawal-reversing) effects of morphine in monkeys acutely deprived of morphine; 2) antagonizing discriminative stimulus effects of nalbuphine in untreated monkeys discriminating between 0.178 mg/kg of nalbuphine and saline; and 3) in antagonizing analgesic effects of mu opioids *(e.g.,* alfentanil) in untreated monkeys. Apparent affinity estimates for NTX and NMF, determined by Schild analyses, were similar (pA_2 = 7.9-8.3) among all of these experimental conditions and the slopes of the Schild plots were consistent with a simple, competitive interaction between mu agonists and each antagonist. NTX and NMF also antagonized analgesic effects of the kappa agonist CI977; however, as compared to NTX, relatively larger doses of NMF were needed to antagonize CI977. NMF also had a longer duration of antagonist action as compared to NTX and naloxone. Thus, the pharmacological profile of NMF in rhesus monkeys appears to be similar to that of NTX, although it has a longer duration of antagonist action as well as a greater selectivity for *mu* over *kappa* opioid receptors.

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OPIATE GENERALIZATION IN RATS TRAINED TO DISCRIMINATE NALORPHINE VS MORPHINE WITHIN THE CONDITIONED TASTE AVERSION PROCEDURE

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In previous work from our lab (Kautz & Riley, Problems of Drug Dependence 1992: 5:247; 1992). animals were trained to discriminate nalorphine (10.0 mg/kg) from morphine (5.6 mg/kg) in a two-drug discrimination procedure within the taste aversion baseline of drug discrimination learning. Specifically, animals injected with nalorphine prior to a Saccharin (Sacc)-LiCl pairing and morphine prior to Sacc alone consumed less Sacc relative to controls following nalorphine than following morphine. If this discrimination was based on the different receptor activity of these two compounds, then the administration of probe compounds with select opiate receptor activity should engender drug-appropriate responding in subsequent generalization tests. That is, compounds with mu antagonist and kappa agonist properties should generalize to nalorphine *(i.e.,* animals should avoid Sacc), whereas compounds with mu agonist properties should generalize to morphine *(i.e.,* animals should consume Sacc). This prediction was assessed in the present experiment in which animals previously injected with nalorphine prior to a Sacc-LiCl pairing and morphine prior to Sacc alone were tested for the generalization of stimulus control to various compounds with kappa agonist (U50,488), mu agonist (methadone) and mu antagonist (naloxone) activity.

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EFFECTS OF 5-HT_3 RECEPTOR ANTAGONISTS ACROSS VARIOUS MODELS OF OPIOID ABUSE

G. A. Higgins and E. M. Sellers

We have previously reported the 5-HT_3 receptor antagonists, *e.g.,* ondansetron (OND), MDL72222 (MDL). ICS205-930 (ICS), may attenuate the acquisition of a conditioned place preference to morphine (Higgins et al. 1992). We now describe the effect of these drugs in morphine drug discrimination and heroin self-administration paradigms, to determine whether these agents modify other behaviours related to opioid abuse.

Male, Wistar rats (starting wt. 300g) were used throughout. For the drug discrimination studies, two squads of rats were trained to discriminate morphine from saline using a standard, two-choice, food motivated operant paradigm. In one group (n=12) the morphine training dose was 1.5 mg/kg, in the other group (n=8) a training dose of 3 mg/kg was used. Following the attainment of reliable discriminative control, substitution tests were conducted. In each group both morphine (0.1-3 mg/kg) and heroin (0.03-0.3 mg/kg) generalised completely, but OND engendered vehicle lever responding. Naloxone (0.01-0.25 mg/kg) produced a dose related antagonism of the morphine stimulus in both groups. Pretreatment with OND, ICS (both 0.001-1 mg/kg) and MDL (0.1-3 mg/kg) did not significantly attenuate the morphine discriminative stimulus.

In the heroin self-administration model, rats were trained over a period of 3-4 weeks to respond for intravenous heroin infusions to a final ratio of FR5. Operant sessions were of 60 minute duration, 7 days/week. The heroin infusion dose was 0.03 mg/kg body wt./infusion. Once stable, rats self-administered approximately 10-13 infusions/session. Naloxone (0.01-0.25 mg/kg) produced a dose-related increase in heroin responding. Neither OND (0.01-1 mg/kg) nor MDL (0.1-3 mg/kg) produced any significant effect on either the pattern or number of heroin infusions. Chronic treatment with OND (0.01-1 mg/kg for 5 days) was similarly ineffective. It is concluded that although 5-HT_3 antagonists may block the acquisition of a place preference to morphine, these agents do not influence the discriminative or reinforcing properties of opioids.

Reference available from the first author.

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AN EXAMINATION OF CONDITIONED TOLERANCE AND POTENTIAL COMPENSATORY RESPONSES ON FOUR ASSAYS OF MORPHINE ANALGESIA

S. T. Tiffany and A. Cepeda-Benito

Although many investigations have shown that classical conditioning can contribute to morphine tolerance development, the nature of the conditioned response subserving associative tolerance has been elusive. Some theories predict that conditioned tolerance will be subserved by behavioral responses counterdirectional to the direct drug effects. Evidence regarding the existence of these responses has been mixed and has led to proposals that compensatory responding is not a necessary feature of associative tolerance. These investigations studied the development of conditioned tolerance, indexed as shifts in dose-response curves, on the tail flick, hot plate, paw-pressure analgesiometry, and tail-shock vocalization tests of morphine analgesia in rats. The contribution of conditioned hyperalgesia to any conditioned tolerance effects was also examined.

A three group, discriminative conditioning design was used for all studies. The Distinctive Context group received a series of 8 morphine injections (20 mg/kg, ip, 96 hour IDI) with each injection explicitly paired with a one hour exposure to a distinctive environmental context. The Home Cage group also received 8 morphine injections with each injection explicitly unpaired with distinctive context exposures. The Saline Control group received no morphine but was exposed to the distinctive context over the course of conditioning. After conditioning, animals were brought to the distinctive context, injected with one of several doses of morphine (tolerance testing) or saline (compensatory response tests) and tested for nociceptive responding.

The tail-flick, paw-pressure, and tail-shock vocalization tests revealed strong conditioned tolerance effects but no compensatory responses. Conditioned tolerance was not obtained on the hot plate even when procedures that produced robust conditioning effects on the other assays were used. These results provide further support for the proposition that behaviorally manifest compensatory responses may not be the substrate of conditioned tolerance effects.

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THE EFFECT OF CHRONIC NALTREXONE PRETREATMENT ON MORPHINE TOLERANCE

J. L. Azorlosa

Chronic exposure to an opioid antagonist produces an increase in the analgesic response to morphine. The effects of antagonist pre-exposure on the subsequent development of morphine tolerance is not known. In addition, numerous studies have shown that animals given morphine in the presence of contextual cues previously paired with morphine are more tolerant compared to animals with the same history of morphine administrations paired with different cues. It has been suggested that context-specific tolerance is mediated by different neural processes than other forms of morphine tolerance. The purpose of the present study was to investigate the effects of prior exposure to the opioid antagonist naltrexone on both context-specific tolerance and tolerance not mediated by contextual cues.

Four groups of rats (n=8) were given nine injections during a five day pretreatment period. Two groups received naltrexone (5 mg/kg) and two were given saline. All animals were then given six injections of morphine (5 mg/kg) spaced 48-72 hours apart. Within each pretreatment condition, half the rats had morphine administered in a distinctive environment (paired) and half received the drug in the home cage (unpaired). On the seventh session, all rats received morphine in the distinctive environment and were tested for analgesia using the hot plate (52°C). Within each pretreatment condition, the paired groups were more tolerant than the unpaired groups. The two paired groups displayed almost identical levels of analgesia but the unpaired group pretreated with naltrexone was substantially more analgesic than the unpaired group pretreated with saline. Naltrexone had no effect on context-specific tolerance but attenuated tolerance that was not mediated by contextual cues.

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Available upon request.

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MOTIVATIONAL CONSEQUENCES OF NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

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In addition to the classical physical symptoms, opiate withdrawal is accompanied by aversive affective symptoms that have been hypothesized to be of motivational significance for the maintenance of drug dependence (Koob *et al.,* 1992). In the current study, a quantitative dose-response analysis of naloxone-precipitated withdrawal was undertaken, using the following behavioral measures as dependent variables in separate groups of rats: 1) activity in photocell cages; 2) operant responding for food (FR15); and 3) intracranial self-stimulation (ICSS) thresholds. Physical withdrawal symptoms were also observed in one group of rats. A standardized naloxone dose range, method of dependence induction (morphine pellets), and route of antagonist administration (subcutaneous; s.c.) enabled direct comparisons of sensitivity to naloxone across paradigms.

Male Wistar rats (350-450 gms) received s.c. implants of morphine (2 x 75 mg) or placebo pellets. Between 3 to 10 days after pellet implant, the rats were tested in one of the behavioral paradigms following s.c. injection of saline or one of several doses of naloxone (0.003 - 1.0 mg/kg). In dependent rats, naloxone dose-dependently altered performance in all of the behavioral paradigms, producing: 1) reductions in spontaneous locomotor activity, 2) suppression of operant responding for food, and 3) elevations in ICSS thresholds. The minimal effective dose of naloxone in all cases was 0.01 mg/kg dose produced only a minimal response, with seminal emissions, irritability, and teeth chattering being observed in about 50% of the rats. More profound signs such as jump attempts, weight loss, diarrhea, wet dog shakes, profuse salivation, ptosis, and abnormal posture were absent at this dose. In non-dependent rats, higher doses of naloxone were required to alter locomotor activity and operant responding for food (0.10 and 1.0 mg/kg, respectively), and ICSS thresholds were unaffected even by the 1.0 mg/kg dose.

In summary, the behavioral measures employed in the current study appear to be highly sensitive indices of the aversive affective symptoms of opiate withdrawal. Recent work in our laboratory (Carrera, Schulteis, and Koob, unpublished results) indicates that very low doses of naloxone (0.003 - 0.01 mg/kg) produce reliable and immediate increases in heroin self-administration in dependent rats, suggesting that the affective symptoms of withdrawal produced by these doses are of motivational significance for maintaining drug-seeking behavior. The measures described herein will be useful in the further delineation of the neural substrates involved in the opiate dependence syndrome, and in the evaluation of novel therapeutic interventions for the treatment of opiate addiction.

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MICROINJECTIONS OF DAMGO INTO THE NUCLEUS ACCUMBENS AND OLFACTORY TUBERCLE LOWER BRAIN STIMULATION REWARD THRESHOLDS

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Brain infusions of the mu-specific agonist DAMGO, have been shown to produce a decrease in rate of response for brain stimulation reward (BSR), suggesting a decrease in sensitivity to the stimulation. However, locomotor studies reveal a biphasic "hypoactive/hyperactive" effect of intracranial injections of DAMGO. Therefore, in the present study, the effect of DAMGO on BSR thresholds were determined 75 min post-infusion. Animals were implanted with bilateral cannula positioned above the nucleus accumbens (NA) or the olfactory tubercle (OT), and a single electrode into the ventral tegmental area (VTA). Thresholds for VTA brain stimulation reward were determined. Animals then received microinjections of DAMGO (0.0., 0.125, 0.25, 0.5 and 0.75 µg/.5 µl/side) into the NA or OT. Seventy-five minutes post-injection, reward thresholds were determined. Results reveal that while intracranial infusions of saline have no effect on reward thresholds, DAGO infusions into the NA and the OT lower the threshold for rewarding VTA stimulation. This finding is consistent with the notion that dopamine neurotransmission is facilitated by mu receptor stimulation.

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MORPHINE REGULATES JUN B IN RAT STRIATUM: POSSIBLE INTERACTION WITH NMDA RECEPTORS

M. M. Garcia and R. E. Harlan

Previous studies from this and other laboratories have shown that morphine regulates immediate-early gene expression in rat striatum. We have also shown that chronic morphine administration upregulates the calcium binding protein, calbindin D28k, in striatum, and that this effect is blocked by co-administration of the NMDA antagonist MK-801 (Garcia and Harlan 1992). In the present work, we studied the effects of acute or chronic morphine on the expression of the protein product of the immediate-early gene JunB in rat striatum, as well as examining the effects of MK-801 on JunB levels in the presence and absence of morphine. JunB immunocytochemistry, using an antibody to bacterially expressed JunB protein (a gift of R. Bravo). In acute studies, male Sprague-Dawley rats were given sc injections of saline vehicle, morphine (10mg/kg), or naltrexone (NAL; 10mg/kg) followed immediately by morphine, and killed 3 hr later. In the dorsomedial striatum, cell counts in saline-treated animals were 420±85; morphine, 876±95 ($p<0.01$); and naltrexone-morphine, 496±59. In chronic studies, rats were injected twice daily with saline/saline, saline/morphine (10 mg/kg), MK-801 (MK; 0.2 mg/kg)/saline or MK/morphine for 6 days and sacrificed on day 7. In saline/morphine-treated rats, the number of JunB-immunoreactive cells in caudate-putamen (CPu) were increased compared to saline/saline rats; MK/saline had no effect. In MK/morphine rats, however, the number of JunB immunoreactive cells were significantly decreased compared to both saline/saline and saline/morphine. These findings indicate that acute administration of morphine increases expression of the immediate-early gene JunB, in a specific region of the striatum. In addition, these findings suggest that the interactions between the NMDA receptor system and the mu opiate receptor system may be more complex than originally believed.

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REGULATION OF GLUTAMATE R3 RECEPTOR mRNA IN RAT CEREBELLUM IN RESPONSE TO ACUTE AND CHRONIC MORPHINE

P. S. Tirumalai and R. D. Howells

The cellular and biochemical adaptations which underlie the addictive state are poorly understood. Since it is likely that changes in gene expression accompany the development of addiction, we are examining changes in the expression of candidate genes. In this study, the effect of acute and chronic morphine administration on expression of glutamate R1 and R3 receptor mRNA was examined in rat cerebellum and rat brain (minus the cerebellum).

METHODS:

Adult male Sprague-Dawley rats were injected with saline or with escalating doses of morphine sulfate twice daily for 15 days. Rats were sacrificed 45 min after the last injection, the cerebellum and remaining brain minus the cerebellum were removed, and total RNA was extracted using the acid guanidinium thiocyanate/phenol chloroform method. RNA levels were auantified bv Northern blot analvsis. In addition. other rats received a single injection of morphine (10 mg/kg) and were sacrificed after 43 min, 4 hr, or 24 hr later. The effect of naloxone-precipitated withdrawal on gene expression in morphine-addicted rats was also analyzed 45 min after naloxone (1 mg/kg ip).

RESULTS and DISCUSSION:

The level of glutamate R3 receptor mRNA was decreased to 50% of control levels at 1 and 4 h following acute morphine administration in the cerebellum. Tolerance developed to these effects in that the decrease was not observed in rats that were chronically injected with morphine. Glutamate R3 receptor mRNA was unaltered in the whole brain minus the cerebellum under any condition. No change in glutamate Rl receptor mRNA was observed in the cerebellum or brain minus the cerebellum under any circumstance. Naloxone-precipitated withdrawal had no effect on the levels of R1 or R3 receptor mRNA. The differential effect of acute vs chronic morphine on glutamate R3 receptor gene expression may be an important aspect of the adaptation of the nervous system to morphine.

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INTRACEREBROVENTRICULAR INFUSION OF FORSKOLIN INDUCES STRIATAL PREPROENKEPHALIN AND PREPRODYNORPHIN mRNA IN RATS

J. N. Simpson, S. R. Childers and J. F. McGinty

Intracerebroventicular (ICV) infusions of forskolin coupled with in situ hybridization histochemistry (ISHH) were utilized in order to determine whether prepro-opioid mRNA levels in the rat striatum could be induced by prolonged activation of the adenylate cyclase cascade. In addition, the ability of the kappa opioid agonist, U50,488, to block forskolin-induced prepro-opioid mRNA was investigated. Mini-osmotic pumps (rate of 1 µ1/h) with attached injection cannulae were used to infuse drugs unilaterally or bilaterally into the lateral ventricles of rats. Rats received infusion of H_2O-soluble forskolin (Calbiochem), 1,9-dideoxyforskolin (Calbiochem), or U50,488 (RBI) for 6, 24, or 72 hours. Following infusions, the brains were removed and quickly frozen for ISHH. 35_S-dATP labeled 48mer oligonucleotides for preproenkephalin (PPE) and preprodynorphin (PPD) were hybridized onto 12 µm sections taken through the striatum. After stringent washing, slides were placed on Kodak X-OMAT film for 6 days (PPE) or 14 days (PPD) along with ^{14}C standards. ^{35}S equivalences obtained from ^{14}C standards were used to convert raw gray scale transmittance values into dpm/mg. The hybridization signal of a 20x75 pixel region in the striatum adjacent to the lateral ventricle was analyzed using the IMAGE software (W. Rasband, NIMH) and represented as mean density (dpm/mg). A non-parametric analysis of ranked data followed by Least Squares Means test was used. In the first set of experiments, 1 mM forskolin was infused unilaterally ICV for either 24 or 72 hours. Increased hybridization signals of PPD and PPE mRNA were limited to the region of the striatum adjacent to the lateral ventricle and were significantly greater than controls at both time points ($p<0.05$). In order to demonstrate that forskolin induces PPE and PPD mRNA through the cAMP second messenger cascade, 1,9-dideoxyforskolin (dideoxy) was compared with forskolin's ability to increase prepro-opioid mRNA levels. Rats were infused with dideoxy (1 mM) in their left ventricle and forskolin (1 mM, Sigma) in their right ventricle for 24 hours. PPD and PPE mRNA signals in forskolin-infused striata were significantly increased compared to the dideoxy side ($p<0.05$). Finally, the ability of U50,488 (U50) to attenuate forskolin-induced PPD and PPE mRNA was investigated. Rats were infused unilaterally ICV for 6 hours with U50 (10 µg/µl), forskolin (1 mM), or U50 and forskolin simultaneously. Striatal mRNA signals of the untreated side served as controls. U50 alone did not alter the striatal PPE or PPD mRNA signal. Forskolin alone increased PPE mRNA; U50 attenuated this increase but not significantly. Forskolin alone significantly increased PPD mRNA compared to controls ($p<0.0125$) and U50 blocked this increase ($p<0.0125$ compared to forskolin alone). In conclusion, *in vivo* activation of the adenylate cyclase/cAMP second messenger cascade induces striatal prepro-opioid mRNA. In addition, administration of U50,488 during activation of this second messenger cascade attenuates the induction of striatal prepro-opioid mRNA most likely via kappa receptor-mediated inhibition of adenylate cyclase.

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SINGLE INJECTION OF AMPHETAMINE OR METHAMPHETAMINE CAUSES AN INCREASE IN PREPRODYNORPHIN, BUT NOT PREPROENKEPHALIN, mRNA IN THE RAT STRIATUM

A. J. W. Smith, W. T. Bohler, and J. F. McGinty

Methamphetamine (METH - 15 mg/kg) caused a significant increase in striatal dynorphin immunoreactivity (dyn-ir) 6, 18. and 24 hours after a single injection (Hanson *et al.,* Eur J Pharmacol 1988). Amphetamine (AMPH - 5 mg/kg) caused a decrease in striatal dyn-ir 1 hour after a single injection; however, injections administered twice daily for 7 days caused an increase in striatal dyn-ir 16 hours after the last injection (Li *et al.,* J Pharm Exp Ther 1988). To investigate the effect of an acute injection of METH or AMPH on striatal preprodynorphin (PPD) and preproenkephalin (PPE) mRNA by *in situ* hybridization, male Wistar rats (200-225 g) were injected ip with a single dose of d-AMPH sulfate (5 mg/kg), METH HCl (15 mg/kg), or saline. The animals were rated behaviorally at 5 minute intervals for 1 hour after the injection. At 3.6, and 18 hours after the injection, the rats were anesthetized and decapitated. Brain sections were hybridized with a 48-mer oligonucleotide probe to PPD and PPE following a modification of the protocol of Young *et al.,* (1986). After stringent washing, the slides were dried and apposed to Kodak X-OMAT film with ^{14}C standards for 2 and 1 week, respectively. The AMPH-injected rats exhibited increased locomotion, repetitive exploration, sniffing, and rearing. The METH-injected rats did not exhibit increased locomotor behavior, but displayed a repetitive swimming motion, increased sniffing and head bobs. Statistical analysis of the ratings was done by calculating the area under the curve (AUC) generated when rating versus time was plotted. The AUC values were compared in an ANOVA with a Tukey's test for group comparisons. The behavioral ratings of AMPH- and METH-treated rats were significantly different from controls, as well as from each other. The integrated density (mean density X number of labeled particles/area) of the hybridization signal in the dorsomedial striatum was measured on films using a Macintosh IIci and Image software (Wayne Rasband. NIMH). The data were subjected to a least square means ANOVA with multiple observations per animal. Quantification showed that 3, 6, and 18 hours after either METH or AMPH, striatal PPD mRNA was significantly greater than in controls; however, AMPH-induced PPD mRNA at 18 hours was beginning to decline. There was no significant change in PPE mRNA expression after either AMPH or METH. Thus, even though AMPH and METH had different effects on locomotor activity, an increase in striatal PPD mRNA expression occurred with the same time course after a single dose of either drug. These data support the association of striatal PPD mRNA expression with stereotypes common to the behaviora1 syndromes elicited by AMPH and METH.

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REGULATION OF TYROSINE HYDROXYLASE AND TRYPTOPHAN HYDROXYLASE LEVELS FOLLOWING COCAINE ADMINISTRATION

S. L. Vrana, K. E. Vrana, T. R. Koves, J. E. Smith and S. I. Dworkin

Cocaine **(COC)** inhibits the reuptake of dopamine **(DA)** and serotonin (5-HT) in the **CNS** through its blockade of the specific transporter sites. Tyrosine hydroxylase **(TH)** and tryptophan hydroxylase **(TPH)** catalyze the rate-limiting reactions in **DA** and 5-HT biosynthesis, respectively, and therefore dictate the amounts of these biogenic amines that are synthesized. TH and TPH activity were measured in the mesolimbic and nigrostriatal **DA** regions **(TH)** and in the raphe nuclei **(TPH)** following response-independent, *i.v.* **COC** administration (7 days; 0.33 mg/inf; 45 inf) to rats. **TH** mRNA was also measured in **DA** cell body regions. Relevant enzyme activities were increased significantly in all three cell body regions (ventral tegmental area **[VTA],** substantia nigra **[SN],** raphe nuclei) compared to controls, but were not changed in the terminal field regions (corpus striatum, nucleus accumbens) following **COC** treatment. TH mRNA levels were also significantly elevated in the **VTA** and **SN**. The effect of **COC** on **TH** and **TPH** activity levels was then examined in *i.v.* self-administering rats. The yoked-box paradigm was utilized. in which one animal was aiven the opportunity to self-administer **COC.** another received response-independent **COC** infusions, and a third received response-independent saline infusions. **COC** (0.33 mg/inf) was accessible for 6 hr/day over 30 days. In contrast to the effects of **COC** on **TH** and **TPH** after seven days, there was no significant change in **TH** or **TPH** activity following 30 days of **COC** administration as compared to controls. Although there was a trend toward increased TH following **COC,** it did not attain statistical significance. The lack of effect can be attributed to a number of experimental differences. The behavioral nature. of the triad paradigm produces variations in acquisition of self-administration as well as differences in the total amount of drug administered daily. As a result, individual animals can have dramatically different drug administration histories. In conclusion, although significant increases in activity and mRNA are observed at seven days, the increases are modest (ca. 50%) and may represent direct drug effects unrelated to the reinforcing effects of **COC.**

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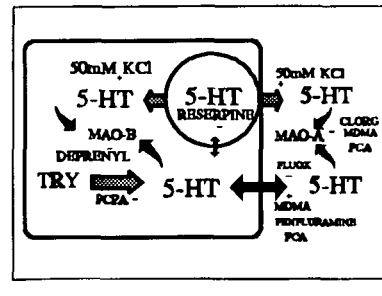
INTEGRATIVE TRANSPORTER-MEDIATED RELEEASE FROM CYTOPLASMIC AND VESICULAR 5-HT STORES IN CULTURED NEURONS

X. F. Gu and E. C. Azmitia

Substituted amphetamine, "Designer Drugs," are potent releasers of 5-HT and induce neuropathology. Paradoxically, the neurotoxicity can be blocked by drugs that interfere with both vesicular and cytoplasmic release mechanisms. In order to study this finding in greater detail, a unique system combining tissue culture of fetal raphe brainstem with HPLC-EC was used to monitor both the endogenous 5-HT levels inside and outside the neurons. Advantage was taken of the fact that Monoamine Oxidase B (MAO-B) is located inside 5-HT neurons while MAO-A exists outside. The release from vesicular stores of 5-HT is Ca^{2}+-dependent, stimulated by K+-induced depolarization and blocked by reserpine, a blocker of the transporter molecule on the vesicular membrane. Release from cytoplasmic stores of 5-HT is Na+-dependent, stimulated by substituted amphetamines and blocked by fluoxetine, a specific 5-HT uptake blocker. In acute studies (< 2 h), MDMA induced release of 5-HT from the cytoplasmic stores. This release was blocked by 10^{-7} M of fluoxetine. After long-term exposure (> 3 h), MDMA-induced release was depressed by a decrease of external Ca^{2}+ or exposure to reserpine. Evidence of integrative cytoplasmic/vesicular release was obtained by combining K^{+}- and MDMA- induced 5-HT release. In fetal cultures exposed to high K^{+} (50 mM) for 3h, MDMA-induced release of 5-HT was greatly augmented by a mechanism independent of exocytosis. This suggested that K^{+} led to a vesicular release of 5-HT into the cytoplasm. This vesicular-cytoplasmic flux was confirmed by the finding of a substantial increase in intracellular 5-HT levels when K^{+} was combined with either fluoxetine which prevented the release of cytoplasmic 5-HT or deprenyl which inhibited MAO-B activity.



In summary, 5-HT synthesized from tryptophan is stored in the vesicles. Depolarization induces release of 5-HT from the vesicular into both the cytoplasmic and extracellular spaces. Transferring of 5-HT from the vesicles into the cytoplasm also occurs when the cytoplasmic 5-HT contents are low. The released 5-HT into the extracellular space can be taken up into the cytoplasm via the 5-HT transporter. In the cytoplasm, 5-HT can be either transferred to vesicular stores or released by drugs that act on the transporter. The existence of an integrative release mechanism opens up new strategies for treating release-induced drug dependency and any subsequent toxicity.

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EXPRESSION OF A CANNABINOID RECEPTOR USING THE BACULOVIRUS SYSTEM

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The baculovirus system has been employed to express a cannabinoid receptor. A baculovirus transfer vector, used to construct a recombinant virus, was produced by inserting the coding sequence of the cannabinoid receptor cDNA from the SKR6 plasmid (Nature 1990 346:561). Co-transfection of Sf9 cells with the recombinant transfer vector and linearized wild-type baculovirus DNA (AcNPV) allowed for the production of a cannabinoid receptor recombinant virus (SKR6-AcNPV). Northern blot analysis revealed novel hyper-production of a 3.3 kb transcript in Sf9 cells infected with SKR6-AcNPV. To assess recombinant viral protein expression: Sf9 cells were infected with SKR6-AcNPV at various multiplicities of infection (MOI) and were pulsed with ^{35}S-Met. Novel protein expression was observed in SKR6-AcNPV-infected cells at multiplicities of 5 and 2.5. Transmission electron microscopy of Sf9 cells infected with SKR6-AcNPV (MOI 20) showed extensive membrane perturbation and electron-dense cytoplasmic perinuclear accumulation of receptor glycoprotein expression. Radioligand binding studies using ^{3}H CP55,940, revealed greater than 50% specific binding in crude P2 membrane preparations from SKR6-AcNPV-infected Sf9 cells. Uninfected Sf9 cells did not specifically bind CP55,940. Scatchard analysis of the saturation plot determined the Bmax to be equivalent to that observed in P2 preparations from rat brain. Antibodies produced to a fusion protein consisting of the external domain of the cannabinoid receptor and the highly immunogenic Hepatitis B core antigen (HBcAg) have been produced, immunoabsorbed with purified HBcAg, and quantitated. Positive immunofluorescent staining was obtained in SKR6-AcNPV infected Sf9 cells when the purified receptor antiserum was used. Uninfected cells did not fluoresce when exposed to purified receptor antiserum. Western immunoblotting, performed with purified antiserum, recognized two specific immunoreactive bands with relative molecular weights of 56 kD and 72 kD in SKR6-AcNPV-Sf9 cell lysates. These data suggest that the baculovirus expression system is a viable means of expressing functional cannabinoid receptor recombinant protein.

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[$^{123/125}$I]RTI-121: A SELECTIVE *IN VITRO* AND *IN VIVO* BINDING LIGAND FOR THE DOPAMINE TRANSPORTER

J. W. Boja, U. Scheffel, D. Wong, R. Dannals, E. Shaya, F. I. Carroll, A. H. Lewin, P. Abraham, and M. J. Kuhar

The cocaine analog 3ß-(4-iodophenyl)tropan-2ß-carboxyl acid isopropyl ester (RTI-121) has previously been shown to a very selective inhibitor of dopamine transporter compared to either the serotonin or norepinephrine transporters (Boja *et al.,* 1992). [^{125}I]RTI-121 bound to both a high (0.2 nM) and low (1.9 nM) sites with a density consistent with that of the dopamine transporter. The pharmacological profile demonstrated by displacement studies using 15 pM[^{125}I]RTI-121 was also consistent with the dopamine transporter. As in the striatum, [^{125}I]RTI-121 bound to both a high (0.5 nM) and low (12.1 nM) affinity sites in the frontal cerebral cortex. The number of sites was however, much lower. The pharmacological profile demonstrated by [^{125}I]RTI-121 in the frontal cerebral cortex was consistent with that of the dopamine transporter.

The *in vivo* distribution of [^{123}I]RTI-121 in mice showed highest accumulation in the striatum and olfactory tubercles (Scheffel *et al.* 1992). Significantly lower tracer concentrations were observed in other brain regions. Blocking studies also confirmed the selective labeling of the dopamine transporter. Single photon emitted computerized tomography (SPECT) images of [^{123}I]RTI-121 binding in the baboon brain indicated labeling occurred in the basal ganglia. The results of this study indicate that because of its high selectivity, specificity and affinity [$^{123/125}$I]RTI-121 is a superior ligand for the study of the dopamine transporter.

Displacement of specific binding of [^{125}I]RTI-121 (15 pM) by various uptake blockers.

Drug	Striatum IC_{50} (nM)	Frontal Cortex IC_{50} (nM)
GBR 12909	0.42	0.65
Mazindol	5.40	5.39
Benztropine	27.81	31.45
Cocaine	65.68	21.90
Nomifensine	37.52	27.88
Desipramine	205.57	115.83
Citalopram	6295.98	5384.62

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DAILY I.V. COCAINE INFUSION DECREASES *IN VIVO* [^{3}H] WIN 35,428 AUTORADIOGRAPHIC BINDING IN BEHAVIORALLY RELEVANT BRAIN AREAS FOLLOWING WITHDRAWAL

E. J. Cline, N. S. Pilotte, U. Scheffel, W. M. Mitchell, and M. J. Kuhar

Mesostriatal DA pathways are important for many of the behavioral and affective effects of cocaine. In animals, daily i.v. cocaine treatment followed by withdrawal results in neurochemical alterations in these areas consistent with decreased dopaminergic function. The purpose of this study was to assess whether regulation of cocaine recognition sites was detectible using *in viva* autoradiographic binding after daily intravenous cocaine administration, and whether any changes observed were influenced by length of cocaine withdrawal. Rats received saline or lmg/kg cocaine infusions every 12 minutes (total dose 10mg/kg) in 2 hr sessions for 10 days. After 1 or 10 days withdrawal, in vivo binding was measured 1 hr after i.v. injection of 20μCi (2.5μM/I) [^{3}H] WIN 35,428. Brains were sectioned coronally (25μm), mounted on slides, and exposed to [^{3}H] sensitive film. Areas sectioned and quantitated included subdivisions of the nucleus accumbens, caudate nucleus, midbrain, and cerebellum/pons. Adjacent sections were Nissl stained for comparison with corresponding autoradiograms. After exposure, quantitation was done with templates based on stereotaxically defined rostro-caudal brain areas. Cerebellar cortical binding (nCi/gm TE) was not affected by cocaine treatment [t(20)=0.20, p=0.842], and was subtracted from other brain areas for each animal to define non-specific binding for that animal. Analysis of data (fmol/mg TE) from controls with respect to withdrawal time showed no differences due to withdrawal [F(1,884)=0.224, p=0.64]; data from each region were then analyzed by 2-way ANOVA with respect to treatment condition and withdrawal time. Cocaine treatment caused a significant (10-36%) reduction in estimates of specific [^{3}H] WIN 35,428 binding (fmol/mg TE) in all 10 regions measured. Longer withdrawal (10 days vs. 1 day) produced significant (9-30%) decreases in nucleus accumbens, Ant CPu and P Med CPu, while Post LC binding was significantly higher (104%) in the 10 day group. 10 day cocaine treatment produced a mom pronounced decrease in binding in P Med CPu than in P Lat CPu [F(1,260)=8.86, p<0.005]. and in N Ac shell than in core [F(1,348)=1.2E2, p<0.0005].

These results demonstrate that daily i.v. cocaine produced decreases in the density of cocaine recognition sites as measured by *in vivo* QAR in behaviorally relevant brain areas. Binding was also influenced by length of withdrawal, with more pronounced effects observed after longer abstinence. Results complement other animal studies showing decreased DA levels, cell activity, and cerebral metabolic rate during cocaine withdrawal, and suggest neuroadaptive correlates to the affective syndrome experienced by abstinent human cocaine abusers.

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AFFILIATIONS: Neuroscience Branch, N.I.H./N.I.D.A. Addiction Research Center, Baltimore, MD; U.S.; Dept. of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD.

SUBSTITUTED 3ß-PHENYLTROPANE ANALOGS OF COCAINE; EFFECTS ON BEHAVIOR AND ON [^{3}H]WIN 35,428 BINDING *IN VIVO*

E. J. Cline, P. Terry, U. Scheffel, J.W. Boja, F.I. Carroll, J.L. Katz and M.J. Kuhar

It has been established that binding of cocaine to striatal dopamine transporters and the resulting inhibition of dopamine uptake is related to potency of cocaine self-administration, and to the psychomotor stimulant effects of this drug. As an extension of this relationship, cocaine, WIN 35,428 and four novel para substituted analogs with very high affinity for monoamine transporter sites in *in vitro* binding assays were examined in mice for their locomotor activating effects and for their ability to inhibit [^{3}H]WIN 35,428 binding *in vivo.* In addition, WIN 35,428, cocaine, and three of these analogs were examined in rats as substitutes for cocaine in drug discrimination testing.

In mice (n=78), the drugs produced dose dependent increases in activity, stereotypy at the highest doses, and in vivo inhibition of [^{3}H]WIN 35,428 binding (n=145). The drugs also produced dose-related increases in responding on the cocaine lever in discrimination studies (n=3-5), and decreased response rates in a manner similar to cocaine. ED_{50} values calculated for the behavioral and *in vivo* binding results revealed subtle differences in the in vivo pharmacology of the different drugs. WIN 35,428 and analogs were approximately 20-100 times more potent than cocaine in producing unconditioned locomotor behavior. Similar high potencies were observed for *in vivo* inhibition of [^{3}H]WIN 35,428 binding, and the analogs tested in the drug discrimination studies were from 6-13 times more potent than cocaine in producing cocaine-appropriate responding. Ratios of *in vitro* to *in vivo* ED_{50} values indicated slight differences among the analogs in CNS penetration and in potency in the different behavioral tests. Such slight differences in the relative potencies of these compounds may be due to pharmacokinetic factors and/or effects of the drugs on other systems that may interfere with the expression of the measured response. This remains for future investigation.

Direct comparison of i.v. activity with i.v. *in vivo* binding data for the Cl^- analog (RTI-31) indicated that at doses of RTI-31 producing significant locomotor activation (2-3 µmol/kg), near 100% striatal transporter occupancy was necessary for this effect. This parallel of the relationship between in vitro structure activity studies in striatal tissue and behavioral effects of cocaine-like drugs underscores the importance of this relationship between binding and behavior in understanding how cocaine exerts its effects.

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THE EFFECT OF ASSOCIATION RATE ON OPIATE EFFICACIES

L. Toll

Primary goals in opiate research are the discovery of analgesics with lower abuse potential, and the development of potential treatment compounds for opiate narcotic abuse. The partial agonist buprenorphine has shown some usefulness for these purposes, suggesting that the addiction liability and effectiveness as a treatment compound may be dependent upon the intrinsic activity, or efficacy, of the compound in question. The efficacy of opiates can be defined as activity at a certain receptor occupancy. We have used the μ and d-receptor containing neuroblastoma cell line SH-SY5Y as a model system in which we can measure both activity (inhibition of cAMP accumulation) and binding affinity in intact cells (from which we can determine occupancy). From these values relative efficacy can be defined as $K_{i(binding}/IC_{50(activity)}$. Preliminary experiments indicated that activation of both μ and d receptors effectively decreased forskolin-stimulated cAMP accumulation in intact cells. Activity at μ receptors could be measured independent of d receptors if experiments were conducted in the presence of 5 μM of the d-antagonist ICI 174,864.

For initial experiments Ki values were determined from equilibrium binding experiments using a 1 h incubation. cAMP accumulation is measured in the linear portion of the curve, for this we used a 10 min incubation. Surprisingly, the order of efficacy at μ receptors for a series of opiates went DAMGO > morphine > etorphine > EKC > buprenorphine. This suggested that perhaps binding affinities derived at equilibrium did not give an accurate indication of occupancy during the activity measurement. Additional binding studies were then carried out for short times to determine affinities prior to equilibrium association or potential receptor desensitization. With short incubations, the apparent affinity of morphine increased slightly, while the apparent affinities of DAMGO, etornhine, and buprenorphine decreased significantly. Using non-equilibrium (10 min) incubation for binding K_i cannot be determined, but efficacy can be defined as $IC_{50(binding)}/IC_{50(activity)}$. Under these conditions, the order of efficacy became DAMGO > etorphine > morphine > EKC > buprenorphine. From these data we can calculate that approximately 9% of the μ receptors must be occupied for DAMGO to elicit a 50% maximal response. These studies also showed that the association and dissociation rates of the opiate can affect the $IC_{50(binding}/IC_{50(activity)}$ ratio, and may be factors in drug efficacy.

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EFFECT OF INTRA-ACCUMBENS ß-FNA ON *IN SITU* OPIOID BINDING

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The exact localization of the effects of reversible antagonists injected into small brain regions is difficult to determine due to the reversible nature of their effects. ß-funaltrexamine (ß-FNA) offers an advantage in that its effects on opiate receptors are irreversible and can be quantitated in vitro following in vivo administration. This study was undertaken to determine the anatomical specificity of µ-opioid receptor alkylation following administration of ß-FNA into the nucleus accumbens. Male, Fischer 344 rats (250-300g) were administered 0, .05, .25, 1.25 or 2.5 nmol of ß-FNA in 1 µl of artificial CSF unilaterally into the centromedial nucleus accumbens through a guide cannula. The animals were sacrificed 24 hr later and [3H]DAMGO binding was assessed in 20 µm slide-mounted sections. Following preincubation for 40 min in buffer (50 mM Tris.HCl, pH 7.4) at room temperature, adjacent sections were incubated for 150 min at 25°C in 2 nM [3H]DAMGO to assess µ-opioid receptor density. Nonspecific binding was determined in the presence of 1 µM DAMGO. Following a 2 minute wash in ice-cold buffer. sections were dried with cool, dry air and apposed to tritium-sensitive film for 9 weeks with tritiated standards. The side contralateral to the injection serves as control. Quantification of the autoradiograms was accomplished with computer-assisted densitometry.

Microinjection of artificial CSF into the nucleus accumbens was found to have no effect in any region. The effects of ß-FNA on [3H]DAMGO binding are summarized in the table below as %decrease in control binding (mean (s.d.)) from at least 3 animals.

REGION OF ACCUMBENS	ROSTRAL FROM BREGMA (mm)	ß-FNA (nmol) 0.05	0.25	1.25	2.50
ANTERIOR	2.7	71 (12.7)	74 (5.8)	51 (10)	76 (0.8)
	2.2	48 (7.9)	46 (17.0)	30 (3.8)	78 (8.6)
SHELL	1.7	25 (7.7)	24 (7.2)	52 (15.1)	69 (6.6)
	1.2	17 (1.0)	23 (9.7)	64 (19.0)	60 (8.4)
	0.7	14 (4:0)	15 (5.8)	64 (14.0)	32 (8.4)
CORE	1.7	27 (15.3)	30 (2.3)	20 (7.1)	76 (19)
	1.2	23 (1.7)	18 (5.8)	12 (10.5)	23 (4.4)
	0.7	11 (10.1)	14 (6.2)	11 (15.0)	17 (22.0)

[3H]DAMGO binding to regions in close proximity to the accumbens, such as the medial prefrontal cortex and caudate putamen, was not affected by ß-FNA administration. This procedure should be useful in assessing the involvement of µ-opioid receptors within the nucleus accumbens in drug reinforcement mechanisms.

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ENHANCED SENSITIVITY TO NALTREXONE IS ASSOCIATED WITH CHANGES IN THE NUMBER OF MU AND DELTA OPIOID RECEPTORS IN RAT BRAIN

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Enhanced sensitivity to some of the behavioral effects of the opioid antagonist naltrexone (NTX) develops following once-weekly injections of cumulative doses of the drug. Rats treated with this regimen of NTX injections show enhanced sensitivity to the operant response rate decreasing effects of NTX. Enhanced sensitivity to NTX has also been observed for NTX-induced salivation. The enhanced sensitivity observed on operant responding is long-lasting and appears to be produced through conditioning, where the higher doses of NTX serve as the unconditioned stimulus and the lower doses serve as the conditioned stimulus. The enhanced sensitivity observed on salivation is also long-lasting and probably produced through conditioning processes. We have conducted saturation binding assays to determine the number and affinity of μ and ∂ opioid receptors in cortical, midbrain and hindbrain membrane preparations from Long-Evans rats treated once weekly for 8 weeks with cumulative doses of the drug (1, 3, 10, 30 and 100 mg/kg). ^{3}H-DAMGO (0.5 - 21 nM) and ^{3}H-pCl-DPDPE (0.04 - 4 nM) were used to characterize μ and ∂ receptors, respectively. NTX treatment bad no effect on ^{3}H-DAMGO binding in cortex, but decreased binding in midbrain and increased binding in hindbrain. Saturation analyses revealed that these differences reflected changes in the number, but not the affinity of μ receptors (Table I). NTX treatment also increased the amount of ^{3}H-pCl-DPDPE bound to ∂ receptors in midbrain and hindbrain, but not in cortex (Table II). Again, these changes were due to changes in the number of receptors. Thus, the repeated administration of NTX differentially affects the number of μ and ∂ opioid receptors in various brain regions.

Table I. Scatchard analvses of the binding of 0.5 - 21 nM ^{3}H-DAMGO to μ opioid receptors after saline or NTX treatment

REGION	TREATMENT	K_D	B_{MAX}
Cortex	Saline	2.02 ± 0.29	56.4 ± 8.5
	Naltrexone	1.77 ± 0.12	54.7 ± 4.0
Midbrain	Saline	2.51 ± 0.03	226.0 ± 17.7
	Naltrexone*	2.93 ± 0.30	185.4 ± 7.7
Hindbrain	Saline	2.06 ± 0.43	112.9 ± 8.9
	Naltrexone*	2.83 ± 0.20	175.7 ± 8.2

Table II. Scatchard analyses of the binding of 0.04 - 4 nM ^{3}H-pCl-DPDPE to ∂ opiod receptors after saline or NTX treatment.

REGION	TREATMENT	K_D	B_{MAX}
Cortex	Saline	0.78 ± 0.07	99.5 ± 7.1
	Naltrexone	0.79 ± 0.09	100.4 ± 6.0
Midbrain	Saline	1.43 ± 0.03	78.8 ± 4.8
	Naltrexone*	1.48 ± 0.11	96.9 ± 13.3
Hindbrain	Saline	1.11 ± 0.05	72.9 ± 6.8
	Naltrexone*	1.30 ± 0.22	89.0 ± 13.4

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BINDING CHARACTERISTICS OF THE NOVEL HIGHLY SELECTIVE DELTA ANTAGONIST [^{3}H]H-TYR-TIC-PHE-PHE-OH

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The recently discovered highly specific tetrapeptide delta opioid antagonist H-Tyr-Tic-Phe-Phe-OH (TIPP) [1] was radiolabelled by catalytic tritiation of its precursor [Tyr(3',5'-I_2)^1]TIPP. The specific radioactivity of purified [^{3}H]TIPP was 50.6 Ci/mmol. The tritiated ligand labelled Wistar rat brain membranes as a one site model with a B_{max} of 82.4 fmol/mg protein and a K_d of 0.64 nM. The kinetic experiments revealed an association on-rate (k_{+1}) of $8.53x10^{+6}sec^{-1}.M^{-1}$ and a dissociation off-rate (k_{-1}) of $1.53x10^{-3}sec^{-1}$. The equilibrium constant (K_d) was calculated to be 0.18 nM with the steady state being reached within 15 min using 0.5 nM [^{3}H]TIPP at 25°C. The ligand had less than 30% nonspecific binding and showed stereo-specificity towards the enantiomers levorphanol and dextrorphan which exhibited Ki values of 5.8 and > 10000 nM, respectively. Its high selectivity was demonstrated in competition studies with unlabelled subtype specific opioid ligands which showed a rank order of potencies of delta>>mu>kappa. The delta/mu and delta/kappa selectivity ratios [2] were 600 and 9100 nM, respectively. The extraordinary delta selectivity of [^{3}H]TIPP indicates that this new radioligand may find use as an excellent tool for the investigation of delta opioid receptors in vitro and *in vivo*.

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THE KAPPA OPIOID RECEPTOR EXPRESSED ON THE R1.1 THYMOMA CELL LINE CONTAINS A SULFHYDRYL GROUP AT THE BINDING SITE

D. B. Joseph and J. M. Bidlack

The sensitivity of opioid binding to disulfide bond-reducing reagents and sulfhydryl-alkylating reagents has been reported in studies on neuronal opioid receptors. Studies from this laboratory have shown that the murine thymoma cell line R1.1 expresses a single class of κ opioid receptors (Bidlack *et al.,* 1992). Because the opioid receptor expressed by R1.1 cells has characteristics similar to those of neuronal opioid receptors, studies were performed, to determine if disulfide bonds or sulfhydryl groups are present at the opioid binding site on R1.1 cell membranes. The binding of 50 μM of the κ agonist (-) [^{3}H] bremazocine to R1.1 cell-membranes was unaffected in the presence of 1-130 mM dithiothreitol, a disulfide bond-reducing reagent. In contrast, treatment of membranes with the sulfhydryl-alkylating reagent N-ethylmaleimide (NEM) at 24°C followed by washing resulted in a time-dependent reduction in (-)[^{3}H]bremazocine binding. The concentration-dependence of NEM inhibition of (-)[^{3}H]bremazocine binding was demonstrated in membranes treated with 0.04-10 mM NEM for 10 min. in which binding was reduced by as much as 90% (IC_{50} = 0.76 mM). To determine the mechanism by which NEM reduced (-)[^{3}H]bremazocine binding, saturation binding experiments were performed using untreated and NEM-treated R1.1 cell membranes. The K_d value for (-)[^{3}H]bremazocine was unaffected by treatment of membranes with 1 mM NEM (18.0 ± 1.2 and 18.8 ± 0.5 pM for untreated and NEM-treated membranes, respectively). In contrast, the B_{max} value for κ opioid binding was reduced by almost 50% in NEM treated membranes compared to that of untreated membranes (125 ± 7.8 and 64 ± 3.9 fmol/mg of protein for untreated and NEM-treated membranes, respectively). Since the saturation binding data suggested that NEM alkylates the κ opioid receptor at the binding site, NEM-induced reduction of (-) [^{3}H]bremazocine binding was measured in R1.1 cell membranes pretreated with 1 μM of opioids selective for μ, δ, and κ receptors. The κ-selective opioids U50,488 and U69,593, and the nonselective opioid morphine protected against NEM inhibition of (-) [^{3}H]bremazocine binding, whereas pretreatment with either the p-selective peptide DAMGO or the δ-selective peptide ICI 174,864 was less effective at protecting the κ binding site. The results indicate that the binding site of the κ opioid receptor on R1.1 cell membranes contains a sulfhydryl group(s) and has a minimal requirement for disulfide bonds.

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MICRODIALYSIS AND BEHAVIORAL EVIDENCE OF THE FUNCTIONAL ANTAGONISM OF COCAINE BY THE KAPPA AGONIST U50488

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Recent research has shown that the selective kappa agonist, U50488, produces a decrease in dopamine (DA) levels in the nucleus accumbens. The goal of the present study was to determine the effect of U50488 on cocaine's ability to increase DA in the nucleus accumbens. U50488's effect on cocaine-induced locomotor activity was also assessed. Both experiments used male Sprague-Dawley rats. DA concentrations in the nucleus accumbens were determined using *in vivo* micro dialysis. Anesthetized rats were implanted with a probe in the right nucleus accumbens. Probes were continuously perfused with ringer's solution at 1ul/min and 22 ul fractions were collected. Three baseline fractions were collected and rats were then injected s.c. with U50488 (10 mg/kg) or saline. Three additional fractions were collected and all rats were then injected i.p. with cocaine (10 mg/kg). Four fractions were collected after the cocaine injection. Data was analyzed as a percent of the first baseline fraction. U50488 decreased DA concentrations compared to baseline values and attenuated the increase in DA induced by cocaine. In the behavioral experiment. locomotor activity was assessed in photobeam chambers. Activity was monitored in ten minute blocks. All rats were habituated to the chambers for 30 minutes and then injected with U50488 (5 mg/kg) or saline. Activity was assessed for 1 hour and the all rats were injected with cocaine (10 mg/kg). Activity was then measured for 1 hour. U50488 did not alter activity levels when compared to saline in the first hour of testing but did attenuate the increase in activity stimulated by cocaine. These data suggest that kappa agonists may be functional antagonist of cocaine, however, it remains to be seen in the subjective effects of humans would also be antagonized.

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DYNORPHIN A_{1-13} ADMINISTRATION CAUSES ELEVATION OF SERUM LEVELS OF PROLACTIN IN HUMAN SUBJECTS

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

Dynorphin A_{1-13} is a natural sequence shortened form of the kappa receptor-preferring opioid peptide Dyn A_{1-17}, one of two peptides initially processed from the single gene product preprodynorphin. The hypothesis addressed in this study is that dynorphin. by acting directly or indirectly to lower dopaminergic tone, which tonically inhibits prolactin release, may cause elevation of serum levels of prolactin in human subjects. Ten volunteer male subjects, ages 22-53, were studied: 5 normal healthy volunteers; 2 well stabilized methadone maintained (MM) former heroin addicts; and 3 MM patients with on-going cocaine dependency. All were studied in an NIH-GCRC in-patient unit after overnight stabilization. Thirty minutes prior to study, an intravenous indwelling cannula was placed for administration of Dyn A_{1-13} and for obtaining blood specimens. After obtaining baseline specimens, Dyn A_{1-13} 120 µg/kg was administered to 10 subjects, and on a separate study day, Dyn A_{1-13} 500 µg/kg was administered to 9 of these subjects. Multiple blood specimens for determination of serum prolactin levels by radioimmunoassay techniques were obtained over the next 6 hours. Baseline prolactin levels were (m±SEM) 4.5 ± 0.8 ng/ml and 5.5 ± 0.8 ng/ml in the low and high dose groups, respectively. Prolactin levels rose briskly in all subjects, with peak levels reached at 10 to 20 minutes in the low dose group (15.0 ± 1.8 and 11.2 ± 1.3 ng/ml) and at 10 to 30 minutes in the high dose group (16.9 ± 2.5 and 13.8 ± 2.0 ng/ml). This Dyn A_{1-13} effect on serum prolactin levels was statistically significant ($p<.001$). Since other recent studies from our group (J. Chou. M.J. Kreek, and B. Chait, 1993) have shown that Dyn A_{1-13} is rapidly processed in human blood *ex vivo* to Dyn A_{1-12}, $_{2-12}$, and $_{2-11}$, with minor products, Dyn A_{3-12} and $_{1-6}$, any of these opioid or non-opioid peptides may contribute to prolactin release. A role for dynorphin peptides in modulation of prolactin release in normal and abnormal physiology is suggested by these studies.

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USE OF A MODEL SYSTEM DERIVED FROM HUMAN TISSUE TO INVESTIGATE CHRONIC EFFECTS OF OPIOIDS

M. S. Ahmed, B. Cemerikic, and R. Zamah

In vivo investigations of the effects of chronic opioids use/abuse during pregnancy indicate adverse perinatal and neonatal outcome. These investigations are often criticized for lack of controlled experimental conditions, such as drug dose, duration and frequency of its administration and poly drug use by the patients.

Human placenta is responsible for fetal growth and development during gestation, and use/abuse of opioids during pregnancy can affect its functions. Opioid receptors and peptides regulate the secretion of trophoblast specific hormones human chorionic gonadotropin (hCG) and human placental lactogen (hPL) and the release of acetylcholine. Placentas obtained from abusers of talwin and patients enrolled in a methadone program have lower to undetectable levels of opioid receptors, which was accompanied in the later group by loss of tissue responsiveness to the regulatory action of opioidligands on acetycholine and hCG release, These findings were explained by receptor down regulation/desensitization due to opioids use-during pregnancy.

We report here on the use of explant culture technique of term trophoblast tissue as a model system to investigate the effects of chronic opioid administration on placental kappa receptors and their regulation of hCG release. Tissue viabilitv was monitored during a 6 hay culture period by glucose consumption, lactate dehydrogenase activity and secretion of hCG and hPL (specific markers of trophoblast functional integrity). Results obtained demonstrated that explants retain fully their viability during the first four days, followed by a decline on the fifth and sixth days of culture. Treatment with 1 μM methadone-did not significantly affect tissue viability but changed placental kappa receptors binding properties and mediated responses. In post-partum tissue, kappa receptor has a single high affinity binding site for bremazocine (Kd 0.07 ± 0.02 nM) and kappa selective agonist U-69.593 and antagonist nor-BNI are most effective on hCG release at concentration of 10%. Opioid receptors exhibited 2 binding sites for bremazocine after 24 and 48 of methadone treatment as well as in control tissue. The affinitv for bremazocine decreased (Kd_1 0.17 and Kd_2 23nM) and the number of low affinity binding sites increased in treated tissue but not in control explants. In addition, a 100 fold shift to the right in the concentration response curve of U-69,593 on hCG release from treated tissue, but not control, was observed after 48 hours. Subsequent incubation of 48 h treated tissue in control medium restored its responsiveness to opioids.

Data obtained suggest that: (1) explant culture of trophoblast tissue can be used to investigate the effects of chronic administration of a defined dose of an opioid on kappa receptors and their mediated response(s); (2) chronic in vitro methadone administration affects placental opioid receptors binding properties and their mediated response in a manner similar to that reported for the effect of *in vivo* methadone use.

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MECHANISMS OF OPIOID RECEPTOR-G-PROTEIN-ADENYLYL CYCLASE SIGNAL TRANSDUCTION IN NG108-15 CELL MEMBRANES

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The G-proteins G_s and G_i regulate adenylyl cyclase (AC) activity positively and negatively, respectively. Opioid receptors of the δ type in NG108-15 cell membranes inhibit AC through a G-protein mechanism. Previous studies have revealed that low pH pretreatment of NG108-15 cell membranes produces the following modifications of this signaling pathway: 1) increased inhibition of basal AC by G_i-coupled receptors; 2) increased inhibition of opioid agonist binding by sodium and guanine nucleotides; and 3) decreased stimulation of AC by G_s. The mechanism of action by which this pretreatment increased receptor-mediated inhibition of AC was investigated. The efficacy of the δ opioid agonist DSLET in inhibiting basal AC activity was increased in low pH-pretreated membranes, with no change in the potency of the agonist. Stimulation of receptor-coupled low K_m GTPase by DSLET was not significantly different between control and low pH pretreated membranes. However, the absolute level of basal and DSLET-stimulated low K_m, GTPase activity was decreased by low pH pretreatment. Michaelis-Menten plots indicated that the V_{max} of low K_m GTPase was decreased in low pH pretreated membranes, whereas the K_m for GTP was unchanged. Since there was no change in the level of G-protein immunoreactivity in western blots from control and low pH pretreated membranes, this decrease in V_{max} was due to decreased hydrolysis of GTP by G-proteins. Thus, the increased efficacy of receptor-mediated inhibition of AC by low pH pretreatment appeared to involve decreased GTP hydrolysis by G_i subsequent to its activation by the nucleotide. This hypothesis was supported by concentration-effect curves for GTP in supporting DSLET-induced inhibition of AC, which showed that inhibition of AC by DSLET was increased by low pH pretreatment only at GTP concentrations $\geq$ the K_m for GTP hydrolysis by low K_m GTPase. These results indicate that the efficacy of a receptor-mediated event can be modulated by alterations in the inactivation rate of the G protein to which the receptor is coupled.

Receptor-mediated inhibition of forskolin- and PGE_1 (PGE)-stimulated AC was also increased by low pH pretreatment. Unlike receptor-mediated inhibition of AC, however, inhibition of 1 μM PGE-stimulated activity by the nonhydrolyzable GTP analogue, Gpp(NH)p, was decreased by low pH pretreatment. Moreover, Gpp(NH)p did not inhibit basal AC in control or low pH pretreated membranes. Concentration-effect curves for PGE-stimulation of AC revealed that the magnitude of Gpp(NH)p-induced inhibition increased with increasing PGE concentrations, suggesting that Gpp(NH)p inhibits only G_s-stimulated AC. Thus, the low pH pretreatment-induced decrease in Gpp(NH)p-inhibition of PGE-stimulated AC corresponded to the inhibitory effect of the pretreatment on the magnitude of AC stimulation by PGE. These results indicate that receptor-coupled G_i inhibits AC by a different mechanism than does direct activation of G_i by Gpp(NH)p. The former may involve both direct inhibition of AC by G_i a and shut-down of G_s α by liberation of ßγ units, while the latter may involve the liberation of ßγ units exclusively (Gilman model). These studies exemplify the usefulness of low pH pretreatment as a tool to investigate the mechanisms of G protein mediated signal transduction.

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REVERSAL OF PRENATAL COCAINE-INDUCED MICROENCEPHALY BY POSTNATAL 5-HT-1A TREATMENT

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Cocaine has been shown to be a neurobehavioral teratogen in both laboratory and clinical studies. Clinically, the most frequently reported abnormality has been intrauterine brain growth retardation. In animal studies, prenatal exposure to cocaine has been shown to disrupt the development of the cerebral cortex, retard the serotonin (5-HT) innervation of the forebrain. and impair gliogenesis and glial differentiation. 5-HT has been shown to regulate the availability S-100ß, a glial derived cortical growth factor, which is released upon activation of the 5-HT_{1A} receptor. The microcephaly reported clinically may be due therefore to the reduced availability of S-100ß. In the present study, we examined the distribution of S-100 containing glial cells in the hippocampus and cerebral cortex in the rat following in utero cocaine exposure to see if cocaine exposure results in a change in this growth factor. In addition, the potential therapeutic benefits of ipsapirone, a 5-HT_{1A} agonist, were tested in cocaine-exposed animals.

Pregnant dams were given either cocaine (40 mg/kg) or saline from embryonic day 13 to parturition. Litters were culled to eight pups/litter at birth and each litter divided into two groups. One group in each litter received 1 mg/kg ipsapirone from postnatal day (P) 1 through P5 while the other group received an equivalent volume of saline. On P7, body and brain weights were recorded and S-100 containing glia were identified immunohistochemically. Significant somatic ($P<0.005$) and brain ($P<0.01$) growth retardations were seen in cocaine-exposed pups when compared to saline pups. Ipsapirone administration to cocaine-exposed pups increased both body and brain weights to levels comparable to or higher than saline/saline (SS) treated animals. Anatomically, dramatic differences in the number and distribution of S-100 immunoreactive (IR) glia in the hippocampus and subplate region of the cortex were was reduced in the granule cell layer and hilus of the dentate gyrus, and S-100 IR intensity and glial fiber outgrowth were decreased in the CA1 region of the hippocampus. In the cerebral cortex, a prominent band of S-100 IR cells was seen at the inferior cortical border in SS but not CS rats, indicating an arrest of glial migration from the subplate zone. These cocaine-induced glial abnormalities were also reversed by ipsapirone treatment. Our results indicate that the microcephaly associated with prenatal exposure to cocaine may be due to the diminished availability of the trophic factor S-100ß, and that the microcephaly associated with cocaine may be combated with the use of 5-HT_{1A} agonists which enhance glial maturation and S-100 trophic activity.

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TRANSDUCTION MECHANISMS INVOLVED IN THE SYNERGISM BETWEEN THE CANNABINOIDS AND OPIATES IN THE SPINAL CORD

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We have previously shown that the combination of cannabinoids (i.t.) and morphine (i.t.) produces a greater than additive antinociceptive effect. However, these same cannabinoids produce only an additive antinociceptive effect when administered with morphine icv. Pretreatment of mice with Δ^9-THC (6.25 µg/mouse i.t.) results in a 10-fold parallel shift to the left of the morphine dose response curve. CP55,940 (i.t.) does not shift the morphine dose response curve to the left but does produce a parallel leftward shift of the morphine dose response curve when administered icv. Pretreatment of mice with naloxone failed to block the antinociception of Δ^9-THC, indicating that Δ^9-THC probably does not have a direct interaction at the opiate receptor. However, naloxone does block the antinociception produced by the combination of intrathecally administered Δ^9-THC (6.25 µg/mouse) and morphine. Since both the cannabinoids and morphine modulate $[Ca^{++}]i$, we have investigated the effects of the combination of cannabinoids and morphine on depolarized induced rises in $[Ca^{++}]i$ in the brain and spinal cord in order to determine if $[Ca^{++}]i$ is a mediator through which the cannabinoids enhance morphine-induced antinociception. We have shown that opiate- and cannabinoid-induced antinociception is blocked by K^+ channel blockers. In mouse brain synaptosomes the combination of Δ^9-THC (10^{-6}M) and morphine (10^{-8}M) failed to block depolarized induced rises in $[Ca^{++}]i$. However, inactive concentrations of CP55,940 (10^{-10}M) and morphine (10^{-10}M) in combination inhibit κCl-induced rises in $[Ca^{++}]i$. The inhibition is reversed by administration of naloxone (10^{-5}M). In the spinal cord, the combination of Δ^9-THC (10^{-7}M) and morphine (10^{-8}M) as well as CP55,940 (10^{-10}M) in combination with morphine (10^{-8}M), attenuates κCl-induced rises in $[Ca^{++}]i$. We also examined the interaction of the cannabinoids with K^+ channels. The antinociception of some of the cannabinoids is attenuated by apamin, a blocker of Ca^{++}-gated K^+ channels but not by charybdotoxin, also a blocker of Ca^{++}-gated κ^+ channels. Similarly, the antinociception produced by the combination of Δ^9-THC (i.t.) and morphine (i.t.) is attenuated by apamin (0.01 mg/mouse). but not by charybdotoxin (2.5 ng/mouse).

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COCAINE LEVELS IN MOTHER AND INFANT HAIR: CORRELATIONS WITH LEVELS IN URINE AND SELF-REPORT

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The hair of 111 infants and their mothers, who had used crack cocaine while pregnant, were collected during the post-partum period before random assignment to drug treatment; mean infant age was 103 days at sampling. Maternal urine was screened for cocaine and metabolites; three drug use self-report measures were also collected. Normalizing square-root or log transformations of all hair and urine data (respectively) preceded analyses.

A good initial correlation of mother and infant hair ($r=.52$, $N=111$, $P<.0005$) was found which could be further strengthened ($r=.63$, $N=35$, $P<.0005$) by excluding samples previously flagged by technicians as in poor condition. A correlation of this magnitude means that cocaine levels in the mother's hair represents 40% of the variability in infant hair cocaine (or vice versa). Virtually all (98%) mothers had cocaine in their hair, only slightly fewer (95%) infants did. The levels of maternal urine benzoylecgonine (measured by GC MS) correlated with cocaine in undamaged maternal hair (measured by RIA; $r=45$, $N=45$, $P=.001$). The correlation was weaker when hair samples were not selected for cases in good condition ($r=.32$, $N=136$, $P<.0005$). When using maternal hair as an index criterion of infant exposure, since it has the highest sensitivity, the rate of false negatives are 72% for urine cocaine, 27% for urine benzoylecognine, and 19% for recent self-report. The self-report cocaine measure taken from the ASI and representing the past 30 days of use has a significant full scale correlation with urine benzoylecognine ($r=.27$ $N=131$, $P=.001$) levels, and was weakly correlated with maternal hair cocaine ($r=.17$, $N=136$, $P<.02$). Other self-report measures covering a longer timebase (average regular use and lifetime use) failed to correlate with either urine or hair. This finding can be viewed as endorsing the practice adopted by the ASI of not requesting *quantitative* self-reports about drug use more than one month past. On the other hand, the past thirty days of self-report can be used as a fairly reliable treatment outcome variable if is calculated as *within-subject* change (change relative to one's own baseline), making it is a more accurate index (referenced to hair). The post-intervention change in self-reported use (eight months after the first 30-day self report) correlates well with a variable calculated on the basis of change in hair cocaine ($r=.54$, $N=59$, $P<.0005$) eight months after a basal sample.

Using hair cocaine change as a dependent variable in a stepwise multiple regression of predictors of improvement has shown the usual factors *(e.g.,* higher self-esteem, improved family environment, less legal trouble, and having lower entry scores on some Axis II scales) to be predictive of hair cocaine decline over time in the project. No cocaine use measures, neither analytic nor subjective, predicted survival/dropout in the research program over time. This finding suggests that magnitude of drug use at entry (within a high-using population) is not necessarily a barrier to programming. It is important to consider that passive exposure to environmental smoke may elevate hair-cocaine levels, an effect which may increase false positives *(e.g.,* lower the specificity) of the hair analysis procedure. With that caution in mind, it can be concluded that these results lend conditional support to quantitative validity of hair testing for cocaine both as an infant-exposure and treatment outcome measure.

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RELATIONSHIP OF MATERNAL SUBSTANCE ABUSE TO SUBSEQUENT SUDDEN INFANT DEATH SYNDROME IN OFFSPRING

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Between 1979 and 1989, 1760 cases of Sudden Infant Death Syndrome (SIDS) were identified from a population of over 1.2 million infants born in New York City (rate 1.45/1000 births). Using birth certificate data from the New York City Department of Health and records from the New York City Information and Counseling Program for Sudden Infant Death, the SIDS rate in drug-exposed infants was found to be 5.83/1000, compared to 1.39/1000 in those infants who were not drug-exposed (risk ratio 4.19, $p<.001$). In each mutually exclusive drug group of opiates and cocaine, the SIDS rate was higher than the rate in the general population ($p<.01$). Controlling for known associated high risk variables (race/ethnicity, teen mother, parity, maternal smoking, low birth weight), the risk ratio for SIDS in each drug group was higher compared to the general population (methadone 3.6, heroin 2.3, methadone and heroin 3.2, cocaine 1.6, cocaine and opiates 1.1). Although higher rates of SIDS were associated with maternal opiate use than with maternal cocaine use over the entire decade, the largest rate increase in SIDS during the latter part of the 1980s was seen in cocaine-exposed infants. suggesting that "crack" cocaine may be linked to these increasing rates.

Declines in the overall rate of SIDS during the decade were observed for both the drug-exposed (11.28/1000 to 4.09/1000) and non-exposed (1.70/1000 to 1.05/1000) groups ($p<.001$). Differences in rates of SIDS between major racial-ethnic groups in non-exposed infants (white 0.57/1000, black 2.40/1000, Hispanic 1.18/1000) ($p<.001$) were not apparent if the mothers used drugs during pregnancy (white 5.74/1000, black 5.73/1000, Hispanic 4.93/1000). No differences were found in the seasonal pattern of SIDS deaths between the drug-exposed and non-exposed groups. Seventy-two percent of the drug-exposed SIDS deaths and 71% of the non-exposed SIDS deaths occurred between one and four months of age.

Although SIDS is the leading cause of death in the United States between one month and one year of age, its etiology (etiologies) remains mysterious. Intrauterine exposure to opiates increases the risk of subsequent SIDS in infancy about threefold, while exposure to cocaine is associated with a less impressive increase in the rate of SIDS. The common characteristics shared by drug-exposed and non-exposed infants who die of SIDS suggest that drug-associated SIDS may provide clues in the search for the cause, or causes of SIDS.

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PERINATAL OUTCOME OF INFANTS BORN TO WOMEN IN TREATMENT: DIFFERENCES ACCORDING TO MATERNAL DRUG OF ABUSE

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This ongoing study investigating the effects of prenatal drug exposure reports perinatal outcomes for 201 newborns. All mothers were enrolled in Family Center, a comprehensive treatment program for pregnant drug dependent women. Infant data were analyzed according to maternal drug use: Group 1 *(n*=48) opiate users maintained on methadone; Group 2 *(n*=68) opiate/cocaine users; Group 3 *(n*=41) cocaine users; Group 4 *(n*=44) cocaine users who remained drug free after their enrollment in the treatment program. There was no difference in EGA between groups. Sixty-nine-percent of the infants were full term. Mean birthweight for term infants was 3005 gms; for preterms 2184 gms. Infants' birthweight differed as a function of maternal drug use (F=3.899; *p*=.01) Tukey post hoc multiple comparison revealed differences between Groups 2 & 3. There was a trend at *p*=.052 but no significant difference in head circumference between groups. Preterm infants did not differ in birthweight, length or head circumference as a function of maternal drug use. There were no differences in SGA as a function of term, but SGA did differ significantly as a function of drug group X^2=6.49; *p*=<.05) with most of the SGA infants born to women in the opiate using groups. Groups differed in length of hospital stay *(p*=<.001 on the Kruskal Wallis); x length of stay for Groups 1, 2 was 16 days; x length of stay for Groups 3, 4 was 6 days. However, there was no difference between groups for length of stay for preterm infants; x length of stay across groups was 25 days. These data suggest several implications: 1) the favorable perinatal outcomes of the majority of infants born to women in treatment; 2) the importance of maternal drug use and term status when evaluating perinatal outcome.

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PSYCHOLOGICAL PROFILE OF PREGNANT WOMEN WHO ABUSE COCAINE, ALCOHOL, AND OTHER DRUGS

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Pregnant women who abused cocaine, alcohol, and other drugs, and who were clients of the child protective services system were referred to an outpatient program providing home- and center-based support. At the time of enrollment, a battery of psychological tests were administered, including the Adult Attachment Interview, Family Violence Questionnaire, the Millon Clinical Multiaxial Inventory, and the Addiction Severity Index. To date, 145 women have been assessed. Their mean age is 28.2 years. All of the women reported alcohol use, and most (96%) reported use of cocaine. Seventy-eight percent reported smoking tobacco. With respect to other substances of abuse, 74% indicated marijuana use, 35% reported use of hallucinogenic drugs, 23% reported use of opiates, 21% reported use of barbiturates, and 18% reported use of amphetamines. Preliminary analyses indicate that the majority (70%) reported histories of physical and/or sexual abuse, 42% reported abuse of alcohol and/or other drugs in the family of origin, and 78% reported having been beaten and/or raped. Moreover, 14% reported loss of a parent during childhood either through death or complete lack of contact. On the Millon, all of the women, without exception, described themselves as having symptoms of serious psychological disorders, including paranoid ideation, thought disorder, depression, and anxiety, in addition to alcohol and/or other drug abuse. Years of drug use (mean=5.7) was associated with severity of psychiatric problems, and women with more severe psychiatric problems had more children. The average profile of scores did not fit depression as a clinical diagnosis because of increased scores in paranoia and delusional thinking. It is likely that both the women's traumatic life experiences and their chronic, acute, and ongoing abuse of cocaine and other substances have contributed to their current psychological distress. These findings highlight the need for mental health services as part of a comprehensive supportive services program.

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QUANTITATION OF SPONTANEOUS AND PROTRACTED MORPHINE ABSTINENCE IN RATS USING RADIOTELEMETRY MONITORING

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The acute withdrawal phase following opiate addiction can often be controlled pharmacologically. Despite strong preventative efforts, a high degree of relapse to drug taking occurs after detoxification. This secondary period of vulnerability is mediated to varying degrees by what has been termed protracted withdrawal. Conditioning appears to play a role in this phenomenon since in most cases, when ex-addicts return to their usual environment - once conditioned signs are experienced – drug seeking behavior is resumed. Our studies have indicated that in addition to the characteristic signs of morphine withdrawal in rats, the withdrawal-associated increase in blood pressure (BP) and heart rate (HR) provide an objective measure of the intensity of abstinence. Rats were made dependent upon morphine using a chronic i.v. infusion schedule of increasing concentrations of morphine over five days. During this time, rats were constantly exposed to specific olfactory, visual and sensory stimuli. Abstinence-induced cardiovascular and behavioral symptoms were recorded via radiotelemetry (catheter implanted in the iliac artery) and through automated measurement of locomotor activity. At this time, rats were freely moving in an open field which was apart from the conditioning stimuli. MAP, HR locomotor activity, and stereotypy were measured automatically, and withdrawal body shakes ("wet-doe shakes") were counted visually. The data were collapsed into 30 min bins. During the period of spontaneous withdrawal (0-60 hr after abrupt termination of the morphine infusion), MAP was uniformly higher than that in saline infused controls, reaching a maximum of +22±5 mmHg above pre-withdrawal levels. HR increased to 58±21 beats/mm. By 60 hr after infusion, MAP and HR returned to pm-withdrawal levels. However, when animals were placed back into the conditioning environment, they experienced a second phase of withdrawal caused by the stimuli alone. Stimuli-induced MAP and HR increases with concomitant increased stereotyped activity and withdrawal body shakes were observed over the following 2 hr which were almost as intense as those measured during the preceding spontaneous withdrawal. Saline-infused rats exhibited no significant cardiovascular or behavioral changes throughout the experiment.

A second group of morphine-dependent rats which had undergone spontaneous withdrawal were placed in a third environment in which the stimuli were different from the conditioning environment, but also different from their pre-morphine environment. During the protracted phase of the study, this group exhibited protracted withdrawal which was significantly greater than saline-infused animals, but which was reduced in magnitude from that experienced by the morphine group placed back into the conditioning environment. Thus, the experience associated with morphine administration was correlated with the expression of the protracted phase of abstinence. This model may provide a novel and reproducible approach for quantitating both spontaneous and protracted phases of withdrawal to opiate drugs.

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EFFECTS OF BUPRENORPHINE ON REGIONAL CEREBRAL BLOOD FLOW IN THE RAT

E. A. Stein and S. A. Fuller

Buprenorphine (BUP) is a moderately potent opiate agonist analegesic and, depending upon dose administered, also possesses marked opiateantagonist effects (Lewis *et al.,* 1983). Due to its low abuse liability and mild withdrawal svndrome, BUP has been used as an altemative to methadone (Johnson *et al.,* 1992). BUP reduces opiate self administration (SA) in monkeys (Mello *et al.,* 1983) and man (Mello and Mendelson 1980) as well as decreases cocaine SA in several monkey (Mello *et al.,* 1989) and rat (Carroll and Lac 1992) models. As BUP will decrease, at least temporarily, food intake in monkeys (Mello *et al.,* 1989) and suppress behavior maintained by such abused drugs as ethanol and PCP (Carroll *et al.,* 1992), it may act to depress general reinforcement mechanisms. However, its central sites of action as well as whether it acts as an agonist to replace the reinforcer or as an antagonist to block its effects is not well understood. To begin to study how and where BUP acts within the CNS, we performed a dose-response analysis of BUP's actions by using regional cerebral blood flow (rCBF) as a marker of neuronal activity.

Femoral arteries and vein were catheterized and rats placed in mild restraint by wrapping in a cloth towel. After 5 hours recovery, arterial blood pressure, heart rate, pH, P_aCO_2, P_aO_2 and HCO_3-were measured 10 minutes prior to drug delivery and just prior to the commencement of rCBF determination. Groups of rats received either saline or one of 4 doses of BUP (0.01, 0.3, 1.0 or 10.0 mg/kg) IV. Blood flow determination and subsequent animal sacrifice occurred 15 minutes after BUP or saline administration. rCBF was measured by the autoradiographic method of Sakurada *et al.* (1978).

ANOVA revealed that BUP caused a small decrease in pO_2 and a modest increase in systolic and diastolic blood pressure. Both of these changes were well within the autoregulatory range for CBF. Two distinct patterns of neuronal activity were also seen. Fifteen percent (9/60) of brain regions responded to BUP in a biphasic pattern, with the lowest dose causing a decrease in rCBF followed by a dose dependent increase at either 0.3 (substantia nigra-pars compacta and ventral pallidum) or 1.0 mg/kg *(e.g.,* nucleus accumbens-core and shell, frontal cortex, medial habenula and septum). The 0.01 dose never caused an increase in rCBF. All other regions responding to BUP (26/60), did so in a dose-response fashion *(e.g.,* hippocampus, cingulate). The 10.0 mg/kg dose, was generally ineffective in altering rCBF.

Previous studies have reported similar inverted U shaped dose-response curves for analgesia, locomotor suppression, gastrointestinal motility and respiratory depression (Cowan *et al.,* 1977 a,b). Insofar as other opiate aeonists increase rCBF and bidirectionally alter transmitter turnover and neuronal activity, while opiate antagonists are generally ineffective on these measures, it is likely that BUP acted as a partial opiate agonist (at doses up to 3.0 mg/kg) to selectively activate regional brain structures. Future studies will examine the interaction of BUP with cocaine on rCBF.

REFERENCES: Available upon request from the senior author.

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IN VIVO PROTON MAGNETIC RESONANCE SPECTROSCOPY DETECTION OF HUMAN ALCOHOL TOLERANCE

J. H. Mendelson, T. Chiu, B. T. Woods, S. K. Teoh, A. Levisohn, N. K. Mello, and M. Kaufman

The specific brain mechanisms which subserve the development of ethanol tolerance are unknown. A number of interrelated processes including ethanol-induced changes in plasma membranes and membrane-bound water are probably involved in tolerance. Ethanol tolerance may also be associated with functional modification of neuro transmitters, ion channel activity, secondary or tertiary messenger systems. Binding of ethanol to hydrophilic phosphates of phospholipid head groups located on the surface of cell membranes may vary as a function of ethanol tolerance as a consequence of the effects of ethanol on membrane phospholipid structures. Alcohol tolerance was ascertained with in vivo proton magnetic resonance spectroscopy (MRS) in men who regularly consumed either large (10-20 drinks/week) or small (2-4 drinks/week) amounts of beverage alcohol. Brain ethanol concentrations were determined by MRS and blood ethanol levels were measured by gas chromatography following controlled ethanol administration (0.8 g/kg). Brain-blood ethanol concentration ratios for heavy drinkers were significantly greater than ratios for occasional drinkers ($P<.002$). MRS evaluation of brain ethanol concentrations, at short echo time, may facilitate a better understanding of the basic biological processes of alcohol tolerance and dependence and also contribute to improved clinical diagnosis and treatment of alcoholism.

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ENSEMBLE NEURAL ACTIVITY IN FRONTAL CORTEX AND DORSAL RAPHE FOLLOWING COCAINE ADMINISTRATION

J. M. Paris, S. F. Sawyer, J.-Y. Chang, A. Kirillov, and D. J. Woodward

In the CNS, cocaine acts primarily to block the uptake of dopamine, serotonin (5-HT) and norepinephrine. In in vitro or anesthetized preparations, cocaine increases neurotransmitter concentrations and affects the activity of these neurons both at the cell body by inhibiting activity, and in target areas by facilitating postsynaptic responses. Since the behavioral state of the animal can strongly bias neural activity, the purpose of this study was to examine how cocaine influences firing patterns in the awake, behaving rat. Ensemble neural activity was recorded in: 1) the frontal cortex (FC), a region important in the reinforcing properties of cocaine; and 2) the dorsal raphe (DR) nucleus, source of the 5-HT innervation of cortical and subcortical regions. Two arrays of 16 and 8 microwires were stereotaxically implanted into the FC and-DR, respectively, of female Sprague-Dawley rats. Neuronal activity (groups of isolated single units) was recorded during spontaneous activity following injections of saline and cocaine (10mg/kg, ip; or 1.0 mg/kg, iv via indwelling venous catheters). In the FC, approximately one-third (8/25) of units were inhibited 20-70% after cocaine. several (6/25) showed an increase (25280%) in activity, while the remainder were unresponsive to the drug. In the DR, presumed 5-HT neurons (3/8) were also inhibited 20-50% by cocaine. Interestingly, neuronal activity was *increased* (25-40%) in units identified as *non*-5-HT DR cells. Thus, circuit activities may dominate over simple excitatory or inhibitory effects. Furthermore, the awake, behaving rat must be studied in detail to clarify those components of activity driving self-administration. Current studies are under way to assess the consequences of chronic cocaine in these and other brain regions (VTA, nucleus accumbens).

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CHANGES IN PRL RESPONSE TO DA INFUSION DURING CHRONIC COCAINE SELF-ADMINISTRATION BY RHESUS MONKEY

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Hyperprolactinemia is often reported in clinical studies of cocaine abusers. Since prolactin (PRL) is under inhibitory dopamincrgic control, we used dopamine (DA) infusions as a probe to examine changes in PRL regulation during chronic cocaine self-administration. Exogenous DA acts at the median eminence and adenohypophysis (Yen 1979). The effect of repeated DA infusions (10 mcg/kg/min) on the degree of PRL suppression and the rate and extent of PRL rebound were studied. Preliminary data are consistent with the hypothesis that chronic exposure to cocaine accentuates the rebound increase in PRL following interruption of DA infusion. Before cocaine exposure, basal PRL levels averaged 6.21 ± 1.8 ng/ml and DA decreased PRL levels to between 2.17 ± 0.18 and 3.41 ± 0.39 ng/ml. The rebound increase in PRL after interruption of DA infusion never exceeded the pre-dopamine baseline. In contrast, after daily cocaine self-administration of an average of 3.68 ± 0.34 g/kg/day for 30 to 126 days, the rebound increase in PRL 20 min after interruption of DA infusion consistently exceeded baseline levels. PRL rebound increases of 443 to 579 percent above baseline were measured in some subjects. These data suggest that PRL response to DA is a sensitive index of cocaine-related changes in PRL regulation.

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THE COCAINE-INDUCED RISE IN EXTRACELLULAR DOPAMINE IN THE NUCLEUS ACCUMBENS IS REDUCED BY GBR-12909 PRETREATMENT

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Results from microdialysis studies indicate that the dopamine (DA) reuptake inhibitor 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl] piperazine (GBR-12909) antagonizes the increase in extracellular dopamine (ECDA) elicited by local perfusion of cocaine into the striatum. In the present work, we investigated the effects of *systemic* cocaine, GBR-12909, and combinations of the 2 drugs, on ECDA in the nucleus accumbens of awake rats. Chronic intracerebral guide cannulae and jugular catheters were surgically implanted under pentobarbital anesthesia. At 7-10 days postsurgery, dialysis probes were inserted into guides and iv catheters were connected to extensions. Rats were connected to a fluid swivel that allowed free movement about the cage. Dialysate samples were collected at 20 min intervals beginning 3-4 hr after probe insertion and immediately assayed for DA by HPLC-EC methods.

Both cocaine and GBR-12909 (0.3-3.0 mg/kg, iv) caused dose-dependent elevations in dialysate DA when given alone. Cocaine and GBR-12909 increased ECDA with similar potencies, but the maximal effect of GBR-12909 was less than that of cocaine. The temporal profile of DA overflow was different with each drug: cocaine caused a rapid and short-lived increase in ECDA whereas GBR-12909 was associated with a slow onset of action and persistent elevation in ECDA. In drug combination studies, GBR-12909 or saline was administered 1 hr before cocaine challenge. The increase in ECDA after a modest dose of cocaine (1.0 mg/kg, iv) was significantly reduced from 250% to 175% of baseline by pretreatment with a subthreshold dose of GBR-12909 (0.3 mg/kg, iv). A high dose of cocaine (3,0 mg/kg, iv) increased ECDA to 600% of baseline; this massive rise in DA was decreased to 450% and 325% of baseline by pretreatment with 0.3 and 1.0 mg/kg GBR-12909, respectively. The elevation in dialysate DA evoked by the combination of GBR-12909 plus cocaine was clearly not additive. In a separate experiment, GBR-12909 dramatically blocked the DA-releasing effect of 1.0 mg/kg iv amphetamine.

Our findings demonstrate that GBR-12909 can antagonize the rise in accumbens ECDA produced by systemic cocaine or amphetamine. These results provide further evidence that DA reuptake inhibitors may be useful as cocaine antagonists and/or substitutes in the treatment of cocaine addiction in human patients.

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ELECTROPHYSIOLOGICAL STUDIES OF NUCLEUS ACCUMBENS NEURONAL ACTIVITY DURING COCAINE SELF-ADMINISTRATION IN RATS

J.-Y. Chang, S. F. Sawyer, J. M. Paris, and D. J. Woodward

Chronic electrophysiological recordings of single unit spike activity in the nucleus accumbens (NAc) was performed in freely-moving rats during cocaine self-administration. One hundred and eighty-seven neurons were recorded in 25 male Long-Even rats. The neuronal activity during cocaine self-administration was classified into 5 categories: (1) No change, *i.e.,* no significant alteration in firing rate (45%); (2) excitatory anticipatory (11%) and (3) inhibitory anticipatory (9%) neurons, which exhibited increased and decreased firing rates before lever press, respectively; (4) post-cocaine inhibitory (27%) and (5) post-cocaine excitatory (8%) neurons, which had decreased and increased firing rates after cocaine infusion, respectively. Some of anticipatory neurons exhibited post-cocaine inhibition or excitation. Systemic injection of the D_1 dopamine receptor antagonist SCH-23390 and the D_2 antagonist pimozide did not alter any of the anticipatory responses. Both antagonists blocked the post-cocaine inhibition in the neurons that exhibited excitatory anticipatory responses but exerted no effect on the neurons with only post-cocaine inhibition. Detailed video analysis of behavior indicated the phasic changes in neuronal activity before lever pressing could not be attributed to locomotor activity per se since similar movements *(e.g.,* rearing and turning) that were unrelated to lever pressing did not produce altered spike activity in these neurons. Elimination of cocaine from the syringe pump abolished the post-cocaine inhibition and left the excitatory anticipatory response intact. Computer controlled, random cocaine infusions induced similar post-cocaine inhibitory responses, suggesting the post-cocaine inhibition was due to the pharmacological effects of cocaine. A modified fixed ratio 3 (FR3) schedule (a two second delay after each lever response; the second lever response illuminated a houselight to signal that cocaine would be administered after the third response) was employed to investigate the anticipatory responses associated with each lever press. Well trained rats pressed the lever 3 times within short interval. The anticipatory responses observed prior to each lever press revealed essentially a similar pattern. The anticipatory responses persisted in the conventional FR10 schedule in which the rat continuously pressed a lever during few seconds. This study provides direct evidence for the NAc involvement in behaviors that lead to cocaine self-administration. We propose that the NAc plays a dual role in cocaine self-administration behavior: as an initiator of self-administration behavior (as represented by anticipatory responses), and as a substrate for the reinforcing effects of cocaine (as represented by post-cocaine responses). Dopamine transmission may be involved in the latter but not former mechanism of cocaine self-administration behavior.

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PREPRODYNORPHIN AND ZIF/268 mRNAs ARE INCREASED IN RAT DORSAL STRIATUM FOLLOWING ACUTE AND CHRONIC BINGES ON COCAINE

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Several studies have demonstrated that cocaine increases preprodynorphin (PPD) and immediate early gene (IEG) mRNAs in the dorsal striatum of rats. Multiple, closely spaced exposures to cocaine appear to elicit the greatest increases in dynorphin (Smiley *et al.,* 1990). Therefore, we used a binge paradigm (Spangler *et al.,* 1992) to evaluate changes in mRNA for PPD, PPE, and the IEGs, *zif/268* and *c-fos,* by quantitative *in situ* hybridization histochemistry. Male Wistar rats received three hourly i.p. injections of saline, 10, or 20 mg/kg cocaine HCl (NIDA) for 1, 5, or 10 days. One hour after the last. injection, the rats were anesthetized and decapitated. PPD or PPE 48mer oligonucleotides or 40mer oligos to *zif/268* or *c-fos* were 3'-labeled with ^{35}S-dATP (NEN) using terminal deoxynucleotidyl transferase (Boehringer Mannheim). The sections were then hybridized with the above probes at 37°C for 20 hours. After washing, the slides were apposed to Kodak X-OMAT film for 2 weeks (PPD) or 1 week *(zif/268, c-fos,* PPE) along with ^{14}C brain paste standards. The ^{14}C standards, converted to ^{35}S equivalences, were used to calibrate each film by converting raw gray scale transmittance values into dpm/mg. The autoradiograms were quantified using IMAGE software (Wayne Rasband, NIMH). Statistical significance was determined using at least square means ANOVA. *C-fos* mRNA expression was undetectable in all of the treatment groups. In contrast. when compared to saline, *zif/268* mRNA was increased in a dose-dependent manner (20 mg/kg>10 mg/kg) but the intensity of hybridization signal decreased in a time dependent fashion (1 day >> 5 days > 10 days). When compared to saline, PPD, but not PPE, hybridization signal increased in the dorso-medial striatum in a time-dependent manner at both doses. Repeated exposure to 10 mg/kg of cocaine for 1 day did not alter PPD mRNA levels, whereas this dose elicited increases in PPD hybridization signal on days 5 and 10, with the most robust increase occurring on day 10. Three injections of 20 mg/kg of cocaine elicited a robust increase in PPD signal on days 1 and 5. However. at 10 davs. the increase in PPD mRNA was no longer significantly different than control. These results indicate that repeated cocaine up-regulates PPD. gene expression while down regulating that of *c-fos* as previously reported (Daunais *et al.,* 1993). Further, i.p. cocaine-induced PPD mRNA expression does not follow the pattern of *zif/268* mRNA expression over time, indicating that there is not a close relationship between PPD and *zif/268.* In addition, these data offer further evidence that PPD and PPE mRNA are differentially regulated by the striatal dopaminergic system.

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DEMONSTRATION OF MULTIPLE BINDING SITES IN RAT CAUDATE MEMBRANES FOR THE COCAINE ANALOG [^{125}I]RTI-55

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Other laboratories have shown that the cocaine analog [^{125}I]RTI-55 labels DA and 5-HT transporters with high affinity. Using the method of binding surface analysis, we characterized [^{125}I]RTI-55 binding to membranes prepared from rat caudate nucleus. Two binding sites were resolved: a high. capacity binding site (site 1, Kd=0.76 nM Bmax=11800 fmol/mg protein) and a low capacity site (site 2, Kd=0.21 nM, Bmax=930 fmol/mg protein). The ligand-selectivity of site 1 was highly correlated with that of the classic DA transporter. The ligand-selectivity of site 2 was consistent with that of the 5-HT transporter, but quantitatively different from the 5-HT transporter of non-caudate brain regions labeled with [^{125}I]RTI-55. I.c.v. administration of 5,7.-DHT selectively decreased [^{125}I]RTI-55 binding to site 2. Ketanserin had low slope factors at both [^{125}I]RTI-55 binding sites. Using 50 nM paroxetine to block [^{125}I]RTI-55 binding to site 2 and 100 nM GBR12935 to [^{125}I]RTI-55 binding to site 1, we resolved two components of the DA transporter and two components of the 5-HT transporter. These data provide additional evidence for heterogeneity of binding sites for biogenic amine transporter ligands.

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EVIDENCE FOR ALTERATIONS IN 5-$HT_{2/1C}$ RECEPTOR SENSITIVITY AFTER REPEATED COCAINE INJECTIONS

M. H. Baumann, J. L. Cadet, P. L. Sheng, and R. B. Rothman

Preclinical evidence suggests that chronic cocaine produces alterations in presynaptic serotonergic (5-HT) function. In the present study, we investigated neuroendocrine and behavioral responses to the 5-$HT_{2/1C}$ agonist 1-[2,5-dimethoxy-4-iodophenyll-2-aminopropane (DOI) in rats that were previously treated with repeated injections of cocaine or saline. All rats were fitted with indwelling jugular catheters under methoxyflurane anesthesia. Beginning 2 days postsurgery, rats received cocaine (15 mg/kg, ip, bid) or saline (1 ml/kg, ip, bid) for 7 consecutive days. At 42 hr after the final chronic treatment, rats were challenged with iv DOI (25, 100 or 400 µg/kg) or saline. Serial blood samples were withdrawn immediately before and at 15, 30 and 60 min after DOI; DOI-induced head shakes were counted over the same 60 min. Plasma samples were assayed for prolactin (PRL) and corticosterone (CORT) by RIA.

DOI caused dose-related increases in circulating PRL and CORT in saline-treated and cocaine-treated rats. The PRL-releasing action of 100 µg/kg DOI was potentiated in rats that were exposed to cocaine ($P<0.05$), but the maximal PRL response elicited by 400 µg/kg DOI did not differ between pretreatment groups. The profile of CORT release after DOI was similar regardless of pretreatment condition. DOI dose-dependently increased head shake frequency in saline-treated and cocaine-treated rats. In rats exposed to cocaine, DOI-induced shaking behavior was dramatically enhanced at the 25 and 100 µg/kg doses ($P<0.01$). The maximal head shake response elicited by 400 µg/kg DOI did not differ between pretreatment groups. Preliminary analysis of [^{3}H]-ketanserin binding in forebrain revealed similar K_d and B_{max} values across pretreatment conditions.

These results indicate that repeated cocaine injections enhance the sensitivity of 5-$HT_{2/1C}$ receptor mechanisms in the rat. Our findings are in accordance with the work of others, and suggest that alterations in 5-$HT_{2/1C}$ receptor function may contribute to behavioral symptoms associated with excessive cocaine use in humans. Finally, our data provide further rationale for the use of 5-$HT_{2/1C}$ antagonists as therapeutic adjuncts in the treatment of cocaine addiction and withdrawal in human patients.

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DOPAMINE TRANSPORTER RESIDUES DIFFERENTIALLY IMPORTANT FOR DOPAMINE TRANSPORT AND COCAINE RECOGNITION: IMPLICATIONS FOR MEDICATIONS DEVELOPMENT

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A major goal of anticocaine medications development efforts is to develop drugs that would block cocaine recognition and spare dopamine transport. It is thus important to define if regions of the cocaine receptor/dopamine transporter (DAT) that might be selectively involved in these two processes exist, and to identify the nature of such regions.

Hints that these features might be different have come from studies of posttranslational modification of the wildtype transporter with deglycosylating and thiol-modifying reageants. Most current evidence now arises from studies of DAT molecules with specific site-directed mutations. DAT cDNAs were mutated to alter polar amino acids in transmembrane domains, cysteine residues potentially involved in disulfide bonding, and sites for N-linked glycosylation. The mutant transporters were examined for their abilities to mediate DA uptake and to bind the cocaine analog CFT. Several mutants have little functional effect, many mutants have similar effects on CFT binding and dopamine uptake, but several mutants differentially impact DA uptake and CFT binding.

These data define, for the first time, DAT regions selectively involved with cocaine recognition, and encourage the possibility that selective anticocaine medications that spare DA transport might be found.

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ON LINE SEROTONIN RELEASE PATTERNS IN REWARD CIRCUITS SIGNAL COCAINE-INDUCED DOPAMINE NEUROCHEMISTRY: IMPLICATIONS FOR THERAPY

P. A. Broderick

Data have revealed a striking co-modulation by cocaine of dopamine (DA) and serotonin (5-HT) in mesoaccumbens A_{10} somatodendrites and nerve terminal regions and in the A_9 terminal circuit, in both the chloral hydrate anesthetized and conscious rat paradigms. Using *in vivo* voltammetric (electrochemical) studies, 5-HT was detected concurrently, yet separately, with DA, within a temporal resolution of seconds. The methodology for the construction and assembly of stearate working (indicator), Ag/AgCl reference and stainless steel auxiliary microelectrodes is published (Broderick 1989). Stearate indicator microelectrodes were stereotaxically implanted in ventrolateral Nucleus Accumbens (vlNAcc), Ventral Tegmental Area (VTA) and dorsal striatum (STr) (Pelligrino *et al.* 1979). Reference and auxiliary microelectrodes were placed in contact with cortex. The results show that (SC) cocaine produced an increased and colocalized DA and 5-HT release in VTA and STr in freely moving and behaving rats. Moreover, an increased and colocalized DA and 5-HT release in vlNAcc was seen in the freely moving and behaving rat after (IP) cocaine administration and in the chloral hydrate anesthetized rat after (IV) cocaine administration. The cocaine-induced co-modulation effect consisted of a 5-HT surge which precedes the enhanced DA-ergic response. In vlNAcc, where immunoreactive (IR) tyrosine hydroxylase (TH) and 5-HT axons extensively overlap (Phelix *et al.,* 1993). preliminary new findings show that another 5-HT surge follows the DA-ergic response as well. Finally, pretreatment with the D_3 autoreceptor antagonist AJ76 (Svensson *et al.,* 1986; Sokoloff *et al.,* 1990) caused an enhancement of the cocaine-5-HT surge and a down modulation of the usually profound cocaine-DA-ergic response. Thus, cocaine may utilize 5-HT in DA neuronal circuits even during putative treatment combinations. A role for 5-HT may assume further significance in addiction and withdrawal processes.

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COCAINE INCREASES GLUTAMATE TURNOVER IN RAT NUCLEUS ACCUMBENS (N. ACC.)

S. E. Robinson, J. R. Maher, K. P. McDowell, D. L. Tracey, and P. M. Kunko

Several laboratories have suggested involvement of excitatory amino acids in certain behavioral effects of stimulants. The effects of cocaine HCl and of the cocaine analog methyl-3ß-(p-fluorophenyl)-1 αH,5α]H-tropane-2p-carboxylate 1,5-naphthalenedisulfonate 2/3 hydrate (CFT) were studied on the turnover of the excitatory amino acid glutamate and the inhibitory amino acid GABA in brain regions of male Sprague-Dawley rats. Rats were infused for 6 min with uniformly labeled ^{13}C-D-glucose (75 µmol/kg/min, i.v.) following i.p. injection of either cocaine, CFT, or physiological saline and euthanized by focussed microwave irradiation (1.3 sec, 10 kW) immediately at the end of the infusion. The relative incorporation of ^{13}C into glutamate or GABA was determined by gas chromatography/mass fragmentography and the turnover rate of glutamate (TR_{glu}) and GABA (TR_{GABA}) calculated (Wood *et al.,* 1988). Cocaine and CFT increase% TR_{glu}, but not TR_{GABA}, in the N. Acc. (figure 1). There were no differences in glutamate, GABA, or glucose content or percent incorporation of ^{13}C into glucose in the N. Acc. following any of the above treatments. Thus, the two stimulants cocaine and CFT appear to activate the glutamatergic innervation of the N. Acc., but the time-course of their effect differs.

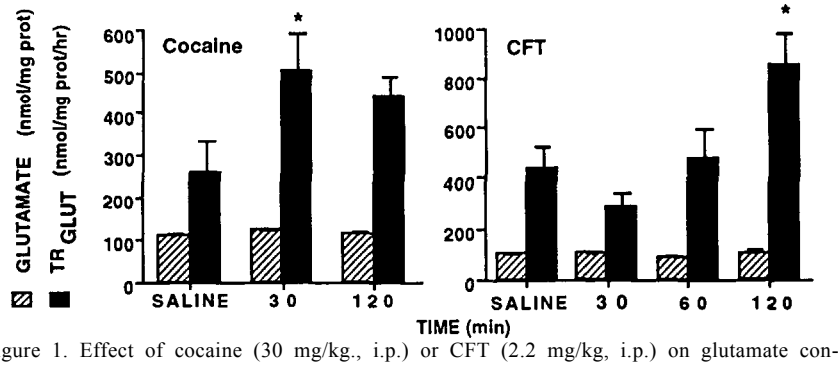

Figure 1. Effect of cocaine (30 mg/kg., i.p.) or CFT (2.2 mg/kg, i.p.) on glutamate content and turnover in the N. Acc. $p < 0.05$ from saline, by ANOVA and Fisher's lsd test.

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TRAMADOL: CONTRIBUTION OF EACH OF ITS ENANTIOMERS TO THE ANTINOCICEPTION AND SIDE EFFECTS IN MICE AND RATS

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The present study investigated the enantiomers of tramadol as a way of understanding its favorable clinical profile. (+)Tramadol's affinity at opioid μ, δ, and κ sites (K_i) was 1.33. 62.4 and 54.0 μM, respectively. (-)Tramadol was >10-fold less potent than the racemate at μ sites, >3-fold less potent at δ sites and about equipotent at κ sites. (+)Tramadol was the most potent inhibitor of 5-HT uptake, (-)tramadol the most potent inhibitor of norepinephrine uptake (K_i = 0.53 and 0.43 μM, respectively). In mice, each enantiomer produced spinally-mediated antinociception in the abdominal constriction test. The effect produced by the racemate was greater than additive (antinociceptive synergy). Synergy also occurred in the 55°C hot-plate (i.p.), but not tail-flick (i.v.), test. The enantiomers interacted less than synergistically in the side effect tests (colonic propulsive motility and rotarod performance). In rats, each enantiomer produced antinociception spinally (tail-flick test). Subthreshold (-)tramadol evoked antinociceotion when combined with subthreshold morphine, as did subthreshold (+)tramadol combined with subthreshold desipramine. In the Randall-Selitto inflammatory pain model, i.p. ED_{50} values (mg/kg) were 2.7, 52.9 and 3.0 for (+), (-) and (±) tramadol, suggesting synergy. Cardiovascular or respiratory effects in conscious rats were transient (15 min) after i.v. injection. The (-) enantiomer enhanced b.p., but the (+) enantiomer did not, resulting in weak enhancement by the racemate. Heart rate was decreased by the (+), but not (-) enantiomer, resulting in weak effect by the racemate. Spontaneous respiratory rate was enhanced by (-)tramadol (phentolamine-sensitive), but not (+)tramadol and, thus, only slightly by the racemate. In summary, each enantiomer produced antinociception, by different mechanisms, and interacted synergistically in several models of analgesia, but not side effects.

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CALCIUM (Ca++) MODULATION OF MORPHINE ANALGESIA: ROLE OF Ca++ CHANNELS AND INTRACELLULAR POOL Ca++

F. L. Smith, D. L. Stevens, and W. L. Dewey

Nearly 30 years ago, Hano *et al.* (1964) reported that intracistenally injected Ca++ ions block the antinociceptive effects of morphine (MOR). Subsequent studies in numerous laboratories have revealed the important role that neuronal Ca++ plays in modulating opioid analgesia, and the development of tolerance and physical dependence. Ratio imaging of fura-2 in mouse brain synaptosomes cultured rat PC12 cells and fetal rat dorsal root ganglion neurons has revealed that raising the extracellular concentration of buffer Ca++ causes an increase in free intracellular Ca++ (Smith *et al.,* 1992). The hypothesis of this study was that Ca++ injected i.c.v. blocks the antinociceptive effects of MOR in the tail-flick test by increasing transmembrane Ca++ influx and by stimulating Ca++ release from intracellular pools. All drugs were administered intracerebroventricularly (i.c.v.) in ether anesthetized mice. Ca++ blocked the antinociceptive effects of MOR (30 nmol), with an ID_{50} value for Ca++ of 110 nmol (95% C.L. 62 to 196). Higher doses were required to block the analgesic effects of etorphine (ETOR) (0.1 nmol) (ID_{50} 297 nmol [95% C.L. 229 to 385]) and [D-Ala^2, N-methyl-Phe^4, Gly^5-01]-enkephalin (DAMGO) (ID_{50} 297 nmol [95% C.L. 229 to 3851). Ca++ (110 nmol) increased the ED_{50} value for MOR 5.9-fold. from 9.5 nmol (95% C.L. 7.6 to 11.8) to 55.8 nmol (95% C.L. 44.0 to 70.8). Ca++ increased the ED_{50} value for ETOR 5.5-fold, from 44.6 pmol (95% C.L. 8.9 to 200.8) to 245.5 pmol (95% C.L. 89.0 to 669.6). Ca++(110 nmol) increased the ED_{50} value for DAMGO 59.5-fold, from 0.11 nmol (95% C.L. 0.03 to 0.45) to 6.5 nmol (95% C.L. 2.4 to 18.2). Although Ca++ reduced the potency of MOR, ETOR and DAMGO, their efficacy was undiminished. Other experiments were designed to determine whether pretreatment with Ca++ channel blockers would prevent the antagonism by Ca++ of MOR antinociception. The L-type blocker nimodipine (48 to 192 nmol) failed to prevent the antagonistic effects of Ca++. A 32.9 pmol dose of the putative N-type blocker omega-conotoxin (GVIA) potentiated the antinociceptive effects of MOR. although no antinociception was noted with this dose alone. A 10-fold lower dose completely prevented the antagonistic effects of Ca++, without itself affecting the potency or efficacy of MOR. We also hypothesized that increases in intracellular Ca++ resulting from transmembrane influx would stimulate Ca++ release from the caffeine/Ca++-sensitive pool. Ryanodine is reported to stimulate release from this pool, followed by blockade of subsequent release by caffeine or Ca++. Ryanodine (2 nmol) was found to significantly attenuate the antagonism by Ca++ of MOR antinociception, although Ca++ still significantly reduced the potency of MOR. Thus Ca++ release from the caffeine/Ca++-sensitive pool may have contributed to the inhibition of MOR. We also hypothesized that agents which release Ca++ from intracelluhar pools would block the analgesic effects of MOR. Thapsigargin (Tg), a sesquiterpene lactone from the plant roots of *Thapsia garganica L.,* selectively causes Ca++ release from the IP_3-sensitive pool and prevents subsequent accumulation by blocking ATP/Mg-dependent ATPase activity. Thapsigargin (2 pmol to 129 nmol) produced no analgesia, although doses from 8 nmol to 129 nmol elicited stiff paralysis of fore- and hind-limbs contralateral to the injection site, and barrel-rolling behavior ipsilateral to the injection site. At the peak-time effect of 60 minutes, Tg blocked the effects of MOR, with an ID_{50} value for Tg of 0.15 nmol(95% C.L. 0.02 to 1.59). Tg (3 nmol) increased the ED_{50} value for MOR 4.8-fold, from 29.4 nmol (95% C.L. 18.7 to 46.2) to 140 nmol (95% C.L. 124.0 to 158.1). The higher ED_{50} value for MOR (9.5 nmol vs. 29.4 nmol) reflects the i.c.v. injection of vehicle DMSO.

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THE EFFECTS OF CHRONIC ADMINISTRATION OF MORPHINE ON NALOXONE- AND CGRP-INDUCED CHANGES IN THE LEVELS OF FREE INTRACELLULAR CALCIUM ($[Ca]_i$) IN DORSAL ROOT GANGLIA (DRG) CELLS

S. P. Welch and F. L. Smith

Dorsal root ganglia (DRG) were used to study the effects of morphine alone, and in combination with calcitonin gene-related peptide, on calcium-induced rises in free intracellular calcium. DRG's were prepared from the spinal cords of neonatal rats on day 15 of gestation. The ganglia were removed from the spinal cords and allowed to incubated in standard growth media containing nerve growth factor for 3 weeks. The DRG cells were then loaded with the calcium indicator fura-2/AM and were monitored for changes in free intracellular calcium using single cell microfluormetric measurement. Exposure of naive DRG's to 3 μM calcium extracellularly results in a 300-400% rise in intracellular free calcium ([Ca]i) which is blocked by the administration of nimodipine (IC_{50} = 1 nM) and cadmium, as well as omega conotoxin. Thus, the entry of the calcium into the DRG's appears to occur via voltage-gated calcium channels. The rise in [Ca]i is blocked partially, but significantly, by morphine (1 μM, 10 μM), but is not blocked by CGRP (0.1-10 μM). However. CGRP significantly enhances the effects of morphine-induced blockade of calcium entry. The combination of morphine (0.1 μM), which does not alter calcium entry, with CGRP (0.1 μM), produces a total blockade of calcium-induced rises in [Ca]i.

CGRP (0.1-1 μM) produces a dose-related increase of nearly 100% in basal [Ca]i (not stimulated by the addition of extracellular calcium). The rise in [Ca]i produced by CGRP is blocked by naloxone. When DRG's are treated chronically for two days with morphine (0.1 μM), the rise in [Ca]i induced by CGRP was similar to that produced in naive DRG's. Thus, chronic opiate presence in the cells does not alter the ability of CGRP to allow calcium entry to the cells. Presumably such entry of calcium occurs via the interaction of CGRP with its receptor which appears to not be altered by chronic opiate treatment of the cells. However, chronic opiate pretreatment of the cells totally abolishes calcium-stimulated rises in [Ca]i. CGRP and naloxone only partially reverse the blockade of calcium entry induced by the chronic exposure to morphine. These data support the hypothesis that CGRP acts as a homeostatic modulator of calcium entry into DRG's. In addition, CGRP appears to function as a calcium modulator in opiate-sensitive pathways. However, the chronic administration of morphine to DRG's, while altering calcium entry to the cells, does not alter the ability of CGRP to modulate calcium entry. Thus, the chronic administration of morphine appears to block calcium entry through the voltage-gated calcium channels, but does not alter calcium entry through the CGRP-activated calcium channels.

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NALTREXONE *IN VIVO* PROTECTS μ-RECEPTOR INACTIVATION BY ß-FUNALTREXAMINE, BUT NOT k-RECEPTOR INACTIVATION BY NOR-BINALTORPHIMINE

C. A. Paronis, A. B. Waddell, and S. G. Holtzman

The k-opioid antagonist effects of nor-binahorphimine (nor-BNI) will persist for up to three weeks *in vivo* following a single central injection of the drug (Horan *et al.* 1992; Jones and Holtzman 1992). The mechanisms responsible for this long duration of action are not yet known. In contrast, the effects of the irreversible μ-opioid antagonist, μ-funaltrexamine (ß-FNA), are believed to be caused by alkylation of the μ-opioid receptor.

The inactivation of receptors by irreversible antagonists can be prevented *in vitro* by pretreatment with competitive ligands. We examined the ability of the competitive opioid antagonist, naltrexone, to protect opioid receptors *in vivo* from inactivation by the nonequilibrium antagonists, ß-FNA and nor-BNI. Male rats were pretreated with 10 mg/kg naltrexone or saline (sc), 30 minutes before being injected intracisternally (ic) with water, 10 μg ß-FNA, or 1.0 or 10 μg nor-BNI. The rats were tested for analgesic responses to cumulative doses of either the k-opioid agonist U69,593 (sc, nor-BNI groups), or the μ-opioid agonist morphine (sc, ß-FNA groups) on a 50° hot-plate, 24 hours later. The animals that received nor-BNI were retested for an analgesic response to U69,593 seven days after the nor-BNI injections. The base-line latencies to paw-lick ranged from 7-12 seconds (cut-off time = 35 seconds), and were unaffected by the 24 hour pretreatments. The mean morphine analgesic ED_{50} in rats that had received water (ic) was 3.2 mg/kg. A dose of 30 mg/kg morphine produced little or no analgesia in animals that had received saline (sc) and 10 μg ß-FNA (ic) 24 hours earlier. However, pretreatment with 10 mg/kg naltrexone attenuated the antagonist effects of ß-FNA. The mean morphine analgesic ED_{50} in this group of animals was 10.8 mg/kg. U69,593 (0.1-10 mg/kg) also produced analgesia in animals that received water (ic), with an ED_{50} of 0.97 mg/kg. This analgesia was dose-dependently blocked by nor-BNI for up to seven days. Naltrexone given before the nor-BNI injections did not inhibit the actions of 10 μg nor-BNI on either day 1 or 7. Thus, naltrexone protected p-receptors *in vivo* from inactivation by ß-FNA, but did not protect k-receptors from onactivation by nor-BNI. These data suggest that the interactions of naltrexone and μ-FNA at the receptor level appear to be different from the interactions of naltrexone and nor-BNI.

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PREVENTING THE DEVELOPMENT OF MORPHINE ANALGESIC TOLERANCE BY MU IRREVERSIBLE ANTAGONISTS BEFORE THE APPEARANCE OF ANTAGONISM

Q. Jiang and J. M. Bidlack

Irreversible opioid antagonists require time before they produce antagonism of agonist-mediated effects *in vivo*. However, in receptor binding assays, these affinity ligands covalently bind to opioid binding sites within minutes. These inconsistent results of time requirements from *in vivo* and *in vitro* studies suggest that irreversible antagonists might have effects *in vivo* that appear before their antagonism. The present study was designed to investigate whether irreversible antagonists, ß-funaltrexamine (ß-FNA) and 14ß-(thioglycolamido)-7,8-dihydro-N(cyclopropylmethyl)-normorphinone (N-CPM-TAMO), altered the development of morphine analgesic tolerance, measured by the 55°C warm-water mouse tail-flick assay. All opioids were given by intracerebroventricular (i.c.v.) administration. Morphine (3 nmol) produced analgesic tolerance 140 min after administration. Neither ß-FNA (20 nmol) nor N-CPM-TAMO (1 nmol) produced any μ antagonism until 8 hr after administration. When co-administrated with morphine, both N-CPM-TAMO and ß-FNA completely blocked the development of morphine tolerance 140 min after injection and their inhibition of the development of tolerance lasted for up to 420 min. during which time morphine was injected up to three times. The δ and κ-selective opioid antagonists, ICI 174,864 (4 nmol) and nor-BNI (0.6 nmol), at a dose which efficiently antagonized DPDPE- and U50,488-induced antinociceptions, respectively, and did not antagonize morphine-induced antinociception, did not have any effect on morphine analgesic tolerance. When co-administrated with morphine and ß-FNA or N-CPM-TAMO, neither ICI 174,864 nor nor-BNI blocked the preventive effect produced by irreversible antagonists on morphine analgesic tolerance, indicating that the preventive effect produced by the irreversible antagonists was not mediated by the δ or κ opioid receptors. These data demonstrate that irreversible antagonists, ß-FNA and N-CPM-TAMO, prevent the development of morphine tolerance before the appearance of their antagonism and that affinity ligands are exerting their preventive effect through the μ opioid receptor. The present data also indicate that irreversible opioid antagonists rapidly react with opioid receptors after i.c.v. administration although their antagonisms have not appeared and the antagonistic mechanism of irreversible antagonists probably is much more complicated.

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GENETIC DIFFERENCES IN INNATE NOCICEPTION AND ITS RELATIONSHIP TO THE POTENCY OF MORPHINE TO INDUCE ANALGESIA IN THERMAL AND CHEMICAL TESTS

J. O. Pieper, S. Negus, S. R. Goldberg, J. H. Woods, and G. I. Elmer

The perceived intensity of a painful stimulus is determined in part by the stimulus intensity and environmental conditions. The purpose of this study was to determine the influence of genetic factors in innate nociception and its contribution to the potency of morphine to produce antinociception.

Eight inbred strains of mice (C57BL/6J, AKR/J, DBA/2J, BALB/ByJ, C3H/HeJ, CBA/J, CXBK/ByJ and CXBH/ByJ) were tested across a range of stimulus intensities in thermal (hot plate) and chemical irritant (acetic acid) nociceptive tests. Stimulus intensities in the thermal test included hot plate temperatures of 51, 53, 55, 57 and 59°C. Stimulus intensities in the chemical irritant test included acetic acid concentrations of .1, .3 and .6%. Linear interpolation of stimulus-effect curves revealed large differences the temperature resulting in a 10" latency on the hot-plate and the acetic acid concentration resulting in 4 writhes. There was no genetic correlation between sensitivity to thermal vs chemical stimuli.

Morphine dose response curves were then determined at a fixed stimulus intensity in each test, 55°C and .6%, to determine analgesic ED_{50} doses for each inbred strain. A significant effect of genotype on relative sensitivity to morphine-induced analgesia in both the thermal and chemical irritant test was found. Innate sensitivity to both stimuli was significantly correlated with morphine ED_{50} values in each respective test. In both tests, strains least sensitive to the nociceptive stimuli were more sensitive to the antinociceptive effects of morphine.

In summary, this study demonstrated a large degree of genetic variability in innate nociception. Innate nociceptive sensitivity to thermal stimuli was unrelated to sensitivity to chemical stimuli. There was a significant relationship between innate nociception and the potency of morphine-induced analgesia in both tests.

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DOSE EFFECTS OF NICOTINE GUM ON ABSTINENCE, WEIGHT GAIN, AND WITHDRAWAL SYMPTOMS

J. Gross, M. Stitzer, and J. Johnson

One of the greatest obstacles to achieving higher rates of abstinence in patients who use nicotine gum is failure to use enough gum properly. Studies examining the abstinence effects of nicotine gum find that subjects will self-administer on average about 7 pieces/day while actual nicotine absorption is unknown. The goal of the present study was to compare the dose effects on abstinence success in subjects randomly assigned to use either 0.7, 15, or 30 pieces/day of nicotine gum (n=177) and to examine the dose effects on withdrawal symptoms and weight gain amongst subjects who had sustained abstinence for 12 weeks (n=42). Biological indices of gum compliance and smoking abstinence were used. Gum group assignment was not related to abstinence success. In the subset of abstinent subjects, there was a strong positive relationship between gum pieces per day used and saliva cotinine but a great deal of variability in cotinine levels for reported pieces/day. Weight gain was related in a dose-dependent manner to salivary cotinine ($p<.007$), but not to gum group, with high, mid-level, and low cotinine subjects gaining an average of 2.4, 5.9 and 6.2 pounds, respectively. Withdrawal symptom reporting was not related to nicotine exposure. Thus, the study confirmed a previously observed relationship between nicotine replacement level and post-cessation weight gain. The study also suggests that biological assessment of nicotine replacement levels may be needed during gum use to verify adequate treatment delivery.

AFFILIATION:

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CARBAMAZEPINE (CBZ) DOES NOT ALTER COCAINE SELF-ADMINISTRATION IN HUMAN COCAINE ADDICTS

D. A. Gorelick, L. L. Weinhold, E. J. Cone, and J. E. Henningfield

The anticonvulsant medication carbamazepine (CBZ) has been proposed as a treatment for cocaine abuse, largely on the basis that it blocks development of cocaine-induced kindling in rodents, and that kindling is a proposed neurophysiological mediator of cocaine craving. Limited open-label clinical testing has shown efficacy, but this has not yet been confirmed by double-blind clinical trials. The goal of this study was to directly evaluate the efficacy and safety of CBZ in reducing cocaine use and craving, using an experimental human cocaine self-administration paradigm.

Eighteen Cocaine-dependent (DSM-IIIR criteria) subjects (14 men; 15 blacks, 3 whites; mean [±S.D.] age 32.9 ±4.5 years; cocaine use in prior 30 days 20.5 ± 7.8 days & 10.4 ± 12.4 gms), with no other current substance dependence except nicotine (n = 8). were housed for 7-10 weeks on a closed research ward. Subjects could pay $1 (in tokens) to initiate an injection self-administration session 3 times (at 2-hr intervals) every Mon., Wed., & Fri., alternating with 3 daily money ($2) sessions. Reinforcers were earned by making the appropriate stimulus-controlled (light panel) operant response (lever pull) on a FI 1 min/FR 10 schedule. The double-blind IV injections were either cocaine-25 mg on 2 days or saline-1 ml on 1 day each week. Cocaine craving was measured by 100-mm visual analogue scales (VAS) each morning before the day's first session and every Sun. p.m. After a week (1) of ward acclimation and a baseline week (2) of self-administration sessions, 6 subjects each were randomly assigned double-blind to one of three targeted CBZ plasma levels: 0, 1-3 ug/ml, or 4-7 ug/ml. CBZ plasma levels were measured twice weekly, and doses adjusted by a non-blind M.D., along with the doses of a yoked placebo subject. All subjects received active placebo of diphenhydramine-25 mg bid. Subject characteristics did not differ significantly between the medication groups.

All subjects maintained targeted plasma levels during weeks 4 & 5, on doses of 200 mg daily (1-3 µg/ml) or 400-600 mg daily (4-7 µg/ml). Thus, outcome measures were tested by comparing week 2 with weeks 4 & 5 with 2-way (Medication x Weeks) ANOVA. There were no clinically significant adverse effects of CBZ; no subject was dropped because of CBZ effects.

Cocaine and money were highly reinforcing (self-administered on 95% and 92% of opportunities) and distinguishable from saline (self-administered on 42% of opportunities, chiefly day's 1st session to determine which drug was available that day). High operant response rates were emitted in almost all sessions (group means 202 to 265 lever pulls/session). CBZ had no significant effect on % participation in cocaine self-administration sessions, operant response rate, or cocaine craving at either time point.

These results do not support the efficacy of CBZ in reducing cocaine use or craving, as evaluated in an experimental setting, but do support the safety of the CBZ-cocaine interaction at the doses used.

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THREE MODELS FOR THE ANALYSIS OF A FLUOXETINE PLACEBO CONTROLLED TREATMENT IN COCAINE ABUSE

L. Covi, J. M. Hess, N. A. Kreiter, and C. A. Haertzen

In a double blind, random assignment, 12 week treatment study for cocaine dependent outpatients, Fluoxetine 20, 40 and 60 mg was compared to an "active placebo," i.e. Diphenhydramine 12.5 mg. Seventy-two subjects using at least one Gm per week were consented. Information on drug use, urine for toxicology and vital signs were collected at each of the three weekly visits. Measurements of cravings, mood and others were collected once a week. Counseling sessions were twice a week. After careful review of every record, 45 subjects were considered valid. For this presentation, attention was focused on the three main weekly measures of treatment effects: 1) amount of self-reported cocaine use; 2) urine toxicology for cocaine; 3) cocaine craving visual analogue scale.

Three analyses were done: by original assignment, by serum level, and by initial visit urine positivity or negativity. This last analysis was seen as a study of relapse prevention. Pre- and post-treatment results were analyzed for 12 weeks with end point carried forward. Two-way analyses of variance (group by time) were used, except for urine toxicology where Fisher's exact test was employed.

The first analysis by original assignment showed decreased use over time for all four groups ($p=.06$). The 60 mg subjects had a higher percentage of positive urine ($p=.04$). Cravings significantly ($p=.0001$) improved over time regardless of group.
The second analysis compared the "placebo" group with the 10 subjects group who achieved sometime in the course of 12 weeks a Fluoxetine/Norfluoxetine level above 100 ng/ml and the 10 who were below that level. The 11 Subjects who had missing blood levels were added. The missing values group significantly ($p=.02$) improved by self reported cocaine usage, but not by urine positivity. The craving measure showed improvement in all groups across time ($p=.0001$). In the third analysis the subjects were stratified according to initial urine cocaine positivity or negativity, and to their assignment to fluoxetine or "placebo." Those initially negative reported less overall use, the initially positive decreased more than those initially negative. Cravings decreased at the level of the other two analyses.

All three models supported the finding of craving decrease across time. Other findings were not confirmed but the relapse prevention model presented interesting possibilities. The blood level model is probably not valid.

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PREDICTORS OF OUTCOME IN A CLINICAL TRIAL OF FLUOXETINE TREATMENT OF PRIMARY COCAINE DEPENDENCE

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OBJECTIVE: The effectiveness of fluoxetine in treating cocaine dependent outpatients was evaluated in a placebo-controlled, double-blind trial.

METHOD: Thirty-two subjects were randomly assigned to 40 mg/day of fluoxetine (FLX) or to (PLA) for 12 weeks. Weekly measures included quantitative urine benzoylecgonine concentrations and self-reports of cocaine use, craving, and psychological symptoms. Regression methods were used to identify predictors of treatment outcome.

RESULTS: Subjects receiving FLX remained in treatment a median of 11.0 weeks compared to 3.0 weeks for the PLA group ($p<.00l$, logrank test). Controlling for length of treatment stay, subjects in the FLX group tended to remain abstinent for longer periods of time ($p=.116$, Mann-Whitney exact inference) than those on PLA. In addition to group assignment, predictors of retention included study medication adherence, age, and stability of housing ($F=10.07$, $p=.0002$). Medication adherence, as well as group assignment, also predicted length of continuous abstinence ($F=7.97$, $p=.003$).

CONCLUSIONS: These results suggest that fluoxetine may be effective in improving outcome in outpatient treatment of primary cocaine dependence. Possible benefits include longer treatment stays and periods of abstinence.

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AFFILIATION:

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FLUOXETINE IN PRIMARY AND SECONDARY COCAINE DEPENDENCE: OUTCOME USING QUANTITATIVE BENZOYLECGONINE CONCENTRATION

S. L. Batki, A. Washburn, L. Manfredi, J. Murphy, M. D. Herbst, K. Delucchi, T. Jones, N. Nanda, P. Jacob III, and R. T. Jones

Objective: Two double-blind, placebo-controlled trials of fluoxetine 40 mg/day were performed to determine its effectiveness in treating primary and secondary cocaine dependent patients.

Method: Both studies employed 12 week parallel group designs. Weekly measurement of quantitative urine benzoylecgonine (BE) concentrations was the main outcome measures. Other outcome measures consisted of retention in treatment and self-reports of cocaine use, cocaine craving, and psychological symptoms. Subjects in the first study were 52 secondary cocaine dependent methadone maintenance (MMT) outpatients, while the subjects in the second study were 32 primary crack cocaine dependent outpatients.

Results: Secondary cocaine dependent subjects assigned to fluoxetine (FLX) had significantly lower adjusted urine BE for weeks 1-12 (median 16,462 ng/mg urine creatinine) than subjects receiving placebo (PLA) (40,559 ng/mg) ($p<.01$, Mann-Whitney U). Primary cocaine dependent subjects receiving FLX were retained in treatment significantly longer, staying in the study for a median of 11 weeks versus 3 weeks for the PLA group ($p<.001$, logrank test). Urine BE concentrations and self-reported cocaine use were not significantly different for the FLX and PLA groups in the primary cocaine study.

Conclusion: These two controlled trials of fluoxetine appear to indicate its potential utility in increasing retention in primary cocaine dependence and reducing cocaine use and craving in secondary cocaine dependence.

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AN OUTPATIENT TRIAL OF METHADONE VERSUS BUPRENORPHINE IN THE TREATMENT OF COMBINED OPIOID AND COCAINE DEPENDENCE

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

Buprenorphine is an opioid partial agonist that may be useful in the treatment of opioid and cocaine dependence. This double-blind, double dummy study compared buprenorphine to methadone in the outpatient treatment of combined opioid and cocaine dependence. Participants were randomly assigned to stabilization doses of 8 mg s.l. buprenorphine or 50 mg p.o. methadone during 16 weeks of treatment. The methadone (n=27) and buprenorphine (n=24) groups did not differ on demographic features: mean age 33 years, 43% white, 71% male. Dose increases in units of 10 mg of methadone and 2 mg of buprenorphine were given if positive opioid or cocaine urinalysis continued. A similar number of subjects received dose increases (81% for methadone and 75% for buprenorphine); the mean dose of methadone was 67 mg and of buprenorphine was 11.2 mg. The groups did not differ on retention in treatment through week 16 ($p=0.97$); mean days in treatment was 72 for each of the groups. There was no significant difference between groups in the rate of opioid (methadone 59.6% versus buprenorphine 54.5%) or cocaine (methadone 63.2% versus buprenorphine 69.0%) positive urines. For subjects who received a dose increase (n=36) them was no significant decrease in the rate of opioid positive urines (62.1% pre- versus 56.8% post-increase), but there was a significant decrease in the rate of cocaine (81.5% pre- versus 66.3% post-increase; $p<0.05$) and opioid-or-cocaine-positive urines (96.3% pre- versus 79.6% post-increase; $p<.01$); there was no significant difference between groups, or a group by time effect. These results provide further evidence buprenorphine is equally effective as methadone in the treatment of opioid dependence. However, these results do not support a differential efficacy of buprenorphine versus methadone in the attenuation of cocaine use in this population.

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BUPRENORPHINE VS. METHADONE MAINTENANCE FOR COMBINED COCAINE AND OPIOID DEPENDENCE

R. S. Schottenfeld, T. R. Kosten, J. Pakes, D. Ziedonis, and A. Oliveto

Because preclinical and clinical studies suggest that buprenorphine (BUP), a partial mu agonist and kappa antagonist, may attenuate cocaine use, we conducted a 26-week, randomized, double blind, clinical trial comparing daily maintenance on sublingual BUP (4 mg or 12 mg) or oral methadone (METH) (20 mg or 65 mg). BUP doses were based on results of a pilot study suggesting that BUP 12-16 mg was optimal. One hundred and twenty subjects meeting DSM-III-R criteria for opioid and cocaine dependence were randomized into the four groups. Urine toxicology testing was performed three times per week and self reports of drug use and craving obtained weekly. There were no significant differences among the four groups in baseline demographic variables, measures of drug abuse or psychiatric history. Retention was highest in the METH 65 and BUP 12 groups, with 62% and 58% of subjects completing 26 weeks, compared to METH 20 (48%) and BUP 4 (31%). The proportion of opiate free urines was greatest for METH 65 (59.6), followed by BUP 12 (42.6). METH 20 (31.6) and BUP 4 (25.7), with Duncan's Mean Range Test (DMRT) showing significant differences for all groups. The proportion of cocaine free urines was significantly lowest for BUP 4 (27.0), with not significant differences found among the METH 65 had a significantly higher proportion of combined opiate and cocaine free urines (32.7) compared to BUP 12 or METH 20 (20.9 and 18.5), while BUP 4 was significantly lower than all other groups (9.1). These results document that higher doses of methadone and buprenorphine are more effective than lower doses, with METH 65 superior to BUP 12; the results suggest the need to evaluate higher doses of buprenorphine and to evaluate combined pharmacologic and psychosocial interventions.

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AFFILIATION:

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ADMINISTERING TWICE THE DAILY BUPRENORPHINE DOSE SUPPRESSES OPIOID WITHDRAWAL FOR 48 HOURS IN OPIOID-DEPENDENT HUMANS

L. Amass, W. K. Bickel, S. T. Higgins, and J. R. Hughes

Diversion of take-home medication is a frequent problem associated with the pharmacological treatment of opioid dependence. This problem could be ameliorated by administering medication less frequently than once daily. Previously, the partial μ-agonist buprenorphine (BUP) at 8 mg s.l. administered every 48 hours was less effective than 8 mg daily at stabilizing subjective aspects of withdrawal in opioid-dependent inpatients. However, doubling the daily BUP dose may be sufficient to sustain BUP's withdrawal suppressing effects-beyond 24 hours. The current study assessed the feasibility of alternate dav BUP administration in ooioid-deoendent outoatients, using BUP doses double that given for daily maintenance. Thirteen patients receiving BUP (per 70 kg, s.l.: n=2, 2 mg; n=6. 4 mg; n=5, 8 mg) were enrolled in this double-blind, placebo-controlled, crossover trial. Following a 10 day baseline of daily maintenance dosing, patients received their maintenance dose daily for 21 days and then received twice their maintenance dose every other day with placebo on the interposed day for another 21 days. Condition order was counterbalanced across subjects and within dose. Study participation was contingent on daily attendance and opioid abstinence. Observer and self-report measures of opioid agonist and withdrawal effects, dose IDs and pupil diameter were collected daily prior to receiving BUP. Ten patients (77%) completed the study; 8 patients (62%) participated in a second crossover. Dependent measures obtained during periods of alternate day administration did not differ from those obtained during the baseline or periods of daily dosing; moreover, these effects were independent of dose. These results suggest that BUP can be administered safely every 48 hours by doubling the maintenance dose. Importantly, this dosing schedule permits patients to attend the clinic less frequently without risking diversion, may increase options available to clinics providing buprenorphine treatment, and may be useful in settings in which travel is a barrier to treatment.

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BUPRENORPHINE AND NALOXONE INTERACTIONS IN OPIATE DEPENDENT VOLUNTEERS

R. T. Jones and J. Mendelson

Sublingual buprenorphine appears useful for the treatment of opiate dependence. A combination sublingual dose formulation of buprenorphine and naloxone should have less potential for parenteral use by opiate-dependent individuals. Sublingual buprenorphine and naloxone combinations must have minimal interactive effects when given to individuals treated with buprenorphine.

To assess the effects of sublingual buprenorphine/naloxone combinations on buprenorphine effects nine opiate-dependent, paid volunteer subjects were admitted to our GCRC and received daily doses of sublingual buprenorphine (8 mg) for seven days. At the end of this period only minimal opiate withdrawal symptoms were present. They then received challenge combination doses of sublingual buprenorphine (8 mg) and naloxone (0.4 or 8 mg), under double-blind, placebo-controlled conditions.

No observer or subject-rated differences in symptoms, behavior or physiologic effects were evident between these dose formulations. Sublingual naloxone in combination with buprenorphine did not precipitate opiate withdrawal or have other dysphoric effects. After 11 days exposure to buprenorphine an i.v. dose of buprenorphine (4 mg) and naloxone (4 mg) injected over ten minutes failed to produce either marked opiate agonist or antagonist effects. The effects of sublingual buprenorphine do not appear altered when given with naloxone in a 1:1 or 2:1 ratio.

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A MULTICENTER, LABELING ASSESSMENT STUDY OF LEVO-ALPHA-ACETYLMETHADOL (LAAM) FOR THE MAINTENANCE TREATMENT OF OPIATE ADDICTS

P. J. Fudala, A. Montgomery, S. Herbert, J. Mojsiak, S. Rosenberg, and F. Vocci

Previous studies, involving over 4500 patients who received levo-alpha-acetylmethadol (LAAM) orally, indicated that it can be effectively given in doses of up to 100 mg at 48 to 72 hours over extended periods of time for opiate-dependence treatment. The present study was performed to assess the appropriateness and completeness of the proposed package insert and treatment regulations to guide the safe use of LAAM in a sample of individuals from the current opiate-addict population.

The study consisted of two phases, a 12-week initial treatment phase and a 52-week continuation phase, and was conducted at 26 outpatient methadone treatment sites. Prior to completion of phase I, two sites discontinued participation; one terminated for administrative reasons and another ceased operations due to damage sustained by hurricane Andrew. Six-hundred twenty-three patients received at least one dose of medication, 206 (33%) were female; 443 patients completed phase I. One hundred and nine (33%) of the 329 individuals participating as of June 8, 1993, were female.

Analysis of clinician prescribing behavior and patient responses were used to validate or amend the proposed package insert and treatment regulations. Safety data (including physical exams, urinalyses, complete blood cell counts, clinical chemistry profiles, and others) were also collected at different times throughout both phases of the study.

Twenty-six serious adverse events have been reported through April 19, 1993, including one fatality from an apparent mixed-drug overdosage. The three side effects reported by the most number of individuals have been insomnia, nervousness, and constipation.

Overall, LAAM has been well tolerated and appears to be an effective alternative to methadone treatment. The second phase of the study is currently ongoing with the last patient expected to complete the protocol by February, 1994.

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RELATIONSHIP OF SMOKING STATUS AND DEPRESSION WITH SENSATION SEEKING SCORES IN MALES AND FEMALES

S. Carton, R. Jouvent, and D. Widlocher

We have previously shown that Zuckerman Sensation Seeking Scale (SSS) scores are lower in depressed than in nondepressed subjects, and elevated in smokers. We therefore hypothesized that depressed smokers would. have higher SSS scores than depressed nonsmokers but lower than nondepressed smokers. SSS scores were analyzed for depressed smokers (46 females, 28 males), depressed nonsmokers (25 females, 24 males), nondepressed smokers (36 females, 60 males) and nondepressed nonsmokers (23 females, 45 males). Nicotine dependence was assessed via the Fagerstrom Tolerance Questionnaire (FTQ).

Both depressed and nondepressed female smokers had significantly higher SSS scores than nonsmoking females on 3 of the 4 subscales (Disinhibition [Dis], $p<.000$; Experience-seeking [ES], $p<.01$; Boredom-susceptibility [BS], $p<.000$). Depressed scored significantly lower than nondepressed on ES ($p<.01$). FTQ and SSS scores were significantly correlated in nondepressed females for Dis ($r=+.34$, $p<.05$) and for ES ($r=+.35$, $p<.05$). Depressed males, both smoking and non-smoking, had lower SSS scores than nondepressed males on Dis ($p<.05$), ES ($p<.005$), and BS ($p<.05$), with a trend towards a significant main effect on the Thrill and Adventure Seeking subscale (TAS, $p=.08$). On BS, a trend towards a significant main effect for smoking status emerged ($p=.06$). No significant correlation between FTQ and SSS scores emerged for either depressed or nondepressed male smokers.

Thus, for males, depressive status is a better predictor of SSS scores than is smoking status, whereas in both depressed and nondepressed females, SSS scores seem to be linked with smoking status. Female smokers, regardless of depression status, score higher than female nonsmokers. A significant main effect for depression emerged only for the ES subscale. It may be that tobacco advertising targeting women and linking smoking behavior to independence and experience-seeking enhances the lure of smoking for women who are high in sensation seeking. Our results tend to support a pharmacologically-based explanation—that is, it might be expected that high sensation seekers are particularly sensitive to the stimulant properties of nicotine, and thus particularly vulnerable to becoming dependent smokers. One might speculate that these properties are especially reinforcing for subjects who are also vulnerable to depression. Research on the biological correlates of the sensation seeking trait may contribute to a better understanding of ways in which male and female smokers may differentially "use" the stimulant properties of nicotine to achieve affect regulation.

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CHARACTERISTIC SYMPTOMS OF DEPENDENT AND NON-DEPENDENT SMOKERS

K. Downey and M. M. Kilbey

We examined demographic, smoking history, and DSM-III-R symptoms in 787 people enrolled in or employed by Wayne State University. A questionnaire covering DSM-III-R A (symptoms) and B (persistence/reoccurrence of symptoms) of lifetime nicotine dependence (ND) was used to classify persons as ND or non-ND (n-ND).

DEMOGRAPHICS Age, sex, marital status, and education were similar for the two groups. ND smokers (n=116) were significantly more religious, politically liberal, and were more likely to be white.

SMOKING HISTORY Smokers were defined as anyone who smoked daily for 1 month or more during their lifetime (n=270). ND smokers were more likely to be current smokers (77.3% vs 66.6%). Age at smoking first cigarette was similar for both groups. ND smokers consumed significantly more cigarettes/day (23.8 vs 15.7) than ND smokers (n=154). Smoking this amount had been characteristic of the groups for more than 2 years. Time after arising to smoking their first cigarette was significantly shorter in ND smokers than nND smokers. ND smokers had discussed their smoking problems with a professional (43.1% vs 21.4%) or sought treatment (26.7% vs 11.0%) significantly more frequently than nND smokers.

DSM-III-R CRITERIA A significantly greater number of ND smokers than nND smokers indicated the lifetime presence of every symptom included in the A criteria of ND outlined in DSM-III-R. However. the rank order of symptoms endorsed did not differ between ND and nND smokers. Both groups reported their most common symptoms to be those related to loss of control over smoking (Criteria A1-3). For both groups, giving up or reducing important activities (Criteria A4) because of smoking was the least reported item. “Smoking in spite of problems caused or made worse by it” was the A criteria item with the greatest separation between the two groups. Examining the total number of criteria items endorsed by the nND smokers reveals that over 70% of the nND group endorsed at least three criteria items as required for the diagnosis of ND. However, many of these people did not meet the B criteria which taps persistence or reoccurrence of symptoms.. Only 43.5% of nND smokers indicated that any symptom persisted for at least a month or occurred repeatedly. These data indicate that nND smokers experience considerable adverse symptomotology associated with smoking, but that they do not experience their symptoms as persisting and/or reoccurring. Nevertheless, over 20% discuss their smoking with a professional and 11% seek treatment for it.

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AMBULATORY MONITORING OF ALCOHOL WITHDRAWAL: DIURRAL PATTERNS OF TREMOR AND SWEATING

C. R. Frewin, M. Kaur, J. M. White, and C. McGregor

Abrupt cessation of high dose alcohol comsumption is associated with a range of withdrawal signs and symptoms, including tremor, sweating, anxiety, restlessness and hallucinations. Appropriate management of and research into withdrawal depends on accurate assessment of these signs and symptoms. However, scales used for this purpose typically rely on clinician judgement and patient self-report with associated potential for error and bias.

An ambulatory monitor recording tremor, sweating, skin temperature and activity levels has been developed to provide a more objective means of assessing alcohol withdrawal severity. The monitor also has the advantage of allowing continuous, 24 hour recording rather than measurement only at discrete points in time. The present study evaluated this method of assessment in six subjects undergoing alcohol withdrawal in a detoxification centre.

The subjects were male in-patients aged 26-46 years with a mean intake of 354 grams per day prior to admission. Five of the six had been administered diazepam to reduce withdrawal severity. Controls were age-matched males not withdrawing or using any drug other than caffeine at the time of recording. A single twenty-four hour data sample was collected from each subject.

Levels of sweating were markedly higher in withdrawal subjects compared to controls and there was a difference in the diurnal pattern: for controls the level of sweating was relatively constant through the day, while withdrawal subjects exhibited a pronounced peak at nights. This was associated with a parallel rise in skin temperature between 12:00 midnight and 4:00 a.m.. The diurnal pattern of tremor was similar in the two groups, with a decrease during sleeping hours. However, tremor was elevated in withdrawal subjects compared to controls. Similar changes were apparent in measures of activity and again levels were higher in the withdrawal group.

Using a standard alcohol withdrawal scale subjects in the present study were judged by clinicians to have only minor withdrawal symptoms. In five cases this was due to medication with diazepam, while in the sixth it was due to the low severity of the individual's withdrawal syndrome. In contrast, the results from the ambulatory monitor showed elevated levels of tremor and sweating consistent with a significant withdrawal syndrome. The data also indicate that the severity of alcohol withdrawal symptoms depends on the time at which measurements are taken. Based on the sample used in the present study, ambulatory monitoring may have an important research and clinical role in the assessment and treatment of drug withdrawal syndromes.

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AN EXAMINATION OF DRINKING BEHAVIOR CLASSIFICATION IN THE CONTEXT OF ALCOHOL-RELATED EXPECTANCIES

N. A. Piotrowski and C. C. DiClemente

Studies of alcohol expectancies often use current frequency by quantity of drinking to classify subjects. It was hypothesized that subject classification using current volume by variability of drinking would: (1) identify differences between current drinking pattern and history of problems related to drinking that are not observable using frequency by quantity; and (2) more clearly demonstrate relationships between strength of positive belief in dose-related alcohol expectancies and current drinking behavior than frequency by quantity classification. Self-report data of current drinking behavior, history of problems related to drinking. and alcohol expectancies in a sample of 248 adult human volunteers supported these hypotheses. Volume by variability classification was superior to frequency by quantity classification for demonstrating differences in drinking history, particularly for current abstainers and infrequent drinkers, and high and low variability drinkers in the high daily volume category. Use of volume by variability classification is recommended for studies examining alcohol expectancies as they related to currently drinking behavior; such classification captures important aspects of drinking history germane to alcohol-related expectancies.

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COGNITIVE MAPPING OF "CRAVING SPACES" IN LIGHT AND HEAVY DRINKERS

J. D. Greeley, C. C. Ryan, A. J. Nimmo, Y. M. Tan, K. J. Lawson, and J. Cook

Any adequate theory of craving for alcohol requires a detailed understanding of the salient cues, the *effective stimuli,* which are its triggers. One needs to know precisely how individuals perceive and construe their personal, sometimes idiosyncratic, universe of cathectic cues -- the basis on which they assign values, ascribe significance, impute salience, and draw distinctions. In this study, we used the INDSCAL variant of multidimensional scaling (MDS) to derive cognitive maps of what might be called the desire/craving space of light (L) and heavy (H) drinkers. Subjects (N=39: 25 L/14H) pairwise rated the relative potence of items which appear to have the capacity to trigger the desire to drink: TV beer advertisements; beer posters; and bottles of beer on ice. Materials keyed to Ss preferred and non-preferred beverages were contrasted with neutral soft-drink equivalents. Maps of the craving spaces of light and heavy drinkers were derived and contrasted. In general, maps of light drinkers were mom idiosyncratic. While the data were somewhat noisy, all Ss drew a clear distinction between alcohol and neutral cues but, where light drinkers analysed cues in terms of Abstract Cue Potence, heavy drinkers discriminated cues emphatically on the basis of Beverage Preference. While an Active-Passive dimension underpinned the judgments of all Ss, heavy drinkers saw beer-on-ice as a much more active, engaging, and involving cue than their light drinker counterparts. Subjects were offered mineral water ad-lib during the cue-pair rating session, and beer for ten minute post-testing. While heavy drinkers drank more of both, the between group difference was not significant for water. Heavy drinkers reported significantly greater desire for a beer both before and after the rating session, and at the end of ten minutes of drinking. We conclude that there are nontrivial, readily interpretable, differences in the desire/craving spaces of light and heavy drinkers. Further research is planned to examine the cognitive maps of craving/desire spaces for heavy, dependent drinkers and to track possible changes in these maps as a function of treatment.

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LIVER TRANSPLANTATION CANDIDATES: DEMOGRAPHIC, PSYCHIATRIC, AND TOXICOLOGICAL CHARACTERISTICS

M. E. Olbrisch, D. L. Haller, and D. Green

Alcohol induced cirrhosis causes more than 50% of cases of end stage liver disease although fewer than 10% of transplants are performed on alcoholics. The self induced nature of alcoholism, along with concerns about survival and recidivism, account for this discrepancy. This study provided data of addictive and psychiatric problems among transplant candidates. Thirty-one patients who agreed to participate in a study of success factors in liver transplant were administered the ASI and SCID. A urine drug screen was obtained as were results of a routine psychological evaluation. Eleven patients (36%) were found to have SCID lifetime substance abuse diagnoses: 82% met criteria for diagnosis of ETOH abuse (18%) or dependence (64%), 55% for opioid dependence, 45% for cocaine abuse (18%) or dependence (27%), 45% for cannabis abuse (18%) or dependence (27%), 27% for stimulant dependence, 18% for sedative-hypnotic abuse (9%) or dependence (9%), and 9% for polysubstance abuse. On urinalysis, 23% screened positive for benzodiazepines; however, this may have been due to use of sedatives during a medical procedure, while 14% screened positive for narcotics, and 3% each for cannabis and barbiturates. On the ASI, interviewers rated no areas as currently problematic except medical and psychiatric; patients rated all areas other than medical as non-problematic. MMPI results were similar to those for other medical populations (elevations on Scales 1, 2, & 3); the clinical Scales, Morey Personality Disorder Scales, and three addiction scales (Mac, AAS, APS) were slightly higher for the substance abusers. No Axis I disorders emerged on the SCID except for depression (5% of non abusers, 27% of abusers). Cognitive measures were within normal limits with the exception of Trails; scores tended to be lower for substance abusers. PACT (Psychosocial Assessment of Candidates for Transplantation) scores were also lower for substance abusers. Although they are less desirable candidates for transplant, alcoholics are still rated as acceptable for surgery. In summary, some differences exist between substance abusers and non-abusers applying for liver transplant. Whether these differences have predictive value is unclear. Data suggest the need to improve pre-transplant evaluation strategies by including addiction measures. Further differentiation among patients with a substance abuse history with regard to potential for relapse is advised and development of a risk for relapse PACT scale should be explored.

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PSYCHOPATHOLOGY IN INPATIENTS DEPENDENT UPON COCAINE OR ALCOHOL AND COCAINE

S. C. Cunningham, S. A. Corrigan, R. M. Malow; and I. H. Samason

Recent reports that the physiological and biochemical effects of the combination of cocaine plus alcohol may exceed their individual actions suggest unique properties of this combination of drugs. These findings indicate the need for further investigation into the characteristics and possible treatment needs of dually-dependent patients. Personality profiles of compulsive cocaine users and alcoholics have shown elevated levels of sociopathy, paranoia, mood disturbance and adjustment problems. This study was designed to distinguish between cocaine dependent and cocaine plus alcohol dependent individuals along several psychological variables including personality disorders, anxiety, and depression. It was hypothesized that those subjects meeting criteria for both cocaine and alcohol dependence would show higher levels of disturbance on these measures. Participants were 144 male veterans who met DSM-III-R criteria for Cocaine Dependence, selected from a Department of Veterans Affairs Medical Center Drug Dependence Treatment Unit. At least 10 days following admission, subject were administered the Structured Clinical Interview for DSM-III-R (SCID); the Beck Depression Inventory (BDI); the State-Trait Anxiety Inventory (STAI); the Shipley Institute of Living Scale; and the MMPI. Subjects were assigned to one of two groups based on meeting DSM-III-R criteria for lifetime cocaine dependence (CD; n=113) or simultaneous cocaine dependence and alcohol dependence (CD-AD; n=31).

There were no differences between groups in age, gross income, or current or lifetime drug use. The CD-AD group had significantly lower Shipley estimated IQ scores and fewer years of education. CD-AD subjects scores significantly higher than CD group on measures of depression and anxiety. CD-AD patients were more likely to meet criteria for Avoidant Personality Disorder and Antisocial Personality Disorder than CD patients. CD-AD subjects' scores were higher than the CD subjects' on each of the clinical scales.

Higher rates of depressive and anxiety-related symptomology among inpatients dependent upon cocaine and alcohol may indicate special treatment needs. Furthermore, the degree to which these treatment needs are met may affect treatment outcome. More extensive description of cocaine and cocaine plus alcohol abusers might include examination of Axis I disorders to distinguish more carefully between etiological factors in comorbidity.

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THE ELIMINATION OF COCAINE FROM HAIR IN RECENTLY ABSTINENT, CHRONIC, ADULT, COCAINE SMOKERS

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Fourteen crack addicts were followed for several months to determine how long after cessation of cocaine use, cocaine and its major metabolite. benzoylecgonine. disappear from their urine. Subjects were enrolled after their voluntary admission to an inpatient research unit for routine treatment of substance abuse/dependence. Intravenous drug abuse was an exclusion criterion. Hair, blood, and urine samples were obtained at baseline and at one and two weeks later. Subsequently, hair and urine samples were obtained approximately fortnightly until cocaine and benzoylecgonine were no longer detectable in the hair or until loss to follow-up. Mass spectrometry and gas chromatography were the methods of assay. Results to date indicate that cocaine and benzoylecgonine disappear from the hair of completely abstinent subjects after three and one-half to four months. These findings are discussed as well as the possibility that they may find application in the monitoring of cocaine addicts and in the screening of subjects for prior cocaine use during a longer period of time than is currently possible with urine and blood screening.

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DRUG-RELATED DREAMS IN COCAINE-DEPENDENT PATIENTS SEEKING TREATMENT

S. R. Herr, I. D. Montoya, and K. Preston

It has been clinically observed that drug dreams are frequent among drug abusers although they seldom are spontaneously reported. This study assessed the characteristics of reported drug dreams in cocaine dependent patients. Although theories play a role in the execution of dream analysis, this study inquired only to the content of drug dreams and possible consequences stemming from such phenomena. The prevalence and characteristics of drug dreams with cocaine or cocaine plus heroin dependent patients (DSM-IIIR criteria) were studied by interview using an investigator developed Drug Dream Assessment Questionnaire on 22 volunteers applying for outpatient treatment studies for cocaine dependence at the National Institute on Drug Abuse Addiction Research Center. Patients with other drug dependencies, except nicotine and caffeine, were excluded.

Twenty (91%) cocaine and cocaine plus heroin dependent patients reported drug-related dreams. Demographics: mean (SD) 34.1 (±6.8) years old; 16 (80%) males; 16 (80%) blacks, 4 (20%) whites; 11 (55%) were cocaine dependent and 9 (45%) were cocaine plus heroin dependent. Comparisons between the two diaanosis were made using chi square or Fisher's Exact test and t-test. Patients reported 2.4 (±6.7) dreams in the past 30 days, 95% of them at home, 80% self-administered the drug in the dream, and 70% felt the need to use the drug upon awakening. Comparisons between the two diagnoses showed that: 1) cocaine appeared significantly ($p<.001$) more often in dreams of cocaine dependents than in cocaine plus heroin dependents, 2) a trend ($P=0.095$) among cocaine plus opiate dependent patients to report craving upon waking, suggesting a possible relationship to withdrawal manifestations, 3) all patients who reported drug dreams had the presence of a psychoactive substance in their dreams, 4) all dream scenarios included the patients' participating in an activity related to drug use, 5) upon awakening, the majority of patients felt the need to use the drug about which they had dreamt, 6) those who were solely cocaine dependent reported cocaine as being the only drug in their dreams, 7) those who were both cocaine and heroin dependent were more likely to report heroin as the predominant drug in their dreams, 8) those who were solely cocaine dependent dreamt about the same form of cocaine used, 9) cocaine and heroin dependent intravenous drug users were more likely to dream about powdered heroin than I.V. ready heroin.

Drug dreams are frequent among cocaine dependent individuals and appear to be related to the abused drug. The results also suggest a relationship between drug dreams and drug craving and use that needs to be further studied.

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THE FACE OF CRAVING: FACIAL MUSCLE EMG AND REPORTED CRAVING IN ABSTINENT AND NON-ABSTINENT COCAINE USERS

T. F. Newton, M. E. Khalsa, and F. Gawin

Craving for cocaine is a subjective experience which is difficult to quantify objectively, but which has important implications for cocaine abuse and treatment. Electromyographic activity recorded over selected facial muscles can be used to quantify patterns of muscle activity associated with the experience of craving.

We studied twelve subjects using facial EMG before and after subjects completed questionnaires describing cocaine use, craving, and depression, Half were abstinent and half were current cocaine users. Zygomatic EMG tone decreased after completing the questionnaires in current users and increased in abstinent subjects (mean change -.08 units for current users; +.34 units for abstinent subjects, $p=.05$). Current users reported significantly more craving for cocaine over the past 72 hours compared to abstinent subjects ($p<.05$). Change in zygomatic EMG tone correlated strongly and negatively with reported craving over the past 72 hours ($r=-.89$, $p<.05$). Thus, the greater the craving, the less the zygomatic muscle activity. Self-reported depression correlated strongly with craving and with change in zygomatic EMG tone. After controlling for self-reported depression, the correlation between craving and change in EMG tone was reduced to $r=-.22$ (NS).

This pilot study suggests that facial EMG differs between active and abstinent "crack" cocaine users, and that these differences correlate with the presence and intensity of subjective reports of cocaine craving and anhedonia. Because craving and depression were highly correlated, however, the ability of facial EMG to discriminate between the two constructs is unclear.

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MEASUREMENT OF CRAVING IN PATIENTS WITH COCAINE DEPENDENCE

R. D. Weiss, M. L. Griffin, and C. Hufford

Despite its common use., the term "craving" is controversial. Moreover, its measurement can be problematic, since craving is purely subjective and is highly influenced by setting and drug availability. Thus, one might expect patients in protective settings such as hospitals to experience little craving, despite potentially being at high risk to relapse upon discharge. In this study of 73 patients hospitalized for cocaine dependence, we developed a series of five questions to measure different aspects of cocaine craving: 1) current intensity, 2) intensity during the previous 24 hours, 3) frequency, 4) responsiveness to drug-related conditioned stimuli, and 5) imagined likelihood of use if in a setting with access to drugs. We hypothesized that some hospitalized patients with low craving levels might believe their risk of relapse to be high in another setting. We then examined the relationship between inpatient craving levels and three-month treatment outcome. Results revealed a high level of internal consistency, with Cronbach's alpha scores of .82 to .94 on daily measures; factor analysis revealed unidimensionality; and each of the five items showed significant decreases in craving over time. The question regarding likelihood of use in another setting consistently scored higher than other questions on current craving ($p<.001$). Predictive validity was assessed by examining three-month outcome. Among the 37 patients who participated in a follow-up study, there were no statistically significant relationships between three-month cocaine use outcome and any item on the craving scale. Neither inpatient craving levels nor predictions regarding future use correlated with actual three-month outcome.

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CHANGES OVER TIME IN SOCIAL SUPPORT AND NETWORK DRUG USE AMONG TREATED COCAINE USERS

C. Weisz, B. E. Havassy, and D. A. Wasserman

We examined changes in perceived social support and social network drug use from treatment entry through 6 months of follow-up as part of a multi-site study on the efficacy of in- and outpatient treatments for cocaine dependence. We also explored relations between social relationship factors, treatment outcomes, and demographic variables. Subjects were 242 cocaine-dependent individuals who entered in- and outpatient private treatment and who completed assessments conducted at treatment entry and at 6 weeks, 3 months, and 6 months after treatment entry. Measures included indicators of perceived emotional and tangible support, support for abstinence, and social network cocaine use. Abstinence status was defined as no self-reported cocaine use and no cocaine-positive urines at any assessment beyond 4 weeks of treatment entry through the 6-month follow-up.

Levels of emotional; tangible, and abstinence-specific support increased between treatment entry and the 6-week assessment, and then began to drop. Across assessments, subjects who were abstinent at 6 months reported higher levels of support than subjects who had used cocaine. Significant interactions indicated that increases in support were maintained better by subjects who were abstinent than by those who were not. Regardless of abstinence status, subjects reported a significant decrease between the first two assessments in the proportion of social network members who used cocaine. This decrease was maintained at 6 months.

African Americans reported smaller support networks and less social network cocaine use than Caucasians across assessments and independent of abstinence status. Women reported higher levels of emotional support than men. Significant interactions for all three support variables indicated that, in general, levels of social support differed more for abstinent and non-abstinent men than for women, especially at early assessments. Non-abstinent men had the lowest levels of support across assessments.

Results suggest that maintaining high levels of social support corresponds with maintaining abstinence. Significant differences between African-American and Caucasian subjects warrant further exploration.

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STRESS AND SOCIAL SUPPORT IN PREDICTING COCAINE RELAPSE

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

This study investigated the direct effects model of negative life events, and the direct and stress-buffering effects models of social support, in the prediction of relapse in a group of treated cocaine abusers. Some support is available for each model. Negative life events experienced during both the second (between three and six months post-treatment) and third (between six and nine months post-treatment) follow-up periods contributed uniquely to the prediction of relapse during those same periods. Support was also available for the direct effects model of social support which suggests that support reduces the probability of drug use by enhancing psychological and physical well being independent of level of stress. Our measure reflecting social support status during the first follow-up period (between discharge and three months post-treatment) was significantly inversely associated with cocaine use during that same period. In addition, support during the second follow-up period was inversely associated with cocaine use during the third follow-up period. The significant interaction between level of social support and level of life events at follow-up three in the prediction of relapse during this same period provides support for the stress-buffering model.

The stress-buffering effect of social support found in this investigation parallels that found by Pakier and Wills (1990) in their study of drug use among participants in a methadone program, and suggests that this model warrants further consideration.

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COPING STYLE AS A PREDICTOR OF RELAPSE TO COCAINE ABUSE

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

This study examined patterns of problem-focused and emotion-focused coping which were hypothesized to be useful in predicting relapse in 304 cocaine abusers treated for chemical dependency. A series of stepwise multiple regression analyses were conducted to determine the contribution of scores from each of eight scales from the Ways of Coping checklist in predicting relapse during four separate follow-up periods. Results of this investigation revealed that the use of various emotion-focused coping strategies, such as escape-avoidance and self-criticism, was associated with cocaine use during the same follow-up period. In contrast, the use of such problem-focused coping strategies as planful problem-solving and seeking social support was negatively associated with relapse during the first and second follow-up periods respectively. One additional finding was that positive reappraisal was negatively associated with relapse during follow-up one.

These findings may reflect that emotion-focused coping strategies such as cognitive and behavioral avoidance and self-criticism are ineffective in dealing with life stressors and thereby increase the likelihood of substance abuse as an alternative coping mechanism. Similarly, the use of problem-focused strategies such as seeking social support may reflect more effective coping efforts, which reduce the likelihood of stress-related cocaine use. However, because most measures of such coping strategies during specific periods did not predict relapse or abstinence during subsequent periods, the nature of these associations is uncertain. Clearly, the use of problem-focused or emotion-focused coping may lead to abstinence or relapse, result from abstinence or relapse, or both.

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THE IMPORTANCE OF EVALUATING EARLY ONSET ANXIETY DISORDERS IN COCAINE DEPENDENCE: A POPULATION AT RISK FOR INCREASED HOSPITALIZATION?

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

We report the results of evaluating the ages 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 substance abuse and dependence. Twenty-nine cocaine dependent patients were evaluated at Belmont using the SCID-P. Exclusionary criteria included Psychotic Disorders, *e.g.,* schizophrenia or organic mood disorders.

Fifty-one percent (15 of 29) were diagnosed with early onset anxiety disorder. It was noted that only one patient had been previously asked about anxiety disorders prior to our evaluation. There were no differences between onset of dependence for marijuana, alcohol and cocaine for the anxiety and no anxiety groups. Median days abstinent from cocaine did not differ between groups (9 vs 11 days).

Eleven of twenty-nine patients received no diagnosis of mood disorder. Sixty-two percent (18 of 29) met the criteria for mood disorder of which 14 were diagnosed with Major Depression. For all 18 patients with mood disorder, the first major episode followed age at which patients met criteria for anxiety disorder and preceded any cocaine use. We found significantly more anxiety disorders in those patients with mood disorders: 80% vs 43%; (12 of 15 vs 6 of 14). Additionally, the early onset anxiety group had significantly mom prior hospitalizations (means, 2.2 vs 0.57). More specifically of patients with a pre-existing anxiety disorder and Major Depression, 8 of 9 had been hospitalized compared to 3 of 5 of those with Major Depression and no pre-existing anxiety disorder.

We call attention to the importance of evaluating the relationship between early onset anxiety disorder, major affective disorder, and hospitalization rate in a cocaine dependent population. We use an individualized “time line” method of evaluation which identifies age of meeting criteria for any anxiety disorder, episode of mood disorder and meeting criteria for substance dependence.

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THE RELATIONSHIP BETWEEN CHILDHOOD ABUSE AND COCAINE DEPENDENCE AMONG PREGNANT FEMALES

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

As part of a large cross-sectional study being conducted in a hospital based prenatal clinic caring for a predominately inner-city, poor, and minority population of 209 pregnant women, we assessed the relationship between self-reported histories of childhood physical or sexual abuse and cocaine use.

Women who experienced any childhood abuse reported significantly greater rates of cocaine use than women who were not abused in childhood (39% vs. 14%, $p < .001$). Pregnant women who experienced any childhood abuse also reported significantly more abuse in adulthood (24% vs. 10%, $p < .05$), and during the current pregnancy (17% vs. 4%, $p < .002$) than pregnant women who were not abused in childhood. Thus, childhood physical and sexual abuse appear to be risk factors for cocaine use and subsequent sexual or physical abuse in adulthood.

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CHILDHOOD TRAUMA AND PTSD IN SUBSTANCE ABUSE INPATIENTS

E. Triffleman, K. Delucchi, and C. Marmar

Childhood trauma--defined as abuse or neglect--is prevalent in the US general population. Some estimate that up to 2.5 million children have been physically or sexually abused. Such histories are common in clinical populations, where rates of 15-80% have been found. This study undertook two aims: (1) to examine the prevalence of childhood trauma (ChTr) in adult substance abuse inpatients; and (2) to examine the association of ChTr and adult substance use disorders, controlling for PTSD.

Methods: A convenience sample of new admissions to the San Francisco Veterans Affairs Medical Center Substance Abuse Inpatient Unit. Subjects were screened MMSE $\geq$ 26. Measures included the Traumatic Antecedents Interview (Herman, Perry and van der Kolk, 1989); the SCID PTSD and Psychoactive Substance Use Disorders modules; and the ASI.

Results: N=36 males. Mean age 45±7 yr; 30% homeless; 41% black; 39% white, 20% other. The most common substance dependence disorders were alcohol (95%); cocaine (63%); cannabis (35%) and opioids (35%). Mean yrs of drug use was 14±5 years; Subjects had a mean of 3.4±2.2 lifetime substance dependence disorders. 58% of the sample met lifetime criteria for PTSD. 77% of the sample have been exposed to at least one type of severe childhood trauma, with 46% severe physical abuse, 43% loss/separation, 25% severe sexual abuse and 43% had witnessed severe intrafamilial violence. Mean total ChTr score was 4.6±2.0 (range 0-8). Greater ChTr was associated with greater numbers of substance dependence disorders ($r=52$, $p<01$); ASI drug composite score ($r=0.37$, $p<.01$) and lifetime PTSD ($r=0.33$, $p<.04$). Number of substance dependence disorders, but not ASI drug composite score, was correlated with lifetime PTSD ($r=0.37$, $p<.03$). In a stepwise hierarchical multiple regression, ChTr was found to account for a significant increment of variance after age, ethnicity, family history of alcohol problems and PTSD were controlled for R^2 change=.1348, adjusted (R^2=.2795; final equation $p<.0142$). This model was not predictive of ASI drug composite score.

Discussion: ChTr histories were prevalent in this sample of poor, multiethnic male veterans. This prevalence is consistent with rates reported within other clinical populations. The relationship between childhood trauma and number of substance use disorders may be suggestive of the role of environmental determinants in initiation and/or maintenance of substance use problems. Further research is needed to examine this relationship further, and to examine possible treatment implications.

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EARLY CHILDHOOD LOSSES AS A GATEWAY TO ADDICTIONS

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

Grieving is a healing process for any one who has suffered a loss. Grievers, who have lost a loved one, may experience complaints of decreased appetite, sleeplessness, fatigue, and difficulty concentrating. Often they complain of sadness, despair, anger, and guilt. They may be preoccupied with the deceased person and report frequent dreams having the deceased person as a central theme. A pathologic grief reaction often results when the patient denies or inhibits the normal grief process. They fail to deal with the reality of the loss, which may be demonstrated by experiencing the physical symptoms of the deceased or presenting with false euphoria. The patient often complains of extreme guilt and self reproach. If this course is allowed to continue psychosis and/or symptoms of major depression may ensue.

Bowlby (1979) reported on the psychiatric sequelae of the loss in childhood of a parental figure. He noted that those who suffer from subsequent psychiatric disturbances show impairment of the capacity for affectional bonding. He also states that two syndromes are consistently present: psychopathic personality and depression. He noted that the childhoods of these individuals were surrounded by death, separation, or divorce of the parents or by other events causing problems in affectional bonds. According to Skolnick (1979), loss plays a central role in the etiology of substance abuse. He asserts that drug-addicted individuals resorted to drugs in an attempt to resolve major losses. We present case examples which support failure to grieve the loss of a primary support person in relationship to the development of addictions.

A high incidence of early childhood loss of a primary caretaker or nurturer (mother, father, aunt, etc.) was noted in a pilot sample of drug and alcohol dependent patients. The losses that produced the most pathological effects were centered around death of the primary support person. Three case examples are presented to highlight the need for early intervention at the time of loss in early childhood and adolescence. This indicates a need to develop strategies to deal with loss and bereavement issues as they relates to chemical abuse and addictive behaviors. The data would also suggest a role for psychotherapy during treatment to address unresolved or delayed grief reactions.

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CONDUCT DISORDER AND RISK FACTORS FOR SUBSTANCE ABUSE

G. Dale, Jr. and E. G. Singleton

A relationship between substance abuse and criminal violence among adults is well established, yet little information exists on the association of alcohol and other drug abuse among youth who commit similar offenses. This investigation reviews the case histories of adolescents diagnosed with conduct disorder. Comorbidity of alcohol and other drug problems, mental disorders, and interpersonal violence was examined and increased risks of co-occuring substance abuse and emotional problems were found. The comorbidity of interpersonal violence with alcohol and other drug problems and mental disorder was not evident, but the rate of violence was less extensive than the rates found among adults who commit similar crimes. Specific sets of risk factors and psychological characteristics were associated with increased prevalence rates for each disorder. Four models of risk are presented.

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VIOLENCE AND DRUG USE IN CONDUCT DISORDERED BOYS

S. E. Young, S. K. Mikulich, and T. J. Crowley

Does substance use predict the intensity of physical violence? We addressed this question among 94 Conduct Disordered, substance abusing males referred for residential treatment. Boys reported engaging in antisocial and criminal behavior before their regular substance use and Substance Dependence symptoms began to develop. Severity of Conduct Disorder predicted severity of both a *peak violence* ($p<.01$) score and the number of DSM III-R Substance Dependence Diagnoses ($p<.001$). There was not a significant relationship between violence score and Substance Dependence. Age or onset of these problems predicted the onset of related problems. Those boys who received abuse or dependence diagnoses (n=71) for *both* alcohol and marijuana were more likely to fight while intoxicated with alcohol than with marijuana.

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SCHOOLING, SUBSTANCE DEPENDENCE, AND CONDUCT DISORDER

J. Hardy, S. K. Mikulich, S. E. Young, and T. J. Crowley

How are drug problems and behavioral disorders related to academic performance among severely affected adolescents?

STUDY:

One hundred and eight males (ages 13-19 years) in residential treatment for Conduct Disorder and Substance Dependence are evaluated with the following battery of educational, psychiatric, and behavioral instruments: Diagnostic Interview Schedule for. Children-2, Comprehensive Addiction Severity Index for Adolescents, Composite International Diagnostic Interview Substance Abuse Module, Wechsler Adult Intelligence Scales-Revised (boys > 15 years), Wechsler Intelligence Scales for Children-Revised (boys < 16 years), Modified Lewis Aggression Scale, Conners Teacher's Questionnaire, and Woodcock-Johnson Achievement Tests.

FINDINGS:

All boys meet criteria for DSM-III-R Conduct Disorder; 18% meet criteria for Attention Deficit Hyperactivity Disorder (A.D.H.D.) and 54% report 8 or more symptoms of A.D.H.D. On average, these boys are rated as highly aggressive and meet criteria for Substance Dependence diagnoses for more than 3 drug categories. I.Q. testing reveals average intelligence (full scale = 98.2) but significantly higher performance (101.4) than verbal (96.3) I.Q. scores ($p<.001$). These boys are very academically delayed, averaging 2.4 to 3.5 grade levels behind expected age ability depending upon discipline. History of repeating a school grade is significantly associated with greater academic delay ($p=.01$), but not with I.Q. or behavior variables. For the 49 boys for whom complete data is available, two-step factor analysis identifies three factors accounting for 64% of the total variance and defines the characteristics of: 1-conduct-aggression-drug problems, 2-school ability and intelligence, and 3-classroom immaturity.

CONCLUSIONS:

Youths referred for residential treatment of Conduct Disorder and Substance Dependence may suffer from marked academic delay despite average intelligence continues to strongly correlate with delay. Although drug and conduct problems, as well as high aggression and symptoms of A.D.H.D. are common, they are distinct characteristics which do not correlate with academic ability in our population. These findings underscore the need for specific evaluation and remediation of academic delay in boys referred for residential treatment of Substance Dependence and conduct disturbances without presumption based upon the severity of these referring conditions.

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GENDER COMPARISONS OF PSYCHOLOGICAL SYMPTOMS IN SUBSTANCE-DEPENDENT ADOLESCENTS: SUGAR AND SPICE?

C. L. Martin, T. Moss, S. Mikulich, D. Shanks, K. Hill-Young, and T. J. Crowley

Little research has been done on girls diagnosed with drug dependence and conduct disorder. Therefore, the treatment needs of this population are difficult to evaluate. The present study documents the effect of gender on substance use. conduct disorder, aggression and depression. A population of 74 substance dependent adolescent boys with conduct disorder were compared to a similar population of 20 adolescent girls. No significant differences were found in the number of substance dependent diagnoses or age of onset of first regular drug use. General population studies indicate that boys are significantly more aggressive than girls. In our population, we found only a slight significance. In behaviors such as initiating fights, fighting with weapons and physical cruelty, we found no significant differences. Girls were found to be significantly more depressed than boys and were more likely to run away. Treatment implications are suggested.

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DEVELOPMENT OF A STRUCTURED INTERVIEW FOR THE ASSESSMENT OF CHILD ABUSE IN SUBSTANCE DEPENDENT ADOLESCENTS

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We report preliminary testing of a structured interview for assessing among adolescents childhood experiences of neglect and physical or sexual abuse; we relate that history to substance diagnoses. The 54-item structured interview includes 25 items on neglect, 15 items on physical abuse, 17 items on sexual abuse, and a final section exploring victims' perceptions of the effects of these experiences. A structured probe for each critical-direction response assesses duration or frequency, relationship to the perpetrator, whether victim or perpetrator were intoxicated during the event, and severity of injuries. We have prepared SPSS-based computer entry routines for these data, readily permitting statistical analyses. We report preliminary data on 19 adolescent male and female patients (ages 13-18), who have Conduct Disorder (Diagnostic Interview Schedule for Children) and Substance Abuse or Dependence (CIDI-SAM), and who were admitted for evaluation and/or treatment. All youths report at least one abuse or neglect item, with a mean of 11 positive items per youth. Over three-quarters of youths report a perpetrator intoxicated, and over half report that the victim was intoxicated during an episode of abuse/neglect. One-fourth report rape. Over one-fifth state that the abuse or neglect resulted in their taking drugs or alcohol. There is a significant ($r=0.71$; $p<0.01$) correlation of abuse/neglect duration versus number of drug abuse or dependence diagnoses. These preliminary results reveal a remarkably high prevalence of abuse and neglect in this population and a striking relationship between duration of abuse and neglect and number of drug diagnoses. We discuss plans for further instrument development.

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EVENT-RELATED POTENTIAL INDICATIONS OF RISK FOR DEVELOPING SUBSTANCE ABUSE DISORDERS

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This study utilized event-related potentials to differentiate sons of substance abusers (family history positive, FHP, n=21) from control subjects at average risk for substance abuse (family history negative, FHN, n=27). As part of a longitudinal study of substance abuse risk in prepubertal boys, we studied electrophysiological differences between 10-12-year-old sons of substance abusers and sons of parents with no substance abuse history.

Subjects were assessed with an auditory "oddball" task in which target stimulus probability was manipulated at .10, .30, and .50. ERPs were collected at Fz, Cz, Pz, P3, and P4 recording sites with a .01-30 Hz bandpass. Stimuli were 1000 Hz (non-target) and 2000 Hz (target) presented every 2 seconds. Subjects were instructed to count only target stimuli. Components measured were P3(00) and a negative component at 600 ms post-stimulus (N600).

Four-factor (FH group x Probability x Stimulus x Electrode) multivariate analyses of variance were applied to amplitude and latency data from the P3 and N600 components, with separate analyses for midline and parietal leads. FHP and FHN differed in N600 amplitude and latency. (All statistical probabilities were $p<.05$). N600 amplitude was lower in FHP than in FHN at parietal sites (FH x Stimulus interaction, $F=6.59$, 1,828 df, $p=.01$). N600 latency was longer in FHP (643 ms) than in FHN (544 ms), differing in target and nontarget responses in all probability conditions at midline (FH x Probability x Stimulus interaction, $F=3.70$, 2,828 df, $p=.025$) and parietal ($F=4.96$, 2,828 df, $p=.007$) sites.

Pre-adolescent boys considered at risk for development of a substance abuse disorder showed lower amplitude and longer latency on a show negative deflection or component, 'N600'. This component is believed to be associated with cognitive reprocessing.

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PSYCHOLOGICAL PROFILES OF SUBSTANCE ABUSERS WITH A FAMILY HISTORY OF SUBSTANCE ABUSE

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Initial analyses of intake interview data from 465 clients seeking drug abuse treatment in' Washington, D.C. have revealed that 304 clients (65%) reported that one or more of their family members had a history of alcohol and/or drug abuse. Clients with a family history of alcohol and/or drug abuse received significantly higher scores on eight of nine Brief Symptom Inventory (BSI) derived scores and the BSI General Severity Index, eight of 22 Million Clinical Multiaxial Inventory II scales, five of six State-Trait Anger Expression Inventory scales, and several questions about physical and sexual abuse from the intake interview. Future prevention and treatment efforts with similar client populations need to recognize the critical role that the family may play in affecting clients during and after addiction treatment.

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ANTISOCIAL PERSONALITY DISORDER AMONG HOMELESS MENTALLY ILL SUBSTANCE ABUSERS: A COMPARISON OF THE DIS AND SCID

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

The Diagnostic Interview Schedule (DIS) and the Structured Clinical Interview for DSM-III-R (SCID) both provide a determination of psychiatric diagnosis according to DSM-III-R criteria. The DIS is a structured interview with high reliability that is administered by trained non-clinicians. The SCID is a semi-structured interview that formalizes questions and decision rules, but allows for clinical judgment. This paper examines the agreement between the DIS and the SCID on the diagnosis of antisocial personality disorder (APD) using both the current DSM-III-R, and the proposed short criteria for DSM IV. Both instruments were administered to a sample of men who were enrolled in long term residential treatment programs for mentally ill chemical abusers. The presence and absence of each symptom and the overall diagnosis of Antisocial Personality Disorder were compared for each instrument. The sample consisted of 54 homeless MICA males over the age of 21 who had extensive histories of psychiatric hospital stays, substance abuse, underemployment and homelessness, but comparatively less incarceration.

Agreement between the SCID and DIS on APD is relatively low although consistent with other findings for this disorder. The differences found in assessment of symptoms stem from both the method used to gather the information as well as specific criteria used to test for the presence of a behavioral problem. Symptoms contributed differently to the final outcome of the disorder depending on the instrument used and the criteria set used. For example, given that the DSM-III-R diagnostic rules require any three or more positives out of 12 responses for conduct disorder, a rank ordered comparison based on measures of association provides the basis for conclusions regarding each symptom's relative contribution towards the diagnosis in the sample. In this case, stealing without confrontation, lying and truancy account most strongly for the diagnosis using the SCID and stealing without confrontation, lying and stealing with confrontation for the DIS. The prior example also figures strongly in agreement between DSM-III-R and DSM-IV criteria given that the reduced symptom set consists of stealing without confrontation, lying and truancy. In the case of the DSM-IV criteria set, the agreement rate for the SCID lowers with the exclusion of the other items while the agreement rate for the DIS increases. The agreement rate of the DIS, however, remains lower. The DIS and the SCID show differences in sensitivity to various items which, for this population, may reflect circumstantial rather than pathological conditions. The major criteria used for the "no planning" or "impulsiveness" indicator may actually be more reflective of the condition of homelessness. Likewise, the substance abuse lifestyle may account for the preponderance of illegal behavior, unemployment, unpaid debts and dishonesty.

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ADDICTION, PSYCHIATRIC, AND OTHER CLINICAL SEVERITIES IN ACUTE DUAL DIAGNOSIS UNIT INPATIENTS

R. Ries and M. Mullen

Though a good deal of data exist on persons with psychiatric/addiction comorbidity, most such data come from general population studies or from defined addiction or psychiatric services. This is one of the first studies to report data from a defined dual track treatment unit which is located in a university-staffed urban county hospital in Seattle, Washington. One-hundred and four acute and emergent patients were classified as having no (N=17), past/not current (N=50), or current +/- past (N=37) psychoactive substance dependence (AOD disorder) by using the Computerized DIS-R. Demographic variables were similar among the groups, but more current AODs had had involuntary psychiatric commitments, as well as AOD treatments. Though mostly a depressed mood disordered versus chronically psychotic population, this was about the fifth psychiatric hospitalization for most patients, with some reporting more than 20. There were "consistent" inconsistencies between clinical diagnosis/reason for admission versus research ratings (BPRS/SCL-90 and DIS diagnoses). Elevated scores on BPRS and SCL-90 were found in the current AODs > past > non-duals in inverse proportion to the percentage of clinical diagnoses of mania/schizophrenia. Thus, it appears that these research ratings were significantly influenced by current and even history of AOD disorder. Likewise CDIS-R diagnoses for mania/schizdphrenia appear strongly influenced by both current and history of AOD disorder. The CDIS-R issued research diagnoses of schizophrenia or mania 5-6 times more frequently than clinicians in current AOD, 2-3 times in past, but in equivalent percentages in non-duals. This suggests that even though logic exists in the DIS to screen for substance-induced symptoms, such symptoms appear to highly influence diagnoses. A further finding was that rigorous structured interviews were poorly tolerated by acute psychotic patients leading to decompensations, termination of interviews and/or data bias.

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PREVALENCE OF SOMATIZATION DISORDER (BRIQUET'S SYNDROME) AMONG METHADONE MAINTENANCE THERAPY PATIENTS

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The objective of this study was to report the prevalence of somatization disorder (Briquet's syndrome) in methadone maintenance treatment clients and their pattern of use of health care service. In 1991, at the methadone maintenance clinics in New York City, 715 patients were screened with 4 instruments: Q-DIS, ASI, BDI, and TSR. Using positive diagnosis of somatization disorder of Q-DIS, 31 (4.3%) patients were identified as somatizers. They were mostly blacks (35%), Hispanics (29%), whites (9%), American-Indians (3.2%), others (12.9%) respectively, 100% unemployed and females (77%). Somatizers were also found positive for nicotine dependence (90%), anxiety (5 1.6%), and depression (4 1%). Analysis of variance to test the variable sex and mean TSR score disclosed significant difference between somatic and non-somatic for use of psychological service ($p<0.007$). Using the median TSR score to determine the level of health care used by somatizers, statistical analysis found female somatizers requested more psychological services than male somizaters. Across the general sample, female health care use was greater for medical ($p=0.05$) and psychological services ($p<0.001$).

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DIAGNOSTIC AGREEMENT BETWEEN THE STRUCTURED CLINICAL INTERVIEW FOR THE DSM-III-R AND THE ALCOHOL RESEARCH CENTER INTAKE INTERVIEW

L. J. Felch, R. K. Brooner, K. A. Varner, V. L. King, and G. E. Bigelow

The Alcohol Research Center Intake Interview (ARC) was developed by Schuckit *et al.* (1988) to facilitate structured psychiatric diagnostic assessment of substance abusers. To reduce interview time, the instrument assesses a subset of psychiatric disorders of high prevalence in substance abusers *(e.g.,* major depression, antisocial personality) or high morbidity *(e.g.,* schizophrenia). Schuckit *et al.* (1988) reported agreement rates of 91-100% between the ARC and the SADS, based on a small sample of 20 alcoholics. The present study is the first to examine the lifetime diagnostic agreement rates between the ARC and the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer 1988) in a population of opiate dependent subjects. This study also provides estimates of diagnostic agreement in a large sample.

Patients were 250 opiate abusers newly admitted to an outpatient treatment program that incorporated methadone substitution therapy. Fifty-two percent of the sample was female. The mean age was 34.0 years (s.d.=6.7), with an average of 10.9 years of education (s.d.=2.2). Seventy-four percent were unemployed and 70 percent were Caucasian. SCID and the ARC interviews were given in counter-balanced order between weeks three and four of treatment, with the second interview following the first by three to seven days. The second interviewer was blind to the results of the first interview.

Among the lifetime non-substance use disorders, only major depression and antisocial personality (APD) had prevalences greater than 5%; the kappas were .56 and .75 respectively. The main source of disagreement between interviews was discrepancies in the reports made by patients. For APD, most disagreements resulted from discrepant patient reports on the before-age-15 criteria. As expected in a chronic drug dependent sample, lifetime substance use disorders were frequently diagnosed. Kappas for substance Dependence diagnoses were in the good to excellent range for most substances *(e.g.,* opioid= 1.00, cocaine=.76), with the exception of cannibis (.30). The kappas for substance Abuse diagnoses were uniformly poor (range=-.03 to .17, median=.07). In summary, the overall agreement rates between interviews were good to excellent, with the exception of cannabis Dependence and all of the Abuse diagnoses.

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A COMPARISON OF MMPI AND MMPI-2 HIGH-POINT SCORES AMONG METHADONE MAINTENANCE CLIENTS

S. D. Husband and M. Y. Iguchi

The introduction of the MMPI-2 has raised issues regarding the comparability of the MMPI and MMPI-2, including the degree to which MMPI-2 results may be interpreted based upon the large body of research that is available for the MMPI. This study compared MMPI and MMPI-2 high-point scores in a group of inner-city, methadone maintenance clients. Eighty-nine subjects volunteered to participate and completed both the MMPI and MMPI-2 on two successive days at the methadone clinic they attended. Fifty-one subjects produced valid profiles on both the MMPI and MMPI-2. Of these 51 valid MMPI/MMPI-2 pairs, 57% had the same high point or 2-point code, and 31% had one common scale among the two highest scales on each profile. Twelve percent had no common scale among the two highest scales of each profile.

Thirty-nine pairs had clinical elevations on both profiles in the pair *(T* 70 for MMPI and *T* 65 for MMPI-2). Of these, 61% of the pairs had the same high point or 2-point code, and 31% had one common scale among the two highest scales on each profile. Eight percent of these pairs had no common scale among the two highest scales of each profile.

Using Graham *et al.'s* (1991) 5-point criterion for well-defined profiles, of the 26 pairs in which both profiles met this criterion, 58% had the same high point or 2-point code, and 19% had a well-defined high point on one test which was contained within the well-defined 2-point code of the other. Eight percent had one common scale between the well-defined 2-point code of each profile in the pair. Fifteen percent of these pairs had no common scale among the highest one or two well-defined scales.

Although the sample size is modest, and congruence almost certainly was diminished because of temporal instability and the relatively large number of poorly-defined profile pairs, these results appear to offer support for the use of the MMPI-2 in this population.

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PSYCHOSEXUAL FUNCTIONING IN DRUG-DEPENDENT AND NON-DRUG DEPENDENT WOMEN

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Psychosexual functioning was examined in opioid-dependent women (N=57) who were outpatients in a methadone maintenance program. Results were compared to control subjects (N=50) who were from the same geographic area but did not have a history of drug-abuse problems. In general, both opioid-dependent and control women exhibited a wide range of sexual attitudes, values, and behaviors. Both groups were similar in terms of age of onset and types of sexual experiences reported during their lifetime and over the past 60 days. Analysis of the prevalence of specific sexual behaviors between lifetime and past 60 days revealed similar results in each group. There were no differences in opioid-dependent and control subjects in accuracy of sexual information, sexual fantasy, body image, sexual satisfaction, or level of psychological distress. However, opioid-dependent women reported having a lower sexual drive than control subjects, which may reflect the pharmacological effects of opioids on sexual functioning. Opioid-dependent subjects also were more likely to endorse more stereotypically masculine and feminine gender roles and to have less provincial attitudes about sex than control subjects. The implications of these findings for HIV prevention is discussed.

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PREVALENCE OF ANXIETY AND AFFECTIVE DISORDERS IN A METHADONE MAINTENANCE TREATMENT SAMPLE

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To estimate prevalence of Anxiety and Affective Disorders in methadone maintenance treatment a random sample from three diverse methadone maintenance populations (n=271) was followed after six years by an independent research team. Subjects (n=102) from VAMC's at Philadelphia and Sepulveda and the University of Alabama at Birmingham's program were given a DSM III-R standardized interview to assess Anxiety and Affective Disorders. To assess diagnostic reliability a 44% random sample was administered the DSM III-R interview by the senior clinician immediately following the first interview. To assess diagnostic validity Spielberger Anxiety Scales and the Beck Depression Inventory were administered. Diagnostic reliability, defined as percent agreement between the senior clinician and research interviewers was 75% for Anxiety, 80% for Affective Disorders, and 80% for both when agreement on non-diagnosis was considered. Percent agreements were much lower for specific diagnoses.

Anxiety Disorder was diagnosed in 55%, with PTSD 31% and Generalized Anxiety Disorder 20%, most prevalent. Affective Disorders were found in 57.8% with Major Depression 31.4% and Bipolar Disorder 12.7%. No diagnosis in addition to Substance Use Disorders was found in 25.5%. There was significant co-morbidity of Anxiety and Affective Disorders. In 36.3% of subjects with an Anxiety Disorder there was also an Affective Disorder, Chi Square=5.363, $p < .021$. There was no significant difference in prevalence of either disorder between treatment and no-treatment groups. Significant differences on the Spielberger Anxiety Scales and the Beck Depression Inventory from subjects with vs. without Anxiety or Affective Disorder provide evidence for validity of diagnoses assigned. Subjects with Anxiety Disorders scored significantly higher on the Spielberger State Anxiety Scale than those without Anxiety Disorders, mean=45.69 vs. 34.52, $t=4.98$, $df=100$, ($p<.0000$), and significantly higher on the Trait Scale 46.57 vs. 36.90, $t=5.45$, $df=100$, $p<.0000$. Subjects with Affective Disorders scored significantly higher than those without Affective Disorders on the Beck Depression Inventory, mean=15.07 (SD=11.2) vs 7.77 (SD=6.92), $t=4.10$, $df=98$, $p<.0001$.

Findings suggest opiate addicts in methadone maintenance usually have other co-existing Mental Disorders requiring thorough assessment and treatment in addition to drug counseling. Possible selection bias, based on estimating prevalence from subjects who could be located and followed vs. those who could not, cannot be ruled out. However, analysis of baseline demographic data in followed vs. un-followed groups yielded no significant differences. High prevalence of PTSD is likely associated with the large proportion of followed veterans and may not be representative of treated opioid addicts.

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PERSONALITY DISORDERS AND TREATMENT RESPONSE IN OPIATE ADDICTS

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Personality disorders (PDs) were diagnosed, using the Structured Interview for DSM-III-R Personality (SIDP-R), in 156 males recently admitted to methadone maintenance treatment. Sixty-four percent had at least one PD and 27% had two or more. The most frequently occurring PD was antisocial personality disorder (APD - 36%); no other specific PDs occurred in more than 10% of the sample. Seven month treatment outcome was assessed in seven problem areas - medical, employment, drug, alcohol, legal, family/social and psychiatric status, by comparing intake and follow-up data from the Addiction Severity Index (ASI). Subjects with and without PDs improved over time in most of the problem areas assessed, additionally the magnitude of improvement was generally equivalent for PD and no PD subjects. PD subjects, nevertheless, had more severe problems in most areas at intake and at follow-up. There were several more specific findings. Subjects with more than one PD were particularly psychiatrically symptomatic. Cluster C PDs were related to more psychiatric and family/social problems. APD was associated with more alcohol and legal problems. Although PD subjects do improve with treatment, additional focused interventions may be warranted because of their more severe problem status.

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VALIDITY OF SELF-REPORTS OF HEROIN AND COCAINE USE IN METHADONE MAINTENANCE PATIENTS: DATA FROM REPEATED ASSESSMENTS

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OBJECTIVES: To assess the validity of methadone-maintenance patients' self-reports of heroin and cocaine use across multiple assessments and to identify demographic, treatment-related, and psychological predictors of valid reporting.

METHOD: As part of a study of predictors of needle use during methadone-maintenance treatment, 81 patients from four treatment programs were interviewed twice per week for up to 10 weeks. At each interview, Ss gave a urine sample and reported their drug use. Ss were informed that data would not be shared with treatment staff. Self-reports (SR) of heroin and cocaine use were compared to urine toxicology (UA) screens for morphine and benzoylecgonine. UA findings were considered the "gold standard" for establishing drug use. Validity indices were sensitivity, specificity, and chance-corrected overall agreement.

RESULTS: Ss often did not report drug use when urines were positive, resulting in low sensitivities for self-reports, particularly for cocaine. Ss rarely reported drug use when urines were negative (high specificities). Overall agreement (kappa) between UA results and self-reports was fair to good. Individual Ss varied over time in reporting UA-established drug use. Over half of Ss with 2 or more morphine-positive specimens, or 2 or more benzoylecgonine-positive specimens, were inconsistent in reporting their presumed use. No demographic or treatment-related variables predicted validity of self-reports. Ss with a current DSM-III-R diagnosis of antisocial personality disorder (by the Diagnostic Interview Schedule), however, were *more* likely to report UA-detected cocaine use.

CONCLUSIONS: (1) Methadone patients frequently do not report UA-detected drug use, particularly cocaine, despite confidentiality of the data. (2) Self-reporting of UA-detected drug use tends to be inconsistent over time. (3) Reporting current drug use may correlate with admitting other socially disapproved behaviors.

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TUBERCULOSIS AND ANERGY TESTING IN AN URBAN DEPARTMENT OF VETERANS AFFAIRS (DVA) METHADONE CLINIC: COMPLIANCE AND RESULTS

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

Tuberculosis is a growing concern for inner city residents. Studies of tuberculosis among urban methadone patients have been limited and complicated by the presence of anergy in HIV-seropositive patients (Selwyn *et al.* 1989, 1992). Anergy is defined as the inability to mount a T-lymphocyte mediated delayed-type hypersensitivity (DTH) response to skin test antigens (CDC 1991). In this study, former heroin addicts in methadone treatment at an urban DVA clinic were tested for tuberculosis exposure using the tuberculin purified protein derivative (PPD) skin test. A positive PPD was defined as $\geq$10 mm of induration in known HIV-seronegative patients and $\geq$5 mm in HIV-seropositive patients and those of unknown HIV status (CDC 1991). Patients were tested for cutaneous anergy (response of 2 mm of induration) using the intracutaneous or Mantoux-type method with *Candida* and mumps antigens. Seventy-two patients out of a total urban methadone clinic population of 81 subjects (89%) were tested (six refused testing and three were unavailable). Of those patients who refused or did not complete testing, nine were PPD positive by self report or documentation. Fifty-two subjects or 64% of the total clinic population completed testing. Ten of these patients had a positive PPD response ranging from 14-25 mm of induration; all ten patients subsequently had chest x-rays which were negative for active tuberculosis. Of the patients who completed testing, 19% were PPD positive. HIV status in these patients was unknown (eight) or seronegative (two). Twenty-five patients were PPD negative (but had a positive response to Candida and mumps) and required no further follow-up. Seventeen patients who completed testing were anergic so that exposure to tuberculosis could not be determined by the PPD skin test (of these, 13 patients or 76% were HIV seropositive). All 17 of these patients although asymptomatic were referred to the DVA-affiliated infectious diseases clinic for further evaluation. In the thirteen patients who complied with the referral, there was no clinical or radiologic evidence for active tuberculosis. These findings illustrate some of the difficulties and benefits in screening for tuberculosis in this population and also demonstrate the absence of active tuberculosis found in this urban methadone clinic.

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SUBSTANCE USE IN CHRONIC PAIN PATIENTS: A TOXICOLOGICAL STUDY

K. Ingersoll, D. Hailer, K. Dawson, A. Poklis, and A. Radii

The purpose of this study was to determine base rates of prescription and recreational drug use among chronic pain patients based on the objective data of urine drug screens. Two hundred and ninety-five consecutive admissions to the MCV Pain Center submitted to urine drug screens and provided demographic and medical information at intake. Subjects included 136 men and 159 women aged 16-86. Seventy-one percent were over 35; 72% were Caucasian, 27% African-American, and 1% Asian-American. Pain diagnoses included MDPS (39%), RSD (20%), Back Pain (19%), Neuropathy (9%), Headache (1%), and other (13%). Urines were screened for Rx and recreational drugs using Syva EMIT-d.a.u. Immunoassays and ToxiLab thin layer chromatography system.

RESULTS:

The degree of agreement between self-report and urine toxicology was very poor; Kappas ranged from .25 to .34. Patients over-reported use of narcotics, benzodiazepines, barbiturates, and tricyclics, suggesting noncompliance or sporadic dosing. No patients reported recreational drug use on intake. Urine toxicology revealed that 44% of patients took addictive medications recently enough to be detected. Overall, 32% used prescription drugs (24% opioids, 16% benzodiazepines, and 5% barbiturates). Fifteen percent used recreational drugs (14% THC, 4% cocaine). Tricyclics/metabolites were found in 13%. The percentage of drug free patients was stable across age, sex, and race. However, use patterns varied by race, age, gender, pain cause, worker's compensation, litigation, and smoking status. Specifically, more older patients used Rx drugs; more younger patients used recreational drugs. More Caucasians (35%) used Rx drugs than African-Americans (24%); in contrast, 23% of African-Americans screened positive for recreational drugs versus 13% of Caucasians. More women (35%) than men (29%) used Rx drugs; more men (23%) than women (9%) used recreational drugs. More smokers used recreational drugs (20% marijuana, 6% cocaine) while 9% of nonsmokers used marijuana and 3% cocaine. Litigation was inversely related to drug use. More WC patients used THC than non-WC patients (20% v. 10%).

IMPLICATIONS:

Results indicate that homogeneous sub-groups of drug-using pain patients exist. Chronic pain patients using drugs must be identified in order to provide proper treatment for pain and substance abuse. Pain programs should evaluate patients' use of all dependency-producing substances. However, patients do not volunteer information about recreational drug use, even though 15% are actively using, and patients over-report prescription use. Due to high false positive and false negative rates obtained by self-report alone, we recommend that more rigorous detection methods be incorporated into clinical practice.

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PARTICIPATION IN NON-TREATMENT DRUG ABUSE RESIDENTIAL STUDIES REDUCES SELF-REPORTED PSYCHOPATHOLOGY.

C. Haertzen and I. D. Montoya

Purpose: The growing knowledge of the etiology, effects, and complications of drug abuse has been made possible in part by research on volunteer drug abusing human subjects. The psychological safety of their participation in non-treatment residential drug abuse research protocols has been controversial. To evaluate this, the average raw scores of the Symptom-Check List-90 Revised (SCL-90R) at the time of recruiting and discharge (40.2±15.6 days later) from drug abuse non-treatment residential studies was compared.

Methods: Inclusion criteria were: current diagnosis of drug abuse/dependence, and SCL-90R administered during recruitment and discharge. Exclusion criteria were illiteracy, major medical or psychiatric disorders, pregnancy, and/or clinical evidence of drug intoxication. Comparisons between recruitment and discharge data were made using t-tests for repeated measures. During the time that subjects stayed on the closed residential ward they received no explicit drug abuse treatment, had recreation activities, free meals, and non-alcohol drinks, and had to follow written rules.

Results: Of the 233 drug abusing subjects, 228 were males (97.8%), mean (SD) age was 31.8±5.6) years, and years of education 11.7±1.6). One hundred and thirty five (57.9%) subjects were black, 91 (39.1%) white, and 7 other (3.0%). Self-reported "drug of choice" was cocaine in 68 (29.2%) subjects, heroin 62 (26.6%). marijuana 53 (22.7%). and other 37 (21.5%). There was significant reduction ($p<.01$) between recruiting and discharge for Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Phobic Anxiety, Paranoid Ideation, Psychoticism, and Total Scores. For those who reported cocaine as "drug of choice", there was significant score reduction ($p<.01$) for Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Paranoid Ideation, Psychoticism, and Total Scores. For those who reported heroin, there was significant score reduction ($p<.01$) for Interpersonal Sensitivity, Depression, and Paranoid Ideation. For those who reported marijuana there was significant score reduction ($p<.01$) for Obsessive-Compulsive, Interpersonal Sensitivity, and Psychoticism.

Conclusion: The results showed that participation of drug abusers in non-treatment residential studies is psychologically safe and suggest a therapeutic effect that may be associated with removing those individuals from their drug environment and offering a safe and structured milieu.

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THE VALIDITY OF SELF-REPORTED DRUG USE DURING FOLLOW-UP EVALUATIONS

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

INTRODUCTION: This study examines the validity of patients' self-reports of drug use in a sample of methadone maintained patients at follow-up, six months following treatment admission. Patient self-report data obtained from the Addiction Severity Index (ASI) covering the previous 30 days were compared against the results of weekly, randomly scheduled urinalyses over the same period.

OBJECTIVES:

- Examine the validity of self-reported data at follow-up evaluation using urinalysis as a criterion variable.
- Compare different methods of interpreting/reporting self-report and urinalysis data.
- Identify some of the limitations associated with urine collection and self-reported data.

METHODS: Subjects were recruited from the methadone maintenance program of the Philadelphia (Pa) Veterans Affairs Medical Center and a community based outpatient methadone program as part of a large scale evaluation of methadone treatment. A total of 120 subjects voluntarily completed a baseline evaluation consisting of the ASI and other self-reports. Subjects' drug use was monitored weekly for 24 consecutive weeks through randomized urine testing. At the 24-week evaluation point all 66 subjects still in treatment completed the follow-up version of the ASI and submitted at least one urine sample, comprising our research sample. Urine specimens were analyzed by the EMIT system for opiates and cocaine.

DATA ANALYSIS: Urine results and self-reports for opiates and cocaine were measured as dichotomous variables. Subjects testing negative for drug use on all urine results were identified as abstinent and subjects testing positive on any drug screen were considered non-abstinent. Subjects reporting no days of drug use in the past 30 days on the ASI were identified as abstinent, while reports of any drug use was classified as non-abstinent. Three methods of measuring self-report and urinalysis data were analyzed:

1. All urine screens during the 24 week period (range=1-8 urines)(N=66).
2. Four urine screens, 1 each week (N=35) for 4 consecutive weeks.
3. A single urine screen at time of follow-up interview (N=56).

RESULTS:

- Self-reports were more likely to detect opiate and cocaine use than urinalysis in each of the three methods tested.
- Less than 6.5% of the subjects under reported drug use for both opiates and cocaine.
- The degree to which self-reports agreed with a positive urinalysis was higher for cocaine than opiates. Subjects were more likely to self-report cocaine than opiate use.
- The use of urinalysis and self-reports together as a method to measure drug use was more likely to yield higher rates of drug use than urinalysis or self-report alone.

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A MODEL FOR MAINTAINING QUALITY DATA WITH RESEARCH INTERVIEWS: THE ADDICTION SEVERITY INDEX

I. Fureman, A. T. McLellan, A. Alterman, and D. Zanis

The Addiction Severity Index (ASI) has proven useful in gathering reliable and valid information on substance abuse patients. A "trained" ASI interviewer has been formally exposed to the many documented ASI coding rules and conventions, usually through an ASI training seminar; an "untrained" ASI interviewer has not. It has generally been assumed that (1) the ASI training materials provide clear guidelines about how to code information received during an ASI interview, and (2) the interviewer will remember the rules presented during the initial training seminar throughout the period that s/he will be conducting interviews. Therefore, s/he will make coding decisions that are similar to those being made by similarly trained colleagues. A quiz was recently developed at our center to test the assumption that a group of trained and experienced ASI interviewers would answer ASI questions the same way. A sample of 31 individuals currently responsible for conducting ASI interviews for research projects completed the quiz. Included were 20 research assistants, six research supervisors, and live investigators, who had been conducting ASI interviews at the center for at least six months. The quiz included a series of multiple choice questions that addressed the following areas: (1) coping with difficult interviewing situations, (2) recognizing current coding conventions, and (3) understanding the relationships among the sections of the ASI. *Because the goal of the quiz was to uncover center-wide inconsistencies, the questions on the quiz focused on areas in which rules seemed open to interpretation.* Scores on the quiz ranged from 52% to 97%, with a mean score of 80%. The quiz score was not related to either the number of months that an interviewer worked at the center, or the number of ASI interviews done in a month. The individual questions on the quiz provided the most useful information for quality assurance purposes. If less than 75% of the interviewers answered any individual item correctly, the item was labeled a "problem area." The quiz uncovered problems in understanding the rules used to describe several variables, including drug treatment episodes, cash spent on drugs, and years of "regular" substance use. Based on the data gathered through our coding convention quiz, one might conclude that it is important to regularly monitor the abilities of interviewers to consistently code research interviews such as the ASI. It should be stressed that the ability to memorize the documented coding rules constitutes only one part of administering a structured interview. Certainly, a competent ASI interviewer should also possess the ability to probe, clarify and restate points throughout the interview, without sacrificing rapport. This quiz has not provided us with any information on interviewers' abilities to form rapport with patients. It is recommended that this type of coding convention measure be augmented by direct supervision, to uncover problems with interviewer style, which may not be otherwise revealed. This coding quiz is the first in a series of quality assurance procedures that we have adopted to increase the reliability of the information gathered with the ASI.

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PSYCHIATRIC REFERRAL IN METHADONE MAINTENANCE

A. J. Saxon, P. M. Grekin, D. Voirin, E. A. Wells, D. A. Calsyn, and R. Jackson

This study examined psychiatric referral patterns in a sample of 232 admissions to a methadone maintenance program. At treatment entry patients were assessed with the Addiction Severity Index (ASI) and the Millon Clinical Multiaxial Inventory (MCMI). Methadone counselors remained blind to results of these assessments but could refer patients for psychiatric evaluation based on clinical judgment. Patients provided random weekly urine specimens. Referred patients (n=39, 16.8%) did not differ from non-referred subjects on demographics besides race: Fewer black (n=9, 10.5%) vs. non-blacks (n=30, 20.5%) received referrals ($p<.05$). Referrals had higher ASI composite psychiatric scores (mean=0.34, SD=0.26) than did non-referrals (0.14, 0.19, $p<.0001$). A greater proportion of referrals scored in the range indicating presence of a disorder on the MCMI clinical syndrome scales of Anxiety, Dysthymia, Psychotic Thinking, and Psychotic Depression. Clinical Axis I diagnoses for referrals completing psychiatric evaluation (n=32, 82.1%) included unipolar and bipolar mood disorders (74.8%), Anxiety disorders (25.1%). Eating disorders (6.3%). Schizophrenia (3.1%) and none (25%; Percentages total more than 100 because of multiple diagnoses). Treatments included psychotherapy only (15.6%). medications only (25.0%). both (43.8%). and none (15.6%). Evaluated patients were compared on outcomes with 2 groups of non-referrals who remained in treatment at least 4.5 months (the median time in treatment when referrals were made). The first comparison group (Should Refer, n=61) exhibited comparable psychopathology to the referrals as demonstrated by elevations on at least one of the aforementioned MCMI scales and/or the Psychotic Delusion MCMI scale. The other comparison group (Should Not Refer, n=74) had no elevations on these scales. The evaluated group gave a lower percentage of drug positive urines during the course of treatment (mean=43.0±30.0%) than did the Should Refer group (67.0±23.0%, $p=.001$) and remained longer in treatment (median months=20.6) than did the Should Refer (9.8, $p<.001$) or Should Not Refer groups (10.8, $p<.001$). However, the evaluated and comparisons groups also differed significantly in urinalysis results in the first 4.5 months. Therefore, the ultimate comparison groups consisted of patients who had low drug use during the first 4.5 months. This subset of Should Refer patients (n=27) did not differ from the evaluated group in urinalysis results during any time in treatment. Neither did the evaluated group decrease its percentage of positive urine results following psychiatric better treatment retention than did the comparison groups with low drug use in the first 4.5 months (Should Refer median months=14.4, $p=0.25$; Should Not Refer [n=40] 13.5, $p=.069$). Psychiatric referrals by methadone counselors did accurately target a group with psychopathology, but counselors failed to refer other patients whose MCMI results also indicated psychopathology. No definite improvements in illicit drug use or treatment retention could be demonstrated for psychiatric evaluation and treatment of methadone maintenance patients.

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BEHAVIORAL CHANGE INDEX: A SITUATION BASED BEHAVIORAL ASSESSMENT INSTRUMENT

S. Shoptaw, R. Rawson, and M. McCann

The Behavioral Change Index is a 20-item situation based change measure developed primarily with stimulant dependent individuals that can be self-administered and scored easily in most clinical settings. BCI items measure three general domains: drug and alcohol use behaviors, prosocial behaviors, and activities of daily living. This study provides normative baseline data, presents content validity, and demonstrates psychometric properties of the BCI.

METHOD: ASIs and BCIs were gathered at baseline, 6-months, and 12-months following treatment entry from 246 stimulant dependent subjects at the Matrix Center, 1989-1991. Urine samples were gathered at follow-ups. Treatment data were weeks in treatment.

RESULTS AND DISCUSSION: Average BCI scores for stimulant dependent subjects were 44.36 (7.3) at baseline (n=233); 37.40 (7.7) at 6-months (n=173); and 36.60 (7.3) at 12-months (n=129). Analyses showed statistically and clinically significant reductions in scores from baseline to 6-months (matched $t=9.75$, $df=172$. $p<.001$), baseline to 12-months (matched $t=12.04$, $df=129$, $p<.001$) and 6-months to 12-months (matched $t=2.11$, $df=137$, $p<.05$). To address content validity, BCI scores for subjects for whom cocaine metabolite was detected scored higher on the BCI than those with negative results at 6-months ($M=39.29$ vs $M=35.82$, $F=4.04$, $df=1, 80$, $p<.05$) and at 12-months following admission ($M=38.29$ vs $M=33.06$, $F=9.20$, $df=1, 75$, $p<.01$).

For convergent validity information, the mean BCI score within each time point was used as a cutoff to evaluate ASI protocols. There was a significant positive association between ASI scores and high/low BCI groupings at baseline (ANOVA, $F=3.20$, $df=7,209$, $p<.01$); at 6-months (ANCOVA, baseline covaried, $F=2.76$, $df=7,149$, $p=.01$); and at 12-months (ANCOVA, baseline covaried, $F=2.25$, $df=7,116$, $p<.05$). The BCI also showed adequate internal consistency, with BCI coefficient alphas ranged from 0.67 at baseline to 0.78 at 6-months to 0.74 at 12-month follow-up. Test-retest reliability showed baseline scores were mildly correlated with follow-ups (baseline to 6-month $r=0.24$; baseline to 12-month $r=0.24$), 6-month to 12-month follow-ups showed stronger correlations ($r=0.63$).

The BCI demonstrates many of the necessary elements for use as a brief, valid and reliable, self-report tool for assessing pro-social and drug-related behaviors among stimulant dependent individuals. BCI scores of stimulant subjects reflected clinically and statistically significant behavioral changes associated with drug treatment Psychometric properties for the BCI showed adequate internal consistency and reliability. Findings supported using the BCI as an additional tool with the ASI for measuring drug-related and pro-social behaviors among addicted populations.

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PREDICTORS OF IRREGULAR DISCHARGE FROM INPATIENT SUBSTANCE ABUSE TREATMENT

P. Manu, J. Burleson, and H. R. Kranzler

A controlled cohort study was conducted to determine the characteristics of patients irregularly discharged from a voluntary, inpatient substance abuse treatment unit of a general hospital. The sample consisted of 220 subjects (110 consecutive patients who were discharged early and 110 matched control patients). Structured chart audits were used to collect demographic, socioeconomic and clinical data.

Whereas univariate analysis identified 11 variables that differentiated the two groups, hierarchical logistic regression identified only three predictors of irregular discharge: predominant heroin use, failure to complete high school and age younger than 30 years.

Two randomly selected subsamples of 110 subjects each (55 early discharge and 55 matched control patients) were used to derive and validate an instrument for predicting irregular discharge. In addition to the three above-named variables, the instrument includes current cocaine use and two or more positive results on toxicologic screening performed on the day of admission. The presence of any two of these live items identified 69% of irregular discharges in the derivation set and 78% of irregular discharges in the validation set.

We conclude that readily available information on age, education, psychoactive substance use, and toxicologic screening may be useful in identifying the risk of early discharge from inpatient substance abuse treatment.

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INTER- AND INTRA-GENERATIONAL FAMILY HISTORY OF ALCOHOLISM AMONG FEMALE DRUNK DRIVERS

B. W. Lex, M. E. Goldberg, T. A. Bower, J. H. Mendelson, and N. S. Lawler

Although studies consistently show alcoholism to be influenced by a combination of heritable and non-heritable factors, research on family history of alcoholism has focused almost exclusively on identifying genetic contributions to alcohol addiction. This study investigated a range of inter-and intra-generational patterns of alcoholism among the families of 42 alcoholic women incarcerated for serious drunk driving offenses. All 42 subjects had at least one full sibling with whom they were raised by at least one biological parent. Subjects completed detailed family history interviews based on DSM-III-R criteria. Approximately two-fifths of the subjects had both a parent and a sibling who was an alcoholic. About one-fifth had a parent only, one-fifth a sibling only and one-fifth neither a parent or a sibling. About 60% of fathers, but only about 15% of mothers, were reported to be an alcoholic. However, when parents themselves were excluded, the lifetime percentage of alcoholism among known maternal and paternal first- and second-degree relatives over the age of 15 was almost the same, 32.9% versus 33.6%. Data for relatives of subjects' mothers indicate a pattern of assertive mating in which *non-alcoholic* women from families with a high density of alcoholism marry alcoholic men from families with high density of alcoholism. High density of alcoholism has occurred for several generations in males. Grandfathers showed a rate almost identical to fathers, and rates for mates were similar. Rates have increased for female relatives. Unexpectedly, there were two non-hereditary aspects of family structure associated with drunk driving among females: sibling gender and birth order. Although by chance one would expect equal numbers, subjects had nearly twice as many male siblings as female siblings and nearly twice as many older siblings as younger siblings. This family history data suggest the existence of patterns of risk factors for drunk driving by women which are relevant to both prevention and treatment.

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EPIDEMIOLOGY OF PRESCRIPTION AND OVER-THE-COUNTER DRUGS IN TWO LOS ANGELES SAMPLES

K. Boyle

Subjects were recruited from patients in sexually transmitted disease (STD) clinics and hospital emergency rooms (ER) in Los Angeles County. A total of 341 persons answered questions regarding use and possible abuse of medications. Of the 341 subjects interviewed, 60 percent were men and 40 percent were women. The ethnic breakdown of the sample was as follows: 36 percent were African-American, 48 percent were Latino, and 12 percent were white. The majority of the sample (54 percent) was between the ages of 26 to 40, 28 percent were 18 to 25, and 18% were over 41 years old. Over one third of the sample (37 percent) had used an illegal drug in the previous 12 months, while 61 percent reported no illegal drug in the previous 12 months.

Use of medications seemed low. Only 47 percent of the sample reported ever having used non-opiate analgesics. Five subjects reported use of this drug recreationally, or beyond medically indicated. One subject reported dependence. Sixteen percent of the sample reported use of analgesics with opiates. Of these, six subjects used recreationally and three reported dependent use. Thirteen percent reported use of OTC diet pills. Of these, three used these pills recreationally and one reported dependent use. Ten percent of the sample had used tranquilizers and ten persons reported recreational use, with three of them using dependently. Only six percent had used opiate-containing cough and cold medications; five percent had used sleeping pills; two percent had used prescription diet pills, and two percent had used anti-depressants.

Interviewers with substantial experience in determining illegal drug use patterns were often surprised at the low reporting of use of prescription and over-the-counter (OTC) drugs, especially OTC drugs of common use, such as aspirin and cough syrup. It is not known if there is more denial of use and abuse of these drugs than expected, or if the data collection procedures must be more sophisticated to detect use and abuse.

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DRUG USE AND SEXUAL BEHAVIORS AMONG STD PATIENTS

D. Longshore, Y. Hser, K. Boyle, M. D. Anglin, J. Chen, and G. A. Richwald

This paper reports preliminary results of an ongoing study on drug use and drug treatment utilization among patients in three STD clinics in Los Angeles County. The analysis includes 216 STD patients interviewed between May and September, 1992, and for whom urinalysis results were available. The mean age was 28 years, 54% are men, and 64% African-American, 29% Hispanic, 2% white, and 5% other ethnicities.

Use of drug by injection was reported by 7% of the sample. Urinalysis showed that 29% of the sample tested positive for some illicit drug (17% were positive for marijuana, 12% cocaine, 3% PCP, 1.4% heroin). Sixty-eight patients (32%) were current drug users (evidenced either by positive urine or self-report of use in the past three days), 82 (38%) were considered past users (self-report of past use but not in the past three days and negative urine results), and 66 (30%) reported no history of drug use (self-report of never use and negative urine results). Age and gender characteristics were similar among the three groups but significantly higher percentages of African-Americans were among current and past users (82% and 65%) than among non-users (44%). Past dependent use was reported by 35% of current users and 24% of past users but only 6% of current users and 15% of past users were currently in drug treatment. Multiple sex partners (three or more) in the past year were reported by 55% of current users; 47% of past users, and 18% of non-users. Approximately one third of individuals in each of the three groups reported condom use during most recent sexual activity. Number of STD incidents were 4.0 by current drug users, 2.5 by past users, and 2.9 by non-users. Arrest history was reported by 60% of current users, 48% of past users, and 14% of non-users.

In-depth interviews are planned to follow up these STD patients to better understand their drug use progression and treatment utilization. These results showed high past and current drug use rates among STD patients. Since many of the users may still be in an early stage of use, targeted early intervention may be crucial to prevent them from progressing to the more severe and chronic disorder of drug dependence.

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CONCORDANCE FOR DRUG ABUSE IN ALCOHOLIC TWINS

M. C. LaBuda, R. W. Pickens, and D. S. Svikis

Family, twin, and adoption studies have implicated familial and genetic factors in the development of many psychiatric disorders and alcoholism. Research with regard to the etiology of substance abuse disorders other than alcoholism, however, has been comparatively sparse. Family studies of drug abuse comprise the majority of such research although they cannot distinguish between familial and genetic influences. Adoption and twin studies provide a separation of genetic and environmental effects, based upon certain assumptions. The few existing twin and adoption studies of drug abuse are consistent with a genetic basis for substance abuse but suffer various methodological limitations including small sample size.

The purpose of the present report is to compare MX and DX twin concordance for regular use of various classes of drugs and concordance for problems due to the use of these drugs within a large twin sample. Moreover, patterns of polydrug use were examined to determine if there was evidence of a general underlying vulnerability to drug abuse as opposed to separate vulnerabilities for specific drugs of abuse.

Concordance for drug abuse was assessed in 293 twin pairs (197 same-sex male pairs and 96 same-sex female pairs) ascertained through alcoholism treatment centers. Rates of drug abuse were not significantly different in monozygotic (MZ) and dizygotic (DZ) probands. However, male MZ twin pairs were more likely than male DZ twin pairs to be concordant for regular drug use and problems due to the use of sedatives, stimulants, analgesics, hallucinogens, and cannabis. Concordance rates did not differ significantly for nearly all measures of drug abuse in female MZ and DZ twin pairs. These results may be due in part to lower rates of drug use in females, but different etiological mechanisms for drug abuse in males and females must also be considered. Patterns of multiple drug use in males and females showed considerable overlap between members of twin pairs. Furthermore, the degree of overlap was significantly greater in MZ than DZ twin pairs.

AFFILIATION:

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VIOLENCE AND DRUG PREVENTION IN AFRICAN AMERICAN YOUTH

L. E. Mitchell

The purpose of the project is to reduce the incidence. and prevalence of drug use, abuse, and violent behaviors related to alcohol and other drug abuse in African American youth. Hypothesis: Focused attention on identified risk factors will create a reduction of drug use and violence and increase a buffering effect against drug use. Specific goals are: (1) to nromote conditions for social bonding to "conventional" units of socialization (school, family, church); (2) to promote norms that disavow violence, violent behavior and drug use in those social units; (3) to teach members of those social units the skills to recognize and resist influences to abuse drugs and become involved in violent behaviors.

Objectives: (1) to provide a set of positive family and interpersonal situations and conditions designed to protect at risk African American youth from violence, alcohol, and other drug use; (2) to initiate a process by which “precursors” to juvenile delinquency, violence, and alcohol and other drug use among African American youth at risk can be reduced or eliminated; (3) to provide a risk focused approach that seeks to prevent violence, violent behavior and drug abuse by eliminating, reducing, or mitigating the effect of identified precursors of violence and drug use.

A pool of 200 black youth between the ages of 13-17 and their families are identified for the study. Strategies include group programs linked to the designated risk factor being studied. The conceptual framework for this model is based on social learning and social development theory. It suggests that social bonding to conventional society is a protective factor against adolescent drug use and violent behaviors, especially if those social units disavow these behaviors. Process, outcome and impact evaluations are used. Anticipated outcome includes: (1) improved family functioning and parental control; (2) improved grades and increase in academic competence; (3) devaluation of negative peer groups and gangs by participants groups; (4) improved bonding, positive family relationships and reduced family conflict; (5) improved recognition of problems as measured; (6) improved knowledge of self, societal and family values; (7) improved school bonding as measured by decreased school dropout rate, tardiness, truancy and school vandalism.

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PSYCHO-SOCIAL CHILDHOOD DEPRIVATIONS AND THE MENTAL ILLNESS-CHEMICAL ABUSE (MICA) SYNDROME: SEARCHING FOR ETIOLOGICAL CONNECTIONS

M. Rahav, J. Rivera, D. Ng-Mak, E. L. Struening, B. G. Link, and B. Pepper

Despite the pervasiveness of the mental illness chemical abuse (MICA) dual disorders, very little research has been conducted on their causes. This paper attempts to search for etiological clues to the MICA syndrome in MICA's early age family background. A non probability sample of 335 homeless men seeking community based MICA treatment in New York City is used in a five year longitudinal study. By the time they were 13, 29.6% did not have their mothers at home and 54.6% did not have their fathers. Scales measuring these men's feelings towards and relationship with their parents proved to have good internal consistency/reliability. Feelings about their fathers and whether fathers were at home at early age shows very strong association: those who had their father around expressed significantly more love, pride and trust of their fathers. These feelings about father then correlated with various psychological measures: The more love, pride and trust of father, the less the psycho-pathology on various depression, psychosis and anxiety questionnaire items. Feelings about mother were correlated with whether mothers had a history of drug, alcohol, or mental illness (DAM) problems. MICA's who reported their mothers to have had DAM problems expressed less love for their mothers than those who reported their mothers to have had no problems. A Relationship with Father scale was factor analyzed yielding three factors: "Good Father", "Abusive Father", and "Drug User Father". Total scores on these factors correlated significantly, (inversely) with various measurement items of psycho-pathology.

Although the paper lacks a comparison group from the general population it tentatively concludes that: A. MICAs seem to be characterized by severe parental deprivations. More than 50% of the MICAs did not have their fathers living at home from quite an early age. B. MICAs whose fathers were not at home described their fathers as significantly less loving and less being loved than those MICAs whose fathers were around. C. MICAs' feelings about their fathers correlated with certain psychiatric symptoms. The less love they reported to feel towards and receive from their fathers, the worse was their outlook for the future, their network of friends and psychotic and anxiety symptoms. D. MICAs who scored low on the "Good Father" factor showed significantly more psychopathology than those who scored high (*i.e.* described their father as praising, supportive, helping, loving and proud of them). E. MICAs who reported their fathers to have had DAM problems scored significantly lower on the "Good Father" factor and significantly higher on the "Abusive Father" and "Drug User Father" factors than those whose fathers did not have DAM problems.

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HEALTH CARE UTILIZATION PATTERNS OF PATIENTS TREATED FOR ADDICTIONS COMPARED TO THOSE TREATED FOR NON-PSYCHOTIC ILLNESSES

S. B. Greberman

This outpatient study was designed to determine if mental health treatment results in an increase or decrease in the utilization of other health care services in patients treated for substance abuse and in patients treated for non-psychotic illnesses. The substance abusers in this study were addicted to illicitly obtained prescription medications and/or to alcohol. Most substance abusers were men who remained in treatment $\leq$30 days. The non-psychotic illnesses were: anxiety, depression, or personality disorder. The data consist of information abstracted from mental health and medical records of 155 enrolled patients aged 21 to 40 who received mental health care at a health maintenance organization (HMO) in Washington, D.C. A total of 94 persons received 130 days of mental health treatment: 61 received 31 to 180 days of treatment. Substance abuse was the only diagnosis category that contained more men than women. The non-mental health care visits before, throughout, and after mental health care ended were abstracted from records. In addition to visits, physicians' non-mental health diagnoses were evaluated; it was determined that utilization patterns were not influenced by the presence of illnesses in need of ongoing treatment.

Women who received $\leq$30 days of mental health care maintained essentially the same visit rate before mental health treatment and during and after therapy. Men with $\leq$30 days of mental health care had a different non-mental health visit pattern from that of women who received $\leq$30 days of treatment. Men had a greater non-mental health utilization rate before treatment than the women in every diagnostic category; the men's rate also decreased markedly after mental health therapy began (t-test, $p \leq .05$). Women in each diagnostic group with 31 to 180 days of care for non-psychotic illnesses and men treated for personality disorder for this length of time had enough health care visits to permit the application of time series analysis. In these women, the overall pattern tends to be one of increasing visits during mental health care. Utilization patterns of men with personality disorder differ from those of women with the same diagnosis. The overall pattern for men tends to be one of decreasing non-mental health utilization during mental health treatment. The adjusted R^2 obtained using this time series regression model results in explanation of approximately 90% of the variance in the majority of groups of individuals (F test, $p \leq .05$). Too few substance abusers remained in treatment from 31 to 180 days to permit any statistical analysis.

These results are generalizable only to patients in these age groups with these mental health diagnoses treated in an HMO. Any treatment modality, whether for addiction another mental or medical problem, has time as a component in the patient's response. Nevertheless, many evaluations of the outcomes of treatments for various illnesses do not consider the effects of time in the study design. In this study, the static analysis done on groups of patients who received $\leq$30 days of treatment revealed valuable information, that utilization patterns are influenced by gender. A dynamic statistical method, such as time series analysis, must be used to evaluate the effects of time. Use of time series analysis in this study has revealed that in patients with non-psychotic illnesses who remain in treatment for 31 to 180 days, utilization patterns established prior to entering mental health treatment, along with treatment itself, affect patterns during and after therapy. Depending on gender and primary mental health diagnosis, the responses to treatment over time differed.

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RECALL OF SUBSTANCE USE AFTER 12 YEARS: DATA FROM THE ST. LOUIS EPIDEMIOLOGIC CATCHMENT AREA STUDY

A. M. Shillington, L. B. Cottler, D. E. Mager, W. M. Compton

In a ongoing study on the reliability and validity of substance use disorders, we have been following-up participants from the St. Louis NIMH Epidemiologic Catchment Area (ECA) study. The ECA study surveyed a general population sample during 1981-82 for psychiatric symptoms and illicit substance use. Persons at baseline aged 18-44 years and who reported using a substance more than five times in their lives were eligible for follow-up. Currently, 223 subjects have been interviewed. Reports of drug use at the ECA baseline were compared to the reports made 12 years later. Two types of agreement were found—agreements in reports at baseline and at the 12 year follow-up a particular substance was not used or agreements that a drug was used. Next there are the possible incident cases—those who reported "no use" at baseline and reported "use" 12 years later whose age of onset was older than their age at baseline. In addition to agreements and incident cases, there were three types of discrepancies found. First was the Type I Discrepancy: a person reported "no use" at the baseline interview and then reported "use" at the 12 year follow-up with an age of onset younger than baseline age, indicating that they should have reported use when interviewed 10 years earlier or that they misreported their age of just use. Type 2 Discrepancies: a person reported "use" at both the baseline, indicating that they misreported the age of onset at the follow-up interview or that they mistakenly reported use at baseline. Type 3 Discrepancies: a person reported "use" at baseline but 12 years later denied using the substance, indicating misreporting of use at the follow-up interview or possibly at the baseline interview. Findings indicate that persons interviewed 12 years after their baseline interview are consistent regarding recall, with overall agreement ranging from 74-88%. Type 1 Discrepancies, when a person recalled age of onset younger than their baseline age but said they did not use at baseline, were fairlv low at: 1% for cannabis. 6% for cocaine. 8% for sedatives. 9% for amphetamines. and 11% for opiates: Type 2 Discrepancies, when a person indicated "use" at both interviews but at the follow-up interview reported an age of onset older than the baseline age, were even lower than Type 1 Discrepancies: 1% for cannabis, amphetamines, and sedatives, and 2.7% for cocaine. Type 3 Discrepancies, which was when a person said "yes used" at baseline but denied use at follow-up, were the most frequently found discrepancies: 5% for cocaine, sedatives, and opiates, 12% for cannabis, and 16% for amphetamines. Despite the fact that there were three different ways that people could be discrepant in their reports, the discrepancies were fairly low. The variable "age of onset" appears to be consistent. Finally, it should be encouraging to those doing longitudinal studies, that people can fairly accurately recall their history of substance use even 12 years after their baseline interview.

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THE RELATIONSHIP OF INHALANT USE AND INJECTING DRUG USE

C. G. Schütz, H. D. Chilcoat, and J. C. Anthony

Use of inhalants might prove to be a modifiable risk factor for injection drug use, or alternately an important vulnerability marker, as has been indicated by a few sporadic studies based on restricted populations (most recently Dinwiddie *et al.* 1991 using a population of patients, felons and their relatives). If there is a link between these two different forms of drug-using behaviors, then a statistical association should be found in a epidemiologic study, even after statistical adjustment for plausible confounding variables such as sex, age, socio-economic status, and the use of drugs such as marijuana. To probe this suspected causal association, we analyzed epidemiologic data from NIDA's 1990 National Household Survey. The population for this survey consisted of all household residents aged 12 years and older in the coterminous US, with respondents selected by probability sampling. A total of 9,259 respondents completed the confidential self-report interview conducted by trained interviewers. A history of injecting drugs was reported in 192 cases. Inhalant use was associated with injecting drug use (OR=11.8). After statistical adjustment, using SUDAAN, inhalant users still were 5.4 times more likely than non-users to have injected drugs (<0.001). We extended the multiple logistic regression model to include a number of additional socio-demographic and geographic variables and made persons with no history of inhalant or marijuana use the reference group. This model indicated that respondents who reported use of both marijuana and inhalants were an estimated 85.4 times more likely to have injected drugs ($p<0.001$) than those who had used neither inhalant nor marijuana. Those reporting use of inhalants but not marijuana were an estimated 48.4 times more likely to have injected drugs ($p<0.001$) compared to the reference group. The corresponding odds ratio was 16.0 ($p<0.001$) for respondents having used marijuana, but not inhalants. Despite some methodologic limitations, this epidemiologic evidence strengthens the rationale for a more deliberate focus on inhalant use in future studies that seek to understand etiologic conditions giving rise to injecting drug use, an important issue for HIV and AIDS, as well as drug dependence research.

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CHANGES IN THE PAST FIVE YEARS IN ROUTE OF COCAINE ADMINISTRATION AMONG TREATMENT SEEKING INDIVIDUALS

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The route of illicit drug administration has an impact on public health and also seems to influence the development of drug dependence and duration of cocaine use. The purpose of this study was to document for the first time the change in route of administration over time for 413 consecutively admitted unpaid cocaine dependent (DSM-IIIR) individuals seeking participation in cocaine treatment research protocols over a period of five years (June, 1987 to June, 1992). All subjects were interviewed on their first day of application for treatment. Inclusion criteria: 21-60 years of age, average cocaine use of 1 gram per week in the past twelve weeks, and self-reported cocaine use within the past thirty days. Exclusion criteria: illiteracy, major medical or psychiatric disorders, or other drug dependence except for caffeine or tobacco. Data were analyzed using a one-way ANOVA or Chi square analysis for continuous and categorical data, respectively.

There were no significant differences in age or gender by routes of administration. Smoking was the most commonly reported route over the five-year period while oral use was minimal. Non-whites (Blacks + Hispanics) significantly prefer smoking over intranasal cocaine administration while whites showed less of a preference. A trend towards an increase in smoking (Year 1: 40.3%, Year 5: 66.7%) and a decrease in intranasal usage (Year 1: 26.6%, Year 5: 8.3%) across time was observed. After an initial halving of IV use in the second and third year, there was an increase in each of the next two years. Intranasal users of cocaine started treatment significantly more often and stayed in treatment significantly longer than either intravenous users or smokers.

A comparison of the ARC cocaine outpatient treatment research population with "cocaine-related admissions" to all Maryland certified alcohol and drug abuse treatment programs showed a similar increase in smoking and decrease in intranasal use. While our IV data showed an initial decrease followed by a gradual increase, the Maryland data was less variable and showed a slight decrease.

This study demonstrated: 1) a change in route of cocaine administration among treatment-research seeking individuals, 2) similarities and differences in route of administration between these subjects and a state population of treatment admissions, and 3) route of administration of cocaine had an effect on retention in treatment.

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PROVIDING FREE DRUG ABUSE TREATMENT: BARRIERS TO CARE

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Drug abusers face a number of barriers to entering and completing drug abuse treatment. Overcoming these barriers often requires community efforts beyond providing treatment slots or subsidizing fees. An on-going city-wide research demonstration project designed to reduce the spread of AIDS through community outreach (DA06163) provided an opportunity to describe barriers at three stages of research implementation. Three samples were examined: an outreach sample from a target area of St. Louis contacted between July 1990 and June 1992 (N˜3.500); drug users entering HealthStreet, the City's Health Department satellite outreach center (N=595); and, follow-up interview samples consisting of outreach (N=253) and non-outreach (N=221) subjects. In community outreach were barriers that hinder the hidden drug using population from coming forward (Stage 1). Of 3,500 local residents suspected of drug misuse, contacted through street outreach, 595 entered HealthStreet; yielding the outreach "success" rate of 17%. From this point, during the treatment referral phase, barriers resulted in missed opportunities to transform drug users' spontaneous help-seeking to a commitment to change (Stage 2). Of 595 likely drug abusers who came to HealthStreet, only 50 (8.4%) were admitted to the project treatment protocols. Lastly, even after they entered treatment, barriers surrounding drug users reduced the likelihood of treatment retention (Stage 3). Of the project's outreach subjects who entered treatment, 43% stayed in treatment three months or longer; whereas, among non-outreach subjects recruited by individual treatment centers, 55% stayed in treatment for the same duration. It appears thus that the barriers at the community and treatment referral levels (Stage 1 & 2) are harder to overcome when implementing plans to provide drug abuse treatment. We attempt to identify major barriers to care from the viewpoint of drug users. At the community level, perceptual, economic and class barriers appear to be salient. At the treatment referral level, local organizational barriers appear more responsible than others for dampening drug abusers' desire for treatment. In treatment, social, psychiatric, and personality factors appear important for treatment retention. We suggest how these barriers might be removed. While some barriers, such as persistent class and economic barriers, are impossible to overcome by any one program, others are implementable. For example, treatment matching, and referrals "on demand" would make treatment entry easier, which can be implemented through inter-organizational coordination. Within a treatment center, provisions of psychiatric treatment and network counseling might improve treatment retention.

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CLONIDINE USE AND ABUSE AMONG METHADONE CLIENTS AND APPLICANTS

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Thirty known or suspected clonidine-abusing clients were interviewed and 48 applicants were anonymously surveyed at two Baltimore methadone clinics regarding their clonidine use and abuse. All of the clients and 22 of 48 applicants had used clonidine illicitly, with 19 of 30 clients and 4 of 22 applicants admitting to current use. Common reasons listed for using clonidine illicitly included (clients; applicants): to decrease opiate withdrawal symptoms (66.7%. 68.2%); to "boost" their methadone (96.7%. 31.2%); to achieve a high (83.3%. 18.2%); to make them feel relaxed (93.3%, 36.4%); to make them feel drowsy (80%. 59.1%); and to get a "nod" (70%. 31.8%). More than half of the clients claimed they had experienced the following side effects from their clonidine use: dry mouth, lightheadedness, sedation, weakness, and withdrawal symptoms. All clients reported using clonidine intentionally with their methadone, and some had taken it with other drugs, including cocaine, opiates (heroin), alcohol, marijuana, benzodiazepines, and prescription drugs. Almost all study participants agreed that clonidine was easy to acquire on the street for a median cost of $1 for a 0.3 mg clonidine tablet. Average dose taken at one time for clients was 0.6 mg (range 0.15-2.4 mg), and for applicants was 0.37 mg (range 0.1-0.9 mg). Twenty-seven (90%) clients and 12 of 34 responding applicants (35.3%) believe that clonidine can produce addiction. This small study demonstrates the abuse potential of clonidine by these methadone clients and applicants: Further investigation into the abuse potential of the drug by others seems warranted. The need to develop a urine assay to detect clonidine abuse may also be warranted.

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EMPLOYMENT CHARACTERISTICS OF METHADONE PATIENTS

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Employment is widely viewed as an indicator of healthy functioning and is often a treatment goal identified by both drug treatment staff and methadone clients. Unfortunately, unemployment rates remain high, varying from 33% to 81% in methadone treatment. Previous employment interventions have had only limited success in helping clients achieve and maintain employment. Primarily these interventions have been generic in design and have been applied to all methadone patients regardless of individual skills, characteristics or work patterns. Therefore, we hypothesized that client employment needs may vary in relation to their employment pattern. Thus, the purpose of this work was to investigate the ability of subject characteristics to differentiate among three "stages" of work patterns in the past year (stable workers, employed for a minimum of 12 consecutive months; intermittent workers, employed between 1 and 11 months; and the unemployed, no work history.)

We examined the employment status of 322 subjects in a methadone program in Philadelphia. Subjects completed a questionnaire designed to measure aspects of client functioning considered related to employment among drug abusers and the Beck Depression Inventory. Logistic Regression analyses were conducted with 18 independent variables to examine the ability of each variable to predict current work status. Nine variables, predictive of current work status were selected to construct a mode1 of variables to differentiate subjects among three "stages" of work. These variables included: race, gender, cocaine use, depression, education, length of current treatment episode, legal history and marital status. A multiple discriminate function analysis yielded a Wilks' Lambda value of .86 ($F=4.13$, $df = 6,319$) indicating that the two functions created accounted for 14% of the total variance beyond chance. Univariate F-Test of between-group differences were computed and the Tukey HSD test was calculated to determine if differences existed among the criterion means. Results of these analyses found that stable workers had lower Beck scores and less cocaine usage-than intermittent workers. Intermittent workers were more likely to be male, married and have higher levels of education than unemployed subjects. While we can not be certain of the causal relationships, interventions such as adult education classes, treatment for cocaine use and psychotherapy and/or pharmacotherapy for depression may be necessary preconditions for the initiation and maintenance of employment. To test these assumptions, further investigations of the causal relationship between these interventions and employment status are necessary.

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CORRELATES OF EMPLOYMENT AMONG FORMER OPIATE ADDICTS

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This paper examines the correlates of employment among a population of 429 former opiate addicts currently receiving treatment in a methadone program in the New York metropolitan area. Respondents were primarily male (72 percent), ethnically mixed, possessing limited education and had long experiences with intravenous drug use. Fully 72 percent had been convicted of at least one crime.

Based on multiple regression analysis, lifetime employment was significantly related to a number of psychosocial variables; age, gender, martial status. ethnicity, and adolescent criminality. Age was positively correlated with lifetime employment, and males were more likely to have been employed than females. Married people were more likely to have been employed, and whites were more likely to have been employed than those in minority groups. Those with a history of adolescent criminal involvement were less likely to have been employed for a long period of time than others. Controlling for lifetime employment, young people were most likely to have been employed in the year before treatment began. Even controlling for lifetime employment, those who were court-referred were significantly less likely to have employed than others.

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COHORT CHANGES IN CHOICE OF DRUG AMONG ARRESTEES

B. D. Johnson, A. Golub, and M. Hossain

A central concern to policy makers is determining whether and how much the use of serious drugs has increased or decreased, and how such changes differentially occur in various subpopulations. Several issues are addressed: Have drug-abusing criminals shifted drug(s) of choice in different periods during the past 30 years? Are such changes related to differential experiences with drugs among birth cohorts? What arrestee characteristics are most strongly associated with specific drug abuse patterns?

METHOD: This is a secondary analysis of data from the Drug Use Forecasting program in Manhattan for 1987-91 (N~6.000). DUF interviews 350 adult arrestees (250 men, 100 women) each quarter and collects urine specimens which are analyzed by EMIT for 10 drugs; the analyses below focus on heroin, cocaine powder, and crack. DUF subjects are quite representative of serious drug abusers and criminals arrested for felony charges in Manhattan and other major cities.

RESULT: The average age at onset to drugs (among users of these drugs) occurs mainly during ages 16-20 for all drugs (except crack where almost all users began in 1985-89 regardless of age). Manhattan arrestees born in 1950-54 exhibited the highest rate of opiate positivity (35 percent) and self-reporting intravenous use (46 percent) which is much higher than among arrestees born 1970-74 (opiate positive--7 percent; intravenous use--2 percent). Arrestees born in the 1955-64 period were among the most likely to use cocaine powder and crack. The youngest cohort (born 1970-74) were about half as likely to be cocaine-opiate positive (or self-report lifetime use of heroin or cocaine) as arrestees born 10-20 years earlier. Birth cohort emerged from logistic regression analysis as the strongest independent factor associated with whether arrestees were drug positive for specific drugs (opiates or cocaine). Arrestees most likely to be heroin injectors (all other factors held constant) were whites, born 1950-54, arrested on burglary charges, and whose primary source of income was drug sales. Arrestees most likely to be crack users were blacks, born 1955-59, arrested for drug sales and possession, and whose primary income source was drug sales. Those least likely to be crack users were whites, born 1970-74 (also those born 1900-1944). arrested for miscellaneous charges (prostitution, DWI, probation violations), and on welfare.

IMPLICATIONS: Among very high risk persons (those arrested for crimes) important differences in drug user profiles prevail, particularly across birth cohorts. The best news is that the youngest arrestees (born 1970-74) were the least likely to be heroin injectors or crack users. This may be due to their delayed progression in drug escalation to these drugs. An alternative explanation from ethnographic evidence suggests that inner-city youths may be avoiding both heroin injection and crack abuse. Whether levels of heroin injection and crack abuse remain low among arrestees born in 1970-74, and whether the next cohort (born 1975-79) will continue to avoid (or not initiate) heroin and crack use remains to be documented. DUF-Manhattan data in the mid-1990s can document these important trends among youths in this high risk population regarding changes in their patterns of drug consumption.

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INFLUENCE OF DRUG TREATMENT ON INDIVIDUAL PATTERNS OF SOCIAL DRUG USE

J. C. E. W. Willems, M. Y. Iguchi, V. Lidz, and D. A. Bux

A number of studies have suggested that social affiliations may affect risk for HIV infection among drug injectors. Social relationships may support and maintain both drug use and particular high-risk injection practices. Moreover, as with sexual behavior, risk for exposure to HIV varies with the number of individuals with whom drug use occurs, and with the risk status of these individuals. This pilot study examines drug using networks of IDUs in methadone treatment both currently and, retrospectively, before initiation of treatment. The extent of these networks was assessed through interviews both with in-treatment and out-of-treatment network members.

Subjects were 22 in-treatment and 18 out-of-treatment IDUs in Philadelphia and Camden County, NJ. In-treatment subjects were recruited through posted notices at two methadone matinenance clinics, and out-of-treatment subjects recruited by a modified snowball sampling procedure. Subjects completed a structured survey of drug use, sexual behavior, and health status, and a semi-structured interview identifying IDUs with whom the subject had injected drugs (co-IDUs). Subjects were paid $15 for the interview and $5 for every network member they recruited for an interview.

In-treatment subjects named a total of 75 network members. Six (27%) in-treatment subjects reported no current co-IDUs. Overall, the forty subjects interviewed named 97 network members; 18 (19%) of these were recruited for interviews. Subjects tended not to mention network members who had died, unless specificallv asked about such individuals. This may have important methodological implications this type of research. There was a great deal of variety in the size and complexitv of identified networks, and in the number of generations successfully recruited for interviews. In the more complex networks particularly, the risk posed by even a single HIV-seropositive network member was striking.

The mean size of current (past 3 months) drug-using network was 2.4 (range 0-8, SD=2.35), while the mean size of pre-treatment networks (retrospective; last 3 months prior to treatment) was 4.8 (range 0-11; SD=3.14). This indicated a significant decline during treatment in the reported number of co-IDUs (t=3.32: DF=19: p=0.0036). Thus, treatment may reduce HIV risk in two ways: by reducing risk behavior frequency (i.e.; drug injection) and by reducing the number of people with whom risk behavior occurs. Most of the changes in network size appeared to result from the reduction of injection with acquaintances and strangers, while use with close friends and family members changed to a lesser degree. This trend is consistent with earlier findings (MY Iguchi, unpublished data).

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CAN PERSONALITY CHARACTERISTICS CATEGORIZE SUBSTANCE USERS WHO ARE HIGH'RISK FOR HIV?

D. E. Mager, L. B. Cottler, A. M. Shillington, and W. M. Compton

In the Substance Abuse and Risk for AIDS study (SARA), 539 substance abusers and their sexual partners completed: a) the Diagnostic Interview Schedule (DIS) to assess psychiatric and substance use disorders, b) the Tridimensional Personality Questionnaire (TPQ) to assess personality characteristics, and c) the NIDA HIV Risk Behavior Assessment (RBA). A variable defining a respondent's risk for HIV infection was constructed using: 'Needle sharing', 'Sexual relations with multiple partners without a condom', and 'IDU sex partners'. Using these criteria, 43% (N=232) had at least one high risk behavior and were defined as 'High-Risk' for HIV infection. The Antisocial Personality Disorder (ASPD) section of the DIS, the TPQ, and questions on family history were compared among respondents with and without 'High-Risk'behaviors. Initially, Chi-Square and r-Test statistics were computed to determine which variables best differentiated 'High-Risk'. Next, a stepwise discriminant analysis was used to determine the TPQ subscales. ASP symptoms and family history items which would build the best discriminant function for 'High-Risk'. Among the TPQ items, the 'Impulsiveness' subscale best discriminated 'High-Risk' persons (Wilk's_=.95). Among the ASP conduct symptoms, 'destroying others' property' was best discriminator of 'High-Risk' (Wilk's_=.92). Among the ASP adult symptoms 'failure to conform to social norms' (Wilk's_=.97), 'reckless behavior' (Wilk's_=.91), and 'inability to function as a responsible parent' (Wilk's_=.91) discriminated 'High-Risk'. Family history of problem drug use also categorized significantly 'High-Risk' behaviors (Wilk's_=.93). In total, using these six personality and family history variables, we correctly categorized 66% (N=153) of the respondents at 'High-Risk' for HIV. Implications for assessment of HIV risk behaviors will be considered.

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DEMOGRAPHIC AND DRUG ABUSE-RELATED VARIABLES ASSOCIATED WITH RECRUITMENT OF INJECTING DRUG USERS (IDUs) IN HIV CLINICAL RESEARCH

D. Ajuluchukwu, L. S. Brown, Jr., M. M. Chu, and A. F. Chu

In May 1992, trained research staff, using a standardized questionnaire, systematically recruited 398 HIV positive IDUs (61% male, 51% African Americans, 41% Hispanic American), enrolled in methadone maintenance treatment (MMT), to participate in eight different HIV-related clinical research protocols. The questionnaire included demographic (age, ethnicity, gender, and education) and drug abuse-related variables (MMT enrollment duration, self-reported craving for and use of illicit drugs, and self-reported withdrawal symptoms). We also collected the last three months of urine toxicological results. The participants who were enrolled more than two years in MMT had lower positive urine toxicology rates ($p<0.01$). Patients admitting to heroin, cocaine, or other drug use in the last 30 days had higher positive urine toxicology rates ($p<0.001$); 66% agreed to participate in at least one protocol. The urine toxicology rates between participants and non-participants were not found to be significant.

This suggests that longer duration of enrollment may have positive impact on the recovery of IDUs unrelated to their willingness to participate in HIV-related clinical research.

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ETHNICITY-RELATED DIFFERENCES IN MORTALITY AMONG NARCOTICS ADDICTS IN A LONGITUDINAL STUDY

M. D. Anglin, Y. Hser, and M. I. Mendez

The study compares the mortality among 535 Anglo and Hispanic narcotics addicts admitted to the California Civil Addict Program (CAP) from 1962 through 1964. By 1986, approximately 24 years after the CAP admission, 58 (27%) of the 212 Anglo addicts and 95 (29%) of the 323 Hispanic addicts were deceased. The average mortality rate for Anglos was 13.5 deaths per 1,000 person years and 14.7 for Hispanics. Mean age at death for both groups was about 40 years.

Causes of death were determined from death certificates. Among Anglos, 38% of deaths were drug-related (*e.g.,* overdose, chronic hepatitis, endocarditis), 21% were due to violence or accidents (*e.g.,* homicides, motor vehicle accidents), and 41% were due to other causes (*e.g.,* cirrhosis, emphysema, diabetes, stroke, etc.). Causes of death among Hispanics were 34% drug related, 28% due to violence or accidents, and 38% due to other causes.

Analysis of cumulative frequency of death according to categories of causes showed different patterns between the two ethnic groups. Among Anglos, violent deaths were consistently of the lowest frequency and with slowest increase over time. Furthermore, the accumulation of deaths that were drug-related and that attributable to other causes were similar over most of the follow-up period, but deaths due to other causes prevailed by 1981. For Hispanics, risk of death due to drug use was persistently predominant, followed by violence and other causes. This pattern was stable until approximately 1983, when other causes increased disproportionately, accounting for the highest number of deaths by 1985.

These results parallel the findings of other similar studies (Anglin *et al.,* 1988; Desmond & Maddux 1984), confirming a more serious progression for consequences of narcotic addiction among Hispanic compared to Anglos.

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A PROSPECTIVE OBSERVATIONAL INVESTIGATION OF TUBERCULOSIS PROPHYLAXIS IN HIV INFECTED INJECTION DRUG USERS (IDUs)

M. Hickson, L. S. Brown, Jr., and M. M. Chu

In an observational study of TB prophylaxis, we began enrollment of IDUs in August 1991. The study subjects were derived from patients enrolled in NYC methadone maintenance clinics. In addition to a questionnaire, sera was collected for complete blood counts (CBCs), liver function tests (LFTs) and HIV serology at baseline; CBCs, LFTs and a questionnaire were repeated regularly along with T-cell counts for HIV+IDUs. Of 414 eligible, 204 patients began and completed the one-year of TB prophylaxis; the median follow-up period was 12 months, 80 patients were HIV positive at baseline and 2 patients seroconverted; 23 patients experienced an adverse reaction (leading to study discontinuation in 16 patients), and 3 patients developed clinical tuberculosis. This represents adverse reaction and TB disease rates of 7.89 and 1.03 per 100 person-years.

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DAILY TUBERCULOSIS PROPHYLACTIC THERAPY IN HIV AND TB INFECTED IDUs: CLINICAL AND DEMOGRAPHIC FACTORS ASSOCIATED WITH COMPLIANCE

M. M. Chu, L. S. Brown, Jr., and A. F. Chu

The purpose of this study was to determine factors related to compliance to TB prophylaxis in HIV-infected IDUs. The eligible study population was derived from patients enrolled in selected methadone maintenance clinics in New York City. We enrolled 414 tuberculin positive (PPD+) IDUs. This population included 68% African-Americans, 25% Hispanics, 7% whites, and 30% females. Nearly 170 (41%) of these patients were HIV positive. Of the total, 357 (86%) patients started the one year prophylactic regimen and were given 300 mg of INH and 50 mg of vitamin B6 daily for one year. Two hundred and four of these patients received at least 75% of their doses, a minimum amount necessary to reduce the risk of active TB. However, HIV+ patients had a lower compliance rate ($P<0.001$). Other demographic or clinical factors were not significantly associated with compliance.

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INCREASED HIV RISK BEHAVIORS REPORTED BY SUBSTANCE ABUSERS WITH A HISTORY OF SUICIDAL IDEATION

J. J. Koman III, J. A. Hoffman, S. J. Schneider, J. W. Luckey, P. M. Flynn, and E. D. Wish

Intake interviews and psychological test results from 465 Washington, D.C. drug abusers seeking treatment were analyzed for the present study. A total of 112 (24%) of these clients reported that they had thought seriously about suicide at some point during their lifetimes. Preliminary analyses revealed that clients who had experienced suicidal ideations were significantly more likely to exhibit a wide array of elevated scores on the Beck Depression-Inventory, the Brief Symptom Inventory (all nine symptom scales and the General Severity Index), and the Millon Clinical Multiaxial Inventory II (13 of 22 BR scales). They were also significantly more likely to report needle use for non-medical purposes; however, they reported fewer injections during the 30 day period prior to admission. They were significantly less likely than others to have used latex protection during sexual activity. These results suggest that there exists a group of drug abusers who have a history of depression so severe that they have contemplated suicide seriously; report an extremely wide array of symptoms of psychological distress; and engage in HIV risk behaviors. Depression alone, without a history of suicidal ideation, was not associated with HIV risk behavior. Those with a history of suicide ideation may be unreceptive to present HIV education techniques which stress avoiding disease. HIV education techniques which include psychiatric interventions for lifting depression, easing feelings of helplessness, and increasing self esteem need to be devised to reach this group.

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DOES ANTISOCIAL PERSONALITY DISORDER LEAD TO INCREASED HIV RISKY BEHAVIORS IN COCAINE USERS?

W. M. Compton, L. B. Cottler, A. M. Shillington, and R K. Price

Antisocial personality disorder (ASPD) puts many persons at risk of premature death, particularly from substance abuse, violence and accidents. Human Immunodeficiency Virus (HIV) presents a new danger to this population who may be particularly vulnerable because of the tendency to engage in impulsive activities. Among injection drug users (lDUs), persons with ASPD have been shown to exhibit more HIV-risky needle use behaviors than their non-antisocial counterparts. However, little is known about the relationship of ASPD and HIV high-risk sexual behaviors and no studies have examined the relationship of ASPD and HIV high-risk behaviors among cocaine users. As part of a NIDA-funded (DA05585) project aimed at reducing the risk of acquiring and spreading HIV, 355 persons using cocaine in the six months prior to contact were interviewed concerning DSM-III-R ASPD, drug use histories, HIV high-risk behaviors (both sexual and needle use behaviors), history of having sexually transmitted diseases (STDs), and sociodemographic variables. In the total sample, ASPD was associated with injection drug use (OR 1.7, p<.03). earlier age of first injection (19 vs. 22 years, p<.001), sharing syringes within the previous six months (OR 2.3, p<.09), having had gonorrhea (OR 2.1, p<.001), having had genital lice (OR 2.7, p<.001). sexual promiscuity (OR 2.0, p<.004), sex outside of marriage (OR 1.9, p<.06), being intoxicated during sex (OR 2.1, p<.007), paying money for sex during (OR 4.4, p<.001), giving drugs for sex (OR 5.5, p<.001), receiving drugs for sex (OR 2.7, p<.003), and increased use of condoms (OR 1.9, p<.05). When multiple logistic regression techniques were used to examine several possible predictors of condom use, only prostitution was associated with condom use. As expected, men in the sample had much higher rates of ASPD than the women (43% vs. 15%, p<.001). Among the men (n=255), ASPD was found to be associated with injection drug use (OR 1.7, p<.07), earlier age of first injection (19 vs. 22 years, p<.02), paying money for sex (OR 2.9, p<.04), giving drugs for sex (OR 4.2, p<.001), receiving drugs for sex (OR 17.2, p<.001), being intoxicated during sex (OR 2.0, p<.03), and sexual promiscuity (OR 1.7, p<.04). Among the women (n=100), ASPD was found to be associated with a history of gonorrhea (OR 4.6, p<.05), genital lice (OR 12.7, p<.001), and an increased use of condoms (OR 5.3, p<.05). Again, when multiple logistic regression techniques were used to examine several possible predictors of condom use, only prostitution was associated with condom use. In summary, cocaine users with ASPD are at higher risk for acquiring HIV because of both injection drug use and sexually risky behaviors. In particular, male cocaine users may be at higher risk for acquiring HIV than female cocaine users not only because of overall increased rates of ASPD among men (with resultant increased high risk behaviors) but also because of the stronger association of ASPD and high risk behaviors among male cocaine users.

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AIDS RISK AND COCAINE DEPENDENCY: A KAP MODEL

J. H. Fisher, H. A. Siegal, R. C. Rapp, and J. H. Wagner

Injection drug use is well established as a method for the transmission of AIDS. The association of drug abuse and AIDS risk behavior, however, goes beyond IDUs. Research in Dayton, Ohio, indicates that non-injection drug users, particularly those smoking crack, engage in high risk sexual activities. High risk behaviors are associated with the economic needs of female crack users and the evolving culture of crack use. Safe sex practices have not yet been successfully introduced in this sub-population.

The Enhanced Treatment Through Induction and Case Management Project encourages clients to practice safer drug use and safer sex. Clients engaged in drug abuse treatment are instructed in safe sex practices in the process of running HIV tests. Knowledge, attitude and practice (KAP) variables are compared between the initiation of treatment and six month follow-up.

Findings indicate that there are significant unmet needs with respect to AIDS education and safe sex practices. While 80% of persons have thought about being exposed to AIDS, 80% also engaged in unprotected sex, over half with more than 2 partners in the past year, 38% travelling to other cities. A majority were under the influence of drugs when they engaged in unprotected sex.

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APPLIED FIELD, CLINICAL AND LABORATORY STUDIES IN HALTING THE SPREAD OF AIDS

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The University of Miami research team has utilized multidisciplinary techniques studying multiple aspects of high risk behaviors - with emphasis on IDUs and their sexual partners and the socio-cultural environments in which these behaviors take place. These typically include: demographic, ethnographic, survey research, behavior modification, psychosocial counseling, and virologic laboratory analytic techniques and methods.

One emphasis of the University of Miami team involves studies of the presence of HIV in IDU's drug administering implements and to specify conditions/procedures required to kill the virus with household bleach. This ongoing series of studies employs a combination of ethnographic, survey and sophisticated virological research techniques.

Two initial studies in this series focused on the environment of shooting galleries. In the first phase of each of these studies, discarded syringe/needle units were collected from shooting galleries, using a controlled design informed by ongoing ethnographic research to determine where, when, and how to harvest this equipment. In the first study, the goal was primarily epidemiological and the focus was on prevalence. Consequently, syringe/needle units were then graded according to the presence of visible blood and tested using standard laboratory techniques for the presence of HIV antibodies. Based upon the various rates of seropositivity, estimates of risk of encountering HIV infected needles were derived, controlling for important variables relative to shooting gallery behavior and socio-cultural conditions as revealed by both ethnographic and survey ongoing research which included participants who had used these galleries.

The second study in this series followed the same implement collection methodology, but the emphasis was on injection prevention and the focus was the efficacy of bleach in cleansing syringe/needle units. The collected and graded syringe/needle units were randomized into two groups: an experimental group which was cleansed in 100% bleach utilizing the cleaning techniques taught within the NIDA supported NADR and CARE Co-operative interventions; and, a control group, which was uncleansed. All syringe/needle units were then tested as to the presence of HIV.

Follow-up laboratory studies have been conducted by the Miami team – utilizing variant dilutions from 100% to 10% – to derive more precise solution strength/exposure time estimates regarding the potential of household bleach to inactivate HIV. Multiple tests of the presence of HIV within variant blood conditions also are being conducted.

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HIGH RISK SEXUAL BEHAVIORS IN OPIOID ABUSERS ENTERING METHADONE TREATMENT

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Heterosexual transmission of HIV-1 among intravenous drug abusers is growing in importance. Unfortunately, changes in high risk sexual behavior in this group have lagged behind reported reductions in their high risk drug use practices. The present study examined the frequency of specific sexual behaviors and condom use in 165 intravenous drug abusers (47% female, mean age 34.1 years) entering outpatient methadone maintenance treatment and compared this data to other studies of sexual behavior. A detailed, structured clinical interview determined the number of vaginal, oral, and anal acts, number of partners, frequency of condom use, and involvement in commercial sex (giving or receiving money or drugs for sex) over the past year. The median number of sexual partners for the population was one. Commercial sex occurred in 16% of the subjects and was associated with significantly more sexual acts and partners. Condom use was infrequent (15%) in vaginal sex in the non-commercial group, but was substantially higher (42%) in the group involved in commercial sex. Most commercial sex was oral, but none of the males and only half of the females used condoms at all during this behavior. Although anal sex was uncommon in the total population (7% of males and females), condoms were infrequently used during this particularly high risk behavior. Most patients (84%) denied commercial sex, and this group reported rates of monogamy and sexual abstinence (81%) that were comparable to general population data. Rates of condom use in vaginal sex in the non-commercial group (73% of males and females never used condoms) were also similar to general population data. HIV-I high risk sex in the study patients not involved in commercial sex was remarkably similar to sexual behavior in the general population at risk for HIV-1 infection.

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PSYCHOSOCIAL CORRELATES OF CONDOM USE IN MINORITY SUBSTANCE ABUSING MALES

S. A. Corrigan, R. M. Malow, S. J. Ireland, J. A. West, J. M. Pena, and S. C. Cunningham

Although strategies for decreasing injection drug use have met with moderate success, efforts to decrease high risk sexual behaviors have been less successful. Because condom use reduces HIV transmission, it is critical to identify the attitudinal, emotional and behavioral factors associated with using condoms. Guided by the AIDS Risk Reduction Model (ARRM), psychosocial correlates of condom use were investigated in a predominantly African-American, economically disadvantaged sample of 230 consecutive male admissions to a VA drug dependence inpatient treatment program.

Based on sexual history data, patients with multiple female sexual partners during the past 3 months were classified into a group that typically used (n =52), or did not use (n =84) condoms. Subjects who used condoms reported significantly higher levels of self-efficacy, greater condom use skills, and more sexual communication with partners than non-users. However, the group did not differ in perceived susceptibility, anxiety concerning HIV transmission, response efficacy, or knowledge regarding HIV. These findings have several implications for clinical intervention. First, these results support previous research indicating that knowledge regarding HIV risk does not necessarily result in condom use and suggest that HIV prevention efforts need to routinely go beyond providing general risk-reduction information. Second, interventions should emphasize skills enhancement, particularly skills used in negotiating safer sexual activity and condom use. Finally, effective intervention efforts must focus on eroticizing condom use and developing cognition and skills to enhance the hedonic value of using condoms. As in other areas of clinical intervention, multimodal approaches will likely be required to maximize behavior change.

	Condom Users		Non-users	
	M	SD	M	SD
Susceptibility	22.52	27:95	23.13	24.71
Anxiety	1.21	1.17	1.30	1.20
Knowledge	23.54	2.51	23.30	3.27
Response Efficacy	3.28	0.82	3.23	0.87
Self-Efficacy[2]	3.91	0.96	3.34	0.85
Communication Skills[2]	3.88	0.74	3.39	0.96
Condom Skills[1]	3.67	1.29	3.67	1.18

1 $p \leq 0.005$ 2 $p \leq 0.001$

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CULTURAL INFLUENCES ON SELF-REPORTED HIV RISK BEHAVIORS DURING PSYCHOSOCIAL DRUG TREATMENT

T. Nagata, S. Shoptaw, R. Rawson, and S. Minsky

Stimulant use is now suspected as a vector for HIV transmission. Effective stimulant treatment may be one method for limiting HIV transmission. This study asked: 1) How effective is outpatient drug treatment for initiating and maintaining safer sexual behaviors among stimulant addicts; and 2) Does such drug treatment effectiveness vary by cultural factors.

METHOD:

Subjects were 146 stimulant addicts (81% male, 19% female; 91.1% cocaine, 8.9% methamphetamine) in a MDA funded treatment demonstration project. Demographic and sexual behavior data were collected with questionnaires at baseline and 6-month follow-up. Treatment data were weeks in treatment and program activities per week. Treatment length was dichotomized into shorter and longer groups using the mean treatment for all subjects (20 weeks). Drug use data were self-report and urinalyses. Safe sex was: 1) one partner or serial monogamy over 6-months; 2) condom use in every sexual encounter with multiple partners; and 3) no sex for drugs or cash. Comparisons across time (baseline (BL) to 6 months (6Mo)) and across factors were made using X^2 tests. X^2 tests were run on full contingency tables. Data presented were percentages of subjects who reported safer sex behaviors. Interval data were analyzed using t-tests or ANOVA.

RESULTS AND DISCUSSION:

Question 1: Do subjects' sexual behaviors change with drug treatment? Results showed there were significant increases from baseline to 6 month follow-up in the percentages of subjects who reported safe sex behaviors among the following groups: males, cocaine users, homosexuals, heterosexuals, and those with longer treatments.

Question 2: Is program effectiveness influenced by cultural factors? Cultural variables that influenced safe sex behaviors were gender, education, ethnicity, and sexual orientation. Females reported they were significantly less likely than males to engage in sex while high on drugs at baseline and at 6-month follow-up. Subjects with mom than high school degrees reported more consistent use of condoms during intercourse than those with less education. Caucasian and Latin American subjects showed significantly greater increases in reported safe sex behaviors than African American subjects. Subjects from all sexual orientations showed increases in safer sex behavior as marked by substantial reductions in numbers of partners from baseline to follow-up. These results provide initial empirical support for stimulant treatment as a means of reducing behaviors associated with transmission of HIV. Cultural influences such as gender, education, ethnicity, and sexual orientation are shown to systematically bias changes in sexual behaviors associated with HIV transmission.

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LATINO IDUs: DO THEIR RISK BEHAVIORS DIFFER FROM THOSE IDUs OF OTHER RACIAL GROUPS

L. Abellanas, K. Meyers, D. S. Metzger, and A. T. McLellan

INTRODUCTION

Cultural and language differences between Latinos IDUs and other racial groups is believed to have implications for HIV risk behaviors and subsequent risk reduction interventions. Although these interventions have been in place for some years, very few methods of monitoring behavior change among Spanish-speaking populations have been tested over time. Another important issue is current methods used to monitor risk behavior change among IDUs are designed for English-speaking subjects. While these instruments are often used with bi-cultural populations, their validity and reliability have yet to be examined. We have developed and tested a new measure, the Risk Assessment Battery (RAB) questionnaire. This instrument is a self-administered questionnaire designed to offer a rapid, private, and minimally intrusive method of assessing risk of HIV transmission from needle sharing and cleaning practices and unprotected sex. We have recently designed a Spanish version of this form. In order to address the issues of cultural and languages differences, the responses of 257 methadone maintenance subjects were analyzed. These analyses of risk behaviors were designed to:

Assess racial differences in risk behaviors
Assess racial differences by gender
Assess gender differences among Latinos

To test reliability between the English and Spanish RABs, 41 subjects were recruited from two different methadone clinics in Philadelphia. All the subjects were volunteers who were able to understand Spanish. We assessed the concordance rate of responses on the Spanish and English versions of the RAB in a sample of 23 bi-lingual clients.

SUMMARY

Significant differences in rates of injection, needle sharing, and shooting gallery visits. The Latino subjects were significantly less likely (12.7%) than African-Americans (41.8%) and Caucasians (45.5%) to be injecting and, if injecting sharing needles (Latino=10.4% vs. African-American=31.3% and Caucasian=58.2%). Among Latino IDUs in a non-Hispanic methadone maintenance program, the majority read English and Spanish without problems (61%). However, one-third read only one of the two languages. Thus, both Spanish and English versions of risk assessment tools are necessary in order to assess Latino populations. The bilingual subjects who read and spoke both English and Spanish answered questions similarly on both versions. Thus, within non-Hispanic treatment centers, many Latinos will be able to complete but Spanish versions are indicated. At the same time, it may be that the lack of Spanish instruments prevents a significant segment of the Latino community from participating in research studies. While these outcomes have been obtained from clients enrolled in a general community treatment program, it would be very important to replicate the same study within a predominantly Spanish-speaking treatment program.

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PERCEPTIONS OF GENOCIDE AMONG AFRICAN AMERICANS: IMPLICATIONS FOR HIV/SUBSTANCE ABUSE PROGRAMS

D. M. Poulson and R. Fullilove

Traditional Public Health Education programs have historically had marginal success in changing problem behaviors, as exemplified by the failure of HIV/Substance Abuse programs to appreciably change behavior in individuals at greatest risk. In minority communities, standard health approaches have not been successful in part, because they fail to address specific nuances of the community - in AIDSPEAK (jargon of the AIDS community), they are not "culturally-sensitive and ethnically-appropriate." In simple terms, health education must meet people where they are at, as opposed to where we think they should be (Friere); programs must be predicated on addressing the beliefs, feelings, and perceptions of the community in question. A review of the pertinent public health literature reveals a reluctance or denial by the black community to "own up" to HIV/Substance Abuse (Dalton 1989). A number of mint and broadcast media stories have also addressed the growing perception among black's that AIDS and drugs are a form of racial warfare and part of a conspiracy to rid America (and the world) of blacks (DeParle 1990; Thomas & Quinn 1991). If these issues are perceived in the black community as part of a "genocidal plot," how effective can risk-reduction programs realistically expect to be?

Studies of this type can demonstrate how acknowledging perceptions of genocide breaks down barriers to health education and prevention programs in the black community. The policy and programmatic implications of such research can also create a foundation for new and more meaningful programs, formulated in conjunction with the community, thereby fostering "ownership" of the issues. Only then will the community truly embrace health education programs, thus allowing for more effective behavior change and positive social action.

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

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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 arc required, this is often limited to a single session. As the present analyses suggest, it may be necessary to examine and respond to individuals' reactions to their antibody status beyond the initial post-test 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 IDUs (114 in-treatment and 49 out-of treatment) completed the Symptom Checklist-90 (SCL-90), the Risk Assessment Battery (RAB), and the Psychiatric Status section (in a face-to-face interview) 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 bc 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 6-month appointment, subjects completed a battery of self-administered questionnaires, participated in a face-to-face interview, received pre-HIV test counseling, and bad 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 to 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 seropositive 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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BASELINE FINDINGS IN A NATURAL HISTORY STUDY OF HIV DISEASE IN INJECTION DRUG USERS (IDUs)

A. F. Chu, L. S. Brown, Jr., and N. Siddiqui

As of August 1991, 350 HIV-1 antibody positive IDUs were recruited to participate in a study of natural history of HIV disease. The participants were recruited from six methadone maintenance clinics in New York City. Baseline assessment included administration of a structured questionnaire regarding sociodemography. drug and sex behavior and presence of AIDS-related symptomatology. In addition, selected laboratory tests such as complete blood count, T-cell subsets, syphilis serology and urine toxicology were performed. Follow-up assessments were completed every six months. The demographic characteristics of the participants at entry were as follows: gender (males 62%) ethnicity (African Americans 57%, Hispanics 38%), age (median 37 years, range 20-63). At entry, the distribution of T-cell subsets were as follows: CD_4 (median=406, range=7–1839). CD_4/CD_8 (median=0.54, range=0.01–2.68). Subjects with CD_4 count of less than 200 were more likely to have cough related symptoms ($p=0.005$). dermatological conditions ($p=0.01$), and lymphadenopathy ($p=0.06$). They were less likely to have engaged in sexual activity ($p=0.02$) and casual sex ($p<0.001$) during the past 12 months. They also had fewer numbers of sex partners in the past 12 months ($p=0.008$).

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QUANTITATIVE CHANGES IN CD4+ T-LYMPHOCYTES FOR HIV+ INTRAVENOUS DRUG USERS

R. Sarro, D. Metzger, G. Woody, H. Navaline, P. Oglesby, and S. Waskow

Depletion of CD4+ lymphocytes characterizes the normal course of HIV infection. Rapid depletion and low values of these cells are frequent indicators of disease progression and poor patient prognosis. Protocols designed to evaluate the effects of drug use on the CD4+ cell in HIV+ IDUs have yielded conflicting results. We determined baseline cellular values for 97 subjects with a history of intravenous drug use who were enrolled in a longitudinal study of HIV and HTLV1/II infection. Subjects were classified by serostatus which included four groups: (A) HIV+/HTLV+, (B) HIV+/HTLV-, (C) HIV-/HTLV+ and (D) HIV-/HTLV-. Mean baseline CD4+ values ranged from 472c/M(HIV+/HTLV+) to 947c/M(HIV-/HTLV-). The data provided an opportunity to examine cellular changes over an 18 month period for 26 baseline HIV seropositives and 11 subjects that seroconverted during the course of our study. Mean baseline CD4+ values were 421c/M for seropositives and 616c/M for seroconverters; the average cell loss per semester was 16 and 4 for each group respectively. The potential effect of sociodemographic variables, treatment status, and drug use on the CD4+ depletion rate was analyzed for seropositives and determined to be insignificant.

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METHYLPHENIDATE FOR COGNITIVE IMPAIRMENT IN HIV-INFECTED DRUG ABUSERS: A PILOT STUDY

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Other investigators have reported clinical improvement from psychostimulant drugs in patients with HIV-related cognitive impairment (Psychosomatics 1988;9:38-46; J Clin Psychopharmacol 1992; 12:268-272). However, amelioration of neuropsychological test performance has remained unproven in a controlled design. The present study examined the efficacy of a psychostimulant drug (sustained release methylphenidate) in a drug abuse population with HIV-related cognitive impairment. Six HIV+ methadone patients (5M, 2F, 39 ± 8 yrs) with impaired neuropsychological test performance participated in an inpatient, randomized, double-blind, placebo-controlled, crossover trial of sustained release methylphenidate 20-40 mg QD. Neuropsychological testing was administered at baseline and after one week of each treatment condition. Two composite measures of neuropsychological test performance were derived: mean Z score for all 17 tests in the battery and mean Z score for each patient's impaired tests. Neither measure revealed a significant difference between methylphenidate and placebo; although both measures showed each treatment condition to be significantly improved from baseline. Improvement from baseline performance appears likely due to the effects of hospitalization or practice. Conclusion: evidence is insufficient for the efficacy of psychostimulant drugs in ameliorating cognitive performance in HIV-related cognitive impairment.

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HIV STATUS AND SUBSTANCE USE IN A METHADONE MAINTENANCE PROGRAM

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We surveyed 240 Methadone maintained subjects in a retrospective study for differences with respect to HIV status and risk behaviors. We obtained detailed demographic information. conducted HIV testing and matched this data to clinical observations while in Methadone' treatment between 1988 and 1992. Clinical monitoring included urine toxicology screens at least once monthly for each subject (total number of observations: 4155).

Eighty-five subjects tested positive for the HIV virus (35.4%). We compared the HIV negative and positive groups with regard to age, gender, race, marital status, steady relationships, education, employment, reported intravenous drug use and positive urine tox-screens. There were no statistically significant differences bv HIV status in age, education and marital status. The two groups differed significantly in: 1) gender: males were overrepresented in the HIV positive group (61 vs. 48%; $p<.05$), 2) race: African Americans constituted only 24% of HIV negatives but made up over 50% of the HIV positive group ($p<.0001$), 3) relationships: 72% of HIV negatives and only 51% of HIV positives reported current involvement in a steady relationship ($p<.001$), 4) employment: HIV negatives reported employment rates four times higher than HIV positives (26 vs. 7 %; $p<.0001$), 5) IVDU: HIV positives reported a third more current intravenous drug use than HIV negatives (62 vs. 45%; $p<.01$). In addition, HIV infected subjects had twice as many urine tox-screens positive for Cocaine (27 vs. 14%; $p<.0001$) and Benzodiazepines (18 vs. 8%: $p<.0001$) while in Methadone treatment. HIV positives also had more Opiate positive urines than HIV negatives (10 vs. 8%).

In summary, our findings suggest that HIV seropositives differ in several aspects from other Methadone maintained subjects in our sample. Males and African Americans are overrepresented. HIV positives report fewer steady relationships and have a higher unemployment rate. Finally, HIV positives use Cocaine and Benzodiazepines twice as frequently.

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CASE MANAGEMENT OF SUBSTANCE ABUSERS WITH HIV INFECTION

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In a random assignment pilot study with hospitalized substance abusers who had HIV disease, two-month follow-ups indicate the feasibility of research and possible efficacy of intensive case management. Case management is a promising intervention that has been used widely in psychiatric settings but not well tested with substance abusers. This pilot aimed to (1) determine the feasibility of randomization and 2-month follow-up interviews; and (2) identify early indicators of success in reducing unsafe sex or needle use and improving quality of living situation, physical health, and psychological status. Forty-six hospitalized substance abusers with symptomatic HIV disease were recruited in-hospital and randomly assigned intensive case management or usual care (brief contact by a counselor). Of the subjects, 74% were men; 39% were African-American and 50% Caucasian. Primary drugs of abuse were amphetamine (28%). crack cocaine (26%), alcohol (17%), heroin-cocaine combination (14%), heroin (10%), and marijuana (5%). At 2-month follow-ups 70% were interviewed, 19% were not located, and 11% had died. Case management was associated with significant improvement ($p < .05$) in subjects' quality of living situation (including social support, employment, and family problems). There were no differences between case management and standard care in unsafe sex or needle use, physical health, or psychological status. We conclude that such research is feasible, and two months of case management may improve patients' quality of living situation.

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TREATMENT PATTERNS AMONG HIV POSITIVE IDUS: A LONGITUDINAL STUDY

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

INTRODUCTION:

Intravenous (IV) drug use represents a substantial risk factor for the acquisition and spread of the human immunodeficiency (HIV) virus. Recent research demonstrates that methadone maintenance treatment reduces high risk behavior and is associated with lower HIV conversion rates among IDUs. While drug treatment has been associated with reduced HIV infection rates and risk behaviors, the effect of serostatus on treatment entry and retention is unknown. The Penn/VA Center for Studies of Addictions' Risk Assessment Project (RAP) tracks over six hundred IDUs in the Philadelphia Metropolitan area. This poster presents the treatment patterns of subjects from the RAP project both in and out-of-treatment over a two year period. The effect, if any. of serostatus on subjects' entry and retention in drug treatment programs is explored.

METHODS:

Data from one hundred fifteen (115) in-treatment and fifty-one (51) out-of-treatment IDUs from the Risk Assessment Project (RAP) with complete data through the first twenty four months of the study were used for these analyses. The RAP project is conducted from the Girard Medical Center Methadone Clinic in North Philadelphia. The Girard Methadone Clinic is the largest in the state of Pennsylvania. Questionnaire, interview and serologic data were collected every six months. The Risk Assessment Battery (RAB) was used to gather the information presented in this poster. The RAB is a self-report measure which assesses drug use and frequency, HIV-risk associated behaviors and demographic variables.

RESULTS:

Although not statistically significant, a higher percentage of HIV positive IDUs remained in treatment as compared to HIV negative IDUs. HIV positive clients from the original in-treatment cohort were more likely than HIV negative IDUs to be in-treatment at all four of the subsequent follow-up points. While treatment patterns did not differ significantly as a function of serostatus. there were important differences between HIV positive and HIV negative subjects. HIV positive clients from the in-treatment cohort first tried heroin at a significantly younger age (17.4 vs. 19.8, $p<.05$). Out-of-treatment IDUs were also more likely to have tried heroin at a significantly earlier age (16.6 vs. 21.6. $p < .01$). There was also a relationship between serostatus and reports of treatment for alcohol problems. Seventy percent (70 %) of the out-of-treatment subjects who were HIV positive had been treated for alcohol problems, as compared to only thirty-three percent (33.3 %) of those out-of-treatment subjects who were HIV negative ($p < .05$). HIV positive subjects reported more prior treatment entries to stop using drugs than out-of-treatment negative (6.2 vs. 1.97, $p < .05$).

DISCUSSION:

Although higher rates of treatment retention were found among HIV positive subjects, the data presented here does not support the conclusion that serostatus has a significant impact on IDU. While treatment patterns did not differ significantly as a function of serostatus, other characteristic differences existed as a relationship to serostatus. Age of first heroin use was related to HIV serostatus. Subjects who were HIV positive began using heroin at a significantly younger age. This relationship existed for subjects both in and out-of-treatment. In-treatment subjects who were HIV positive were also differentiated by their report of alcohol problems. HIV positive subjects were significantly more likely to have reported treatment for alcohol problems, including involvement with Alcoholics Anonymous (AA). Alcohol may disinhibit IV drug users to the extent that they do not act on the risk reduction knowledge they possess. Attention to alcohol problems in treatment, as well as risky drug use behaviors, seems to be important in preventing HIV infection among IDUs.

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AIDS-RELATED DEATHS AMONG INJECTION DRUG USERS IN METHADONE MAINTENANCE

J. A. London, J. L. Sorensen, K. Delucchi, L. Roehrich, T. Wall, R. Stall, and S. L. Batki

Increasing numbers of seropositive drug users are dying from HIV-related causes while in methadone maintenance treatment (MMT). The rise in AIDS-related mortality rates among drug users in MMT may be stressful for patients to experience. This study compared the frequency of AIDS and non-AIDS-related deaths in the social networks of seropositive and seronegative injection drug users in MMT. Substance abusers (N=66) enrolled in a San Francisco county MMT program were interviewed about the number of AIDS and non-AIDS deaths they had experienced in the preceding year. They were also asked about whether the people who had died were marital partners, relatives, close friends, or acquaintances. Results: 61% were male; 41% HIV positive; 57% ethnic minorities; only 9% of MMT patients reported no deaths in their social networks; close friends (50%) and acquaintances within the MMT clinic (32%) were most often reported as dead. In contrast, 21% of acquaintances outside of MMT, marital partners (5), and relatives (18%) had died.

	Seropositive Drug Users (N=68)		Seronegative Drug Users (N=98)	
	Mean	SD	Mean	SD
HIV Deaths	7.3	7.0	4.5	5.3
Non-HIV Deaths	1.8	3.0	2.1	2.4

Conclusion: The frequency of AIDS and non-AIDS-related deaths suggests that substance abusers in MMT are at risk for losing sources of social support. Seropositive substance abusers may even be more vulnerable to experiencing AIDS related deaths. Future research should examine the experience of multiple deaths in the social networks of MMT patients and its relationship to psychosocial difficulties and AIDS risk behavior.

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EFFECT OF RECEIVING INITIAL SSI BENEFITS ON INJECTION DRUG USERS IN METHADONE MAINTENANCE TREATMENT

M. Herbst, S. L. Batki, L. Manfredi, and T. Jones

Objective: A retrospective chart review study examined the effect of receiving initial lump sum disability benefit payments on a group of injection drug users (IDUs) in methadone maintenance treatment (MMT) who became disabled, primarily due to HIV related illnesses.

Method: A review of clinic records revealed 26 patients who had received a retroactive lump-sum initial disability payment while in MMT. Clinic attendance records and drug urinalysis results were compared for three month periods before and after receipt of the initial check.

Results: Check amounts ranged from $1060 to $12,400. The mean amount of initial check was $4,622. Clinic attendance for the overall group was decreased after check receipt (mean days missed increased from three to six, p=.07 Wilcoxon). Among subjects who had a payee when the check was received, there was no significant change in missed clinic days post check receipt, while in subjects without a payee there was a significant increase in missed clinic days after check receipt (mean days missed increased from three to 18, p=.02 Wilcoxon). There was no significant change in % positive drug urinalysis results in the overall group or among subjects who had a payee but a trend towards increased positive drug urinalysis results after check receipt in subjects without a payee (increase from 18% to 21% for subjects with payee, 17% to 38% for subjects without payee P=.09 Wilcoxon).

conclusion: The data suggests that receipt of an initial lump-sum distribution of retroactive Social Security benefits may be associated with worsened outcome as measured by clinic attendance in IDUs who are in MMT, especially if they do not have a payee.

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COUPON DISTRIBUTION TO OUT-OF-TREATMENT IDUs IN NEW JERSEY: FACILITATING FIRST-TIME TREATMENT ENROLLMENT

D. A. Bux, M. Y. Iguchi, V. Lidz, and J. J. Platt

A key strategy in controlling AIDS among IDUs is to increase the number of addicts in treatment. However, large numbers of out-of-treatment IDUs have never been treated for their drug abuse. Cost is a significant barrier to treatment entry in many parts of the US, where publicly-funded treatment slots are limited. Short-term detoxification remains common among opiate addicts but is largely ineffective, while the more effective methadone maintenance often is less attractive to addicts who may resist an indefinite commitment to treatment. Long-term detoxification may provide an alternative which is more appealing than maintenance, and better engages the client in treatment than short-term detoxification. The objectives of this research were: 1) To evaluate participation in a coupon distribution program for 21- or 90-days of free methadone detoxification; and 2) To identify subject characteristics which predict participation.

Four thousand, eight hundred and forty IDUs were recruited through street-based outreach to offices in Newark and Jersey City, NJ. Subjects completed detailed interviews on drug using and sexual behavior and gave blood samples for HIV testing. Subjects reporting current heroin use were offered a coupon for either 21 or 90 days (randomly determined) of free methadone detoxification.

Of 4,390 coupons distributed, 2,570 (59%) were redeemed, including 1,151 of 2,022 (57%) 21-day coupons and 1,419 of 2,368 (60%) 90-day coupons. Ninety-day coupons were redeemed significantly more often than 21-day coupons. Among redeemers, 1,031 (44%) had never received formal drug treatment, and 1,019 (45%) were HIV seropositive. Univariate and multiple logistic regression analyses identified frequent heroin use, prior drug detoxification, frequent drug injection, cleaning needles with bleach, non-black race, hispanic ethnicity, and Newark residence as predictive of coupon redemption.

Outreach-based coupon distribution is a successful means of recruiting never-treated and HIV-infected IDUs into treatment. The 90-day coupon was more effective in facilitating treatment entry. Blacks, never-treated IDUs, less frequent injectors, and less frequent users of heroin, were all less likely to participate in the program. Bleach users were more likely to participate, perhaps reflecting greater motivation for behavior change. Outreach to never-treated IDUs focusing on education and motivational interviewing to encourage treatment entry is recommended. Treatment recruitment via needle exchange and bleach distribution programs may also be effective. Further study of barriers to treatment for less frequent users and blacks, and the development of alternative risk-reduction measures, are encouraged. Further evaluation of 90-day detoxification is also recommended.

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WHAT PREDICTS DISCHARGE FROM METHADONE MAINTENANCE FOR IDUs AT HIGH RISK OF HIV INFECTION?

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

Injection drug users (IDUs) have become a focal point of HIV prevention because of their role in transmitting HIV, both to other IDUs and to non-IDUs through sexual contact and prenatal transmission. As part of a NIDA-funded (DA06250) project, 500 IDUs were selected into methadone maintenance treatment between 1990 and 1993 who were at high risk for HIV infection and/or transmission. The goal of the study is to test the effectiveness of an enhanced methadone maintenance treatment protocol in reducing HIV risk behavior.

The sample is composed of members of four target groups at high risk: HIV+ individuals, gay or bisexual males, sex workers (prostitutes), and sex partners of any of the above. Data analysis consists of four logistic regression equations tested with simultaneous order of entry. Dependent variables are type of discharge: no discharge, discharge for circumstantial reasons (jail or prison, moved, transfer to another program, hospitalization); discharge for negative reasons (non-compliance, wanted to start using again, and non-attendance for over 14 days). Predictor variables consist of: age, sex, ethnicity, whether the individual was in treatment with his/her partner, whether the individual was under legal supervision, level of depression, level of education, legal job income, HIV status, gay/bisexual male, sex work, treatment group, tranquilizer use within last 30 days, cocaine or crack use within last 30 days, and total time in program.

A higher probability of discharge for any reason was found for individuals who are younger, depressed, HIV+, sex workers, and in the control group. Younger individuals and those in the control group had a higher probability of negative discharge. Discharges for circumstantial reasons were more likely for individuals who are younger, depressed, more educated, HIV+, and sex workers. There was also a greater likelihood of a negative, compared with a circumstantial, discharge if an individual was HIV- and in the control group.

While the analysis confirmed that an enhanced methadone maintenance treatment protocol decreased negative, but not circumstantial, discharge, more analysis is needed to discern the effectiveness of different program elements in increasing retention. Individuals who are HIV+ may require more flexible program structure, transportation assistance, and ability to transfer between programs in order to sustain treatment. Logistic regression models were able to classify and predict candidates at high risk for discharge at about 70% accuracy. Treatment protocols need to be developed to maximize retention of those individuals at highest risk of HIV infection and/or transmission.

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RELATIONSHIP BETWEEN BLOOD PRESSURE LEVELS AND DRINKING HISTORY IN CHRONIC ALCOHOLICS

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Chronic alcoholics often manifest transitory elevations of blood pressure (BP) during intoxication and acute withdrawal. At present, it is not known which drinking parameters are related to alcoholics' hypertension, although withdrawal symptomatology, recent absolute ethanol intake, frequency of drinking episodes, and beverage type have all been suggested. The purpose of the present study was to investigate the association between admission BP and alcohol drinking measures. Dependent variables included estimated chronicity, quantity-frequency for beverage type: absolute number of drinking and withdrawal days, and typical severity of withdrawals. Subjects were 42 inpatient male alcoholics who had consumed their last drink within three days of admission. BPs were taken for each patient three times daily the first 48 hours of admission. After this period. BP levels must have been normal (i.e., <140/90 mmHg). Patients were interviewed about drinking history following several weeks of sobriety. Alcoholics with the highest BP levels upon admission had significantly greater quantity-frequency of drinking, especially liquor, greater number of intoxicated days, and more severe withdrawal symptoms, especially tremors and nausea (all *ps* <.05). Further, multiple regression analyses of all drinking variables showed that quantity-frequency of liquor was the most predictive variable for admission systolic ($r=+.38$, $p<.05$) and diastolic ($r=+.50$, $p<.01$) BP. These findings confirm earlier data by our group showing significantly greater liquor consumption in those alcoholics with the highest withdrawal BPs. Further investigation of the mechanisms of the detrimental effects of liquor consumption *(i.e.,* higher blood ethanol levels, beverage nutrient content, additives, dietary factors) on cardiovascular function is warranted.

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PAROXYSMAL EEG ACTIVITY IN COCAINE ABSTINENCE

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

There are few reports, employing electroencephalographic (EEG) recordings, of subjects recovering from polysubstance abuse who preferentially abused cocaine. Using such methods, we have observed an atypical paroxysmal-like EEG pattern in a subset of subjects with EEGs otherwise within normal limits. The development of this pattern ("C-wave") has a morphology (shape, size) similar to a seizure tracing but the duration of the event is much shorter and the activity is less sharp than what is seen in such tracings. The paroxysmal-like EEG pattern is reminiscent of vertex waves typicallv associated with drowsiness. The first impression is to interpret these as such vertex waves. However, the pattern lacks the waxing and waning ("beating") of alpha and the slow lateral eye drift associated with drowsiness.

The "C-wave" EEG patterns associated with cocaine abstinence are most identifiable by the increased voltage of the alpha-theta burst discharges. These "C-waves" were clearly present in twelve of these cocaine-alcohol abstinent subjects. Variations in the pattern appeared in tracings of the majority of the rest of 30 subjects. The "C-wave" pattern generally has a total duration of six to eight seconds. Onset consists of suppression of already fragmented background activity, lasting about 0.5 seconds. The "C-waves" are sometimes accompanied by slow vertical eye movements but there is no clear correlation. The pattern has two components which occur independently of each other but can be concomitant; one is a burst of pattern alpha, the second is the transient presence of focal frontal theta. Following onset suppression, alpha reemerges occipitally and bilaterally, but with decreased frequency (background alpha = 9-10 hz.; pattern alpha = 7.5-8 hz.). From the occipital position "pattern alpha" progresses anteriorly to the frontal lobe bilaterally with-a generalized burst, then digresses to the posterior head regions. Background suppression follows (with a duration of about 0.5 seconds). The waking record, which is within normal limits resumes with no evidence of the event that had preceded it. The second component, transient focal frontal theta (3-5 hz.), occurs in both waking and drowsy states (sleep tracings are not available). This slowing originates at Fz and spreads discretely to those areas proximal and lateral to this centrofrontal (CF) location. Pattern alpha is sometimes replaced with this slowing, but only in its discrete CF locale. The CF theta is seen more often in the course of a tracing than typical "C-waves".

Typically these subjects do not generate a well organized sustained alpha thus the fragmented background. Pattern alpha tends to be organized and rhythmic. Since pattern alpha does progress into the frontal head regions it could be confused with the dense frontal alpha associated with cannabis abuse (Struve *et al.,* 1989) but morphologically they differ.

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EFFECTS OF COCAINE ON AUTONOMIC FUNCTIONING IN HUMANS

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The adverse sequelae associated with cocaine use has heightened interest in the underlying physiologic mechanisms related to cocaine cardiotoxicity. These sequelae, primarily ventricular arrhythmias, may be due to an autonomic imbalance. Though the risk of autonomic imbalance is likely to be highest immediately after cocaine use, there may be chronic effects that increase the long-term risk of fatal arrhythmias. Therefore, it was the purpose of this study to determine if there are prolonged effects of cocaine on autonomic tone as measured by heart rate variability (HRV) that may predispose chronic cocaine users to arrhythmias. Five methadone-maintained research volunteers, reporting chronic intravenous cocaine use, resided on a clinical research unit for two separate admissions. During several of the daily cocaine or placebo sessions 24-hour Holter records were collected. Additionally, Holter data were collected for a control group. Mean R-R' intervals and HRV were calculated as the mean and standard deviation of all normal beats for each one hour period. The circadian pattern of heart rate and HRV in the methadone-maintained chronic cocaine users were similar to the non-drug users. However, one cocaine user had a marked attenuation in HRV as compared to both the non-drug users and other chronic cocaine users. Similar to previous studies with control populations, 24-hour HRV was a stable measure over time for most of the chronic cocaine users. Spectral analysis was performed for two of the chronic cocaine users on the repeated cocaine session day (32 mg/70 kg/dose). For the chronic cocaine user who had an attenuated HRV pattern, there was a relative increase in parasympathetic tone and a decrease in sympathetic tone during cocaine administration. For the other cocaine user with a normal HRV pattern, there was a relative increase in sympathetic tone and a decrease in parasympathetic tone. For both cocaine users, there was a return towards baseline over time. In conclusion, methadone-maintained cocaine users have a similar pattern of heart rate and HRV compared to control subjects although attenuation of this pattern may be found in certain individual cocaine users. Preliminary data suggest that while there may be an increased risk of arrhythmias during periods of cocaine use due to an alteration in autonomic tone, chronic cocaine use may not produce long-term changes in autonomic functioning for most cocaine users.

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CARDIOVASCULAR TOLERANCE TO COCAINE AND MYOCARDIAL ALTERATIONS IN THE RAT

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Studies on the human and non-human primate have reported a cardiovascular tolerance to the hypertensive effects of increasing iv doses of cocaine: increments in blood pressure are not dose related.

In the present experiments, cardiovascular tolerance to cocaine and cardiac morphology were studied after subacute exposure of the rat to cocaine. Two series of experiments were performed on 8 groups of rats fitted with osmotic pumps in the peritoneal cavity and administered for 7 to 14 days isotonic saline or cocaine solution at the rate of 15 to 40 mg/kg/day. All animals survived this initial period without apparent ill effects.

In a first series, on day 8 or 14. the groups of cocaine or saline treated animals were fitted under pentobarbital anesthesia with an intra-arterial caudal catheter connected via a three way stopcock to a strain gauge and a microcomputer for on line display and analysis of blood pressure. After recovery, they were administered intra-arterially at twenty minute interval 10, 20, and 30 mg/kg of cocaine. Percentage changes in mean blood pressure of rats chronically treated with cocaine or saline, computed between resting mean blood pressure and peak pressure following cocaine administration, were significantly smaller after each challenging dose of cocaine ($p < 0.01$) in the group of animals treated subacutely with the alkaloid. These symptoms are indicative of cardiovascular tolerance to cocaine. The animals treated subacutely with cocaine did not survive the 30 mg dose of the alkaloid while saline controls did.

In a second series, four other groups of saline or cocaine treated rats (40 mg/kg for 7 to 14 days) were studied. After this period, the animals were anesthetized and bled. Their hearts injected with glutaraldehyde, were removed and prepared for light and electron microscopy examination. Cardiac morphology of animals administered saline was normal. Cocaine treated animals presented disseminate focal lesions of the myocardium, disruption of myocyte and myofibrils, areas of atypical contraction and intra cytoplasmic vacuolization. Electron microscopy showed consistent disseminated lesions of the cardiomyocytes with decreased diameter of the myofibrils as compared to saline control ($p < 0.01$) and elongation of the sarcomeres. Mitochondria were swollen with destruction of the crests and a cloudy appearance.

Tolerance to the hypertensive effects of cocaine administration in the rat subacutely administered this alkaloid is associated with dose related myocardial alterations of the cardiomyocytes.

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ACUTE COCAINE ADMINISTRATION STIMULATES PULSATILE SECRETION OF ACTH IN MALE RHESUS MONKEY

Z. Sarnyai, N. K. Mello, J. H. Mendelson, M. Kelly, H. Gelles, M. Erös-Sarnyai, and G. R. Mercer

The activation of the hypothalamic-pituitary-adrenal (HPA) axis by corticotropin-releasing factor (CRF) plays a key role in the regulation of the behavioral and neuroendocrine processes. CRF and/or the adrenal steroids may be important in the mediation of some behavioral and reinforcing effects of psychostimulants. Cocaine stimulates ACTH and corticosterone secretion in rats by a CRF-deoendent mechanism (Rivier and Vale 1987; Samyai *et al.,* 1992) but its effects in rhesus monkey are unknown.

We examined the effects of acute cocaine administration on pulsatile secretion of ACTH in chair-adapted male rhesus monkeys. ACTH is secreted in rapid micropulses and we used an intensive (2 min) intravenous (i.v.) sampling procedure for 60 min before and after cocaine or placebo injections. Plasma samples were analyzed by radioimmunoassay and ACTH and cortisol pulses were identified with Cluster analysis program (Veldhuis and Johnson 1986). Frequent ACTH and cortisol micropulses (~3 pulses/hr) were measured during the pre-cocaine baseline period.

Cocaine (0.4 and 0.8 mg/kg, iv.) stimulated a dose-dependent increase in ACTH secretion. The amplitude and the area under the peaks of ACTH micropulses increased after cocaine administration but there was no change in pulse frequency. Since the amplitude, but not the frequency of ACTH micropulses is under the control of the hypothalamic CRF (Cames *et al.,* 1991). we hypothesize that cocaine stimulates the hypothalamic-pituitary-adrenal axis in monkey through the release of CRF.

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LANGUAGE DEVELOPMENT IN PRE-SCHOOL AGE CHILDREN LIVING WITH COCAINE ABUSING MOTHERS

M. E. Malakoff and L. C. Mayes

The negative environmental conditions associated with cocaine-use, and the effects of the cocaine-use on caretaking skills suggests that a young child growing up in a cocaine-using home is at risk for developmental delays. However, there are no published studies examining the long-term effects of postnatal exposure to maternal cocaine abuse on developmental outcome, whether this exposure is subsequent to or in the absence of prenatal exposure.

Language abilities were assessed among a group of 20 preschool-age children (2 1/2 to 5 years of age) living with 14 cocaine-abusing mothers. The children were recruited from a day care center affiliated with a drug-treatment program for pregnant women using cocaine. All children had been exposed to postnatal cocaine use. Half of the children had also been exposed prenatally to maternal cocaine use. Three standardized language measures were used to assess independently (1) receptive vocabulary (Peabody Picture Vocabulary Test-Revised) and expressive vocabulary (Expressive One-Word Vocabulary Test-Revised) vocabulary and (2) receptive and expressive language ability (Sequenced Inventory of Communicative Development–Revised).

The findings suggest that children living in cocaine-abusing homes are at risk for language delays. However, the presence or absence of language impairment was not significantly associated with prenatal cocaine exposure. Sixty percent of the children in the sample showed serious language delays. Only three of the 20 children showed minimal to no language delay. Children showed a mean delay of 10.8 months SD= 6.6) on receptive vocabulary and 10.9 months (SD=7.3) on expressive vocabulary skills. Older children showed greater language delays. Children over 48 months of age showed mean delays of 16.1 (SD = 4.3) and 14.3 months (SD = 6.3) for receptive and expressive vocabulary, respectively. None of the 9 children over 48 months showed receptive vocabulary skills above the 15th percentile, although three children showed expressive skills between the 15th and 42nd percentile. Performance on the measure of overall language ability (SICD-R) showed smaller language delays, although there was again great heterogeneity in performance. This suggests that when assessing language ability among this population, performance on vocabulary skills are not a good measure of overall language ability.

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COMPARING THE ACUTE LETHALITY AND DEPENDENCE POTENTIAL OF PSYCHOACTIVE SUBSTANCES

R. S. Gable

A literature review was undertaken of the acute lethality and the dependence potential of 20 psychoactive substances, specific to their most common route of administration in non-medical use. Approximately 350 journal articles, published between 1982-1992, were found to give a quantitative estimate of lethality or an empirically derived comparison of dependence potential. Twenty-four replies were received during a two-year period from an *ad hoc* panel of 35 toxicologists and psychopharmacologists who were asked to comment on a summary data table. A "safety margin" (or therapeutic index) was determined for each substance based on the ratio of the estimated median acute lethal dose and the median effective dose for a 70 kg non-tolerant human. Lethal dosages were especially difficult to estimate due to interspecies variability and to extraneous health factors among human decedents. The estimate of dependence potential of a drug was based primarily on its strength as a reinforcer for drug-seeking behavior.

Table 1 tentatively specifies safety margins within a range of therapeutic index ratios. Intravenous heroin appeared to have the least margin of safety and a very high dependence.

Table 1. Acute Lethality and Dependence Potential of Psychoactive Substances

Safety margin	Dependence Potential: High	Moderate	Low
5-19	Heroin (iv), opium (sm), morphine (im)	Alcohol (or)	MDMA (or). Mescaline (or)
20-39	Cocaine (sm), Cocaine (in)	Amphetamine (or) Secobarbitol (or)	Nitrous oxide (ii) Ketamine (tar)
40-59		PCP (sm)	
60-79		Nicotine (sm)	
100-140	Methaqualone (or)		Caffeine (or)
280-300			LSD (or)
1000-2m		Diazepam (or)	
2500-3500			Marijuana (sm), Psilocybin (or)

Note: iv=intravenous, im=intramuscular, sm=smoked, or-oral swallowed, in=intranasal, ih=inhaled

potential. In contrast, oral psilocybin appeared to have the largest safety ratio and very low dependence potential. Other critical factors in assessing the risk of drug use--that were not examined in the present study (such as chronic illness, perceptual distortion, and social dysfunction)--should be incorporated in the formulation of drug control policy.

REFERENCES: May be obtained from the senior author.

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NICOTINE DEPENDENCE AND SCHIZOPHRENIA: THE RELATIONSHIP TO PSYCHOPATHOLOGY AND NEUROLEPTIC MEDICATION DOSAGE AND SIDE EFFECTS

D. M. Ziedonis, T. Kosten, and W. Glazer

PURPOSE AND METHODS:

Nicotine smoking is very common among schizophrenics. A few studies suggest there may be a relationship between nicotine dependence and psychopathology or movement disorders.

This study compared 265 schizophrenic/schizo-affictive patients (n=182/83) according to cigarette smoking status (never-smokers, x-smokers, light smokers, and heavy smokers). RDC diagnostic criteria were made using the SADS-L. Smoking status and history were based on self-report. Psychopathology assessments were made using the structured instruments of the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS). Neuroleptic induced movement disorders were assessed using the clinical exams of the Abnormal Involuntary Movement Scale (AIMS) and the Webster's scale for parkinsonism.

RESULTS AND CONSLUSIONS:

Current smokers (68%) were younger (39 years versus 44 years), more often male (55% vs 37%), with drug abuse (25% vs 7%) or alcoholism (26% vs 13%). Current smokers had significantly higher levels of positive symptoms of schizophrenia (SAPS scores, 7.5 vs 4.3) than non-smokers. Of note, heavy smokers (31%) had the highest level of positive symptoms (9.1). Also, heavy smokers had significantly lower levels of negative symptoms than never-smokers (24%). x-smokers (7%) and light smokers (37%) (SANS scores, 7.1 vs 5.9).

Smokers had similar rates of parkinsonism symptoms except for lower rates of rigidity (21% vs 32%. $p<0.05$). There were no significant differences between groups for tardive dyskinesia (AIMS scale). Of note, cigarette smokers were given more neuroleptic medication (375 mg vs 590 mg) than non-smokers.

In this study smoking status was associated with differences in levels of psychopathology and rates of parkinsonian rigidity and substance abuse. Future studies should be prospective and assess for changes with nicotine abstinence.

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DIFFERENTIAL BINDING OF OPIOID PEPTIDES AND OTHER DRUGS TO TWO SUBTYPES OF OPIOID δ_{ncx} BINDING SITES IN MOUSE BRAIN: FURTHER EVIDENCE FOR δ RECEPTOR HETEROGENEITY

H. Xu, J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman

Previous studies resolved two subtypes of the δ_{ncx} binding site in rat brain. A major purpose of this study was to clarify the relationship between the δ_{ncx} binding sites and the δ_1 and δ_2 receptors. Mouse brain membranes were depleted of μ binding sites using the irreversible ligand. BIT δ_{ncx} binding sites were labeled with [^{3}H]DADL (4-6 hr at 25° C, in 10 mM Tris-HCl, pH 7.4, in the presence of either 100mM NaCl or 100 mM choline chloride). Two binding sites were most readily resolved in the TRIS/SODIUM condition. Several peptides were highly selective for site 1: DPDPE (1546-fold), deltorphin-II (1194-fold), DPLPE (121-fold). Several peptides were essentially non-selective: DSLET (0.5-fold), DADL (4.7-fold) and [pCI]DPDPE (0.74-fold). BNTX and NTB were 30-fold and 0.3-fold selective for site 1. The non-peptide δ agonist, BW373U86, had the highest degree of selectivity for site 2 (21-fold). Both [^{3}H]DADL and (^{3}HJDSLET binding were sensitive to the irreversible effects of DALCE, but not [Cys^4]deltorphin. Viewed collectively with previous studies, these data suggest that the δ_{ncx} binding site is similar to the δ_1 receptor, and provide further evidence for heterogeneity of the δ receptors,

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PROBING THE OPIOID RECEPTOR COMPLEX WITH (+)-TRANS-SUPERFIT: RESOLUTION OF TWO δ_{cx} BINDING SITES

X. Y. Cha, H. Xu, C.-H. Kim, K. C. Rice, and R. B. Rothman

Previous studies from ours and other laboratories support the existence of two δ receptor subtypes termed, δ_{cx} and δ_{ncx} for δ receptors which are associated with, and are not associated with, the μ-ð opioid receptor complex. The δ_{cx} site is optimally assayed with [^{3}H]DADL (10 mM TRIS-HCl, pH 7.4, 100 mM NaCl, 3 mM $MnCl_2$, 2 μM GTP and 5 mM 2-mercaptoethanol) using rat brain membranes depleted δ_{ncx} sites by pretreatment with the δ_{ncx}-selective acylating agent, (+)-trans-SUPERFIT. A recent paper reported that whereas morphine (MOR) and other μ ligands are noncompetitive inhibitors at the δ_{cx} site, DPDPE and other δ-preferring δ ligands are not. The present study determined the effect of a wide range of MOR concentrations (0, 12.5, 25, 50, 100, 200, 400, 800 nM) on the Kd and Bmax of the δ_{cx} site. Low doses of MOR produced a dose-dependent decrease in the Bmax (IC50 < 10 nM, maximal decrease of about 40%). Higher doses of MOR did not decrease the Bmax further, but increased the Kd (Ki = 136 nM). These data suggest that MOR resolved two δ_{cx} sites: a site where MOR is a potent noncompetitive inhibitor (δ_{cx}-1) and a site where MOR is a weaker competitive inhibitor (δ_{cx}-2). [pCl]DPDPE had high affinity for the δ_{cx}-2 site, suggesting a similarity to the δ_{ncx} sites for which it also has high affinity (Ki < 1 nM) (see Xu *et al.,* this meeting). Studies in progress address the hypothesis that the δ_{cx} receptor and the δ_2 receptor are synonymous and also explore the relationship between the δ_{cx}-2 site and the δ_{ncx} binding sites. Viewed collectively with other data, these experiments provide further evidence for heterogeneity of the δ receptor.

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RESOLUTION OF KAPPA$_{2a}$ OPIOID RECEPTOR SUBTYPES IN RAT BRAIN USING [^{125}I]IOXY

Q. Ni, H. Xu, J. S. Partilla, B. R. de Costa, K. C. Rice, and R. B. Rothman

Using guinea pig, rat and human brain membranes depleted of μ and ð receptors by pretreatment with the site directed acylating agents BIT and FIT, previous work demonstrated two subtypes of the kappa$_2$ binding site, termed kappa$_{2a}$ and kappa$_{2b}$. In the present study, we tested the hypothesis that there exist subtypes of the kappa$_{2a}$ binding site. Kappa$_{2a}$ binding sites were selectively labeled with the antagonist ligand, [^{125}I]IOXY, which has high affinity for kappa$_2$ sites. DAMGO (100 nM) was used to suppress binding to the kappa$_{2b}$ site, Binding surface analysis readily resolved two kappa$_{2a}$ binding sites in the absence or presence of 50 μM GppNHp (see below). Dynorphin A (Ki=111 nM) and a-neoendorphin (Ki=542 nM) had moderate affinity and high selectivity for the kappa$_{2a-1}$ binding site. Although additional studies are needed, the data suggest that the two binding sites are distinct sites, rather than two states of a single receptor.

	0 μM GppNHp		50 μM GppNHp	
Parameter	Site 1 κ2a-1	Site 2 κ2a-2	Site 1 κ2a-1	Site 2 κ2a-2
Bmax (fmol/mg protein)	31.4±2.2	117±24	159±12	8.6±1.4
IOXY (Kd, nM)	0.48±0.05	4.77±1.19	1.59±0.13	0.18±0.03
alpha-Neoendorphin (Ki, nM)	542±62	35517±16343	487±39	9095±2870
Dynorphin A (Ki, nM)	111±13	22923±12900	110±10*	17246±5518
CI977 (Ki, nM)	1412±179	1326±320	1877±153	1904±371

Viewed collectively, these data provide additional evidence for kappa receptor heterogeneity.

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STUDY OF DYNORPHIN A (1-17) *IN VIVO* PROCESSING IN RAT BRAIN BY MICRODIALYSIS AND MATRIX-ASSISTED LASER DESORPTION MASS SPECTROMETRY

J. Z. Chou, I. M. Maisonneuve, B. T. Chait, and M. J. Kreek

Recent progress in neuroscience suggests that endogenous dynorphin peptides may play a role in drug addiction. It is essential to study the metabolism of dynorphin in the brain by determining the presence of different peptide fragments, in order to assess their possible opioid and other activities. We are presenting the first studies of the processing of exogenously administered Dyn A (1-17) in brain regions of freely moving rats.

The mass spectrometric analysis of the dynorphin peptides was carried out using matrix-assisted laser desorption at a laser wavelength of 355 nm with α-cyano-4-hydroxycinnamic acid as the matrix. The matrix was dissolved to a concentration of 5g/L in a mixture of 33% acetonitrile and 67% of 0.1% trifluroacetic acid aqueous solution.

The *in vivo* processing study of Dyn A (1-17) in brain regions of freely moving rats was carried out in striatum and cerebellum. A thin plastic tube (0.67 mm, 0.) was positioned in close proximity to a microdialysis probe, such that both were located in a brain region of interest. Dynorphin A (10 mM) was delivered (0.1 µl/min) through the plastic tube and the processed products were collected from the microdialysis probe through the constant infusion (1µl/min) of artificial CSF (146 mM Na^+, 2.7 mMK^+, 155 mM Cl^+, 1.2 mM Ca^{2+}, and 1.0 mM Mg^{2+}). The infusion of Dyn A (1-17) was terminated after 60 mm of delivery, while the collection of dialysate was continued for another 2 hours. A constant amount of substance P was added to the dialysate as an internal standard.

The dialysates, obtained at different time points, are analyzed directly by matrix-assisted laser desorption mass spectrometry without further purification/separation steps. Many processed products (more than 15) were readily identified from the observed nominal masses. The amounts of major processed products, such as DynA (2-17), DynA (3-17), DynA (1-6) DynA (7-17), DynA (8-17) and DynA (9-17) as well as the precursor peptide DynA (1-17), as a function of time in the living rat striatum and cerebellum are analyzed. Similar time profiles were observed for other processed products within a given rat brain region. The data from a preliminary studies of 2 rats shows that more time was needed to process the dynorphin peptide in cerebellum than in striatum. This finding is in concert with the expected higher abundance of enzymes, which are believed to be more specific for dynorphin processing, in striatum than there are in cerebellum.

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QUANTITATIVE ANALYSIS OF L-a-ACETYLMETHADOL (LAAM), L-a-NORACETYLMETHADOL (NORLAAM) AND L-a-DINORACETYLMETHADOL (DINORLAAM) IN RAT PLASMA BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY

B. F. Thomas, A. R. Jeffcoat, J. M. Mathews, M. M. Myers, and C. E. Cook

The long-acting synthetic narcotic 1-a-acetylmethadol (LAAM) is believed to possess several advantages over methadone as a treatment drug for heroin addiction. LAAM taken orally three times weekly establishes more stable plasma concentrations than daily treatment with methadone (Judson and Goldstein 1982). The metabolism of LAAM to norLAAM and dinorLAAM is of particular importance in determining its pharmacological profile because these two metabolites are formed rapidly, are more potent (Bertalmio *et al.,* 1992), and appear to persist for a longer duration of time than LAAM. This report describes the validation and application of a solid-phase extraction method combined with an ammonia/methane chemical-ionization GC/MS assay for the quantitation of LAAM, norLAAM and dinorLAAM in small volumes (0.1 mL) of plasma. Plasma samples are extracted on C-18 solid-phase extraction columns and analyzed with deuterated LAAM. norLAAM, and dinorLAAM serving as internal standards. After derivatization with trifluoroacetic anhydride, the samples are redissolved in 15 mL of toluene for analysis by GC/MS. The gas chromatography was performed on a J&W Scientific DB-1701 capillary column (length 30 m, I.D. 0.25 mm). The selected-ion monitoring (SIM) methodology is essentially that described by Foltz (1989). Chemical-ionization (5% ammonia in methane) is used to-generate intense M+l (protonated) and M+18 (ammonia adduct) ions of LAAM and its N-demethylated metabolites, respectively. Monitoring occurs initially for LAAM, and after elution, changes to monitoring for dinorLAAM and norLAAM simultaneously. Deuterated LAAM, norLAAM, and dinorLAAM are monitored concomitantly with their respective analytes. The calibration curves obtained for each analyte covered a wide dynamic range from approximately 0.1 to 2000.0 ng/g plasma with good linearity (r^2 > 0.95). Analysis of plasma samples that were obtained from male and female rats on days 0, 3, 7, 14, 21, 25, and 28 of chronic daily LAAM treatment (Savage) confirmed that LAAM is rapidly metabolized to norLAAM and dinorLAAM in the rat. The data also suggested that pharmacokinetic tolerance develops after chronic LAAM administration and that female rats, as compared with male rats, tend to have higher plasma levels of LAAM and its N-demethylated metabolites. The levels of all three analytes increased dramatically after ketamine/xylazine anesthesia and jugular cannulation (day 31). The high levels on day 31 may be an artifact caused the presence of the indwelling cannula. However, other possibilities include: 1) that ketamine/xylazine treatment increases the absorption of LAAM from the gastrointestinal tract as reported with oral administration of phenytoin and intraperitoneal ketamine (Sechi *et al.,* 1992) and 2) that microsomal enzymes are being inhibited by ketamine/xylazine. This observation is disturbing in that ketamine/xylazine use is prevalent in laboratory procedures and cannulated animals are frequently used for obtaining pharmacokinetic data. Thus, the effect of ketamine/xylazine treatment on the pharmacokinetics of LAAM requires further clarification.

REFERENCES: Furnished at request of Senior Author.

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BLOCKING OF MORPHINE INDUCED ORAL STEREOTYPY BY THE NMDA RECEPTOR ANTAGONIST MK-801

R. T. Livezey, L. B. Pearce, and C. Kornetsky

Previously we have demonstrated that repeated high doses of morphine sulphate (MS) administered to a rat causes marked repetitive biting behavior that can later be re-expressed by a low dose of MS (4 mg/kg). Both the initial stereotypy and the re-expressed stereotypy can be blocked with a D_1 dopamine antagonist. The experiment by Hurley *et al.,* (this meeting) suggests that glutamate may be involved and if so, the NMDA receptor antagonist MK-801 should block the stereotypy. In order to test this hypothesis male F-344 rats were given, at 12 hour intervals, four 10 mg/kg MS doses (sc). The stereotypy expressed by this dosing regimen was blocked by MK-801 at both one and two weeks following the initial treatment. This experiment supports the hypothesis that the behavioral activating effect of MS may be due to modulation of the glutaminergic influences on dopaminergic transmission.

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OPIOID MODULATION OF NMDA-EVOKED RELEASE OF 3HT DOPAMINE FROM STRIATUM

L. B. Pearce, L. Hurley, and C. Kornetsky

Daily administration of opioids has been shown to have both behavioral stimulatory and inhibitory actions. The stimulatory actions include increased locomotion and stereotypy. Behavioral stimulation has also been observed following acute administration of opioids. These motor stimulant properties of opioids are thought to be due to activation of mesolimbic, mesocortical or nigrostriatal dopaminergic pathways. However, the mechanism of this activation remains unclear. Accordingly, the mechanism by which opioids modulate dopaminergic neurotransmission in rat striatum was investigated. Rat striatal slices (0.4 mm) and synaptosomes were pre-incubated with [^{3}H] dopamine and, under conditions of continuous superfusion in Krebs buffer, pH 7.4, the effects of drugs on the magnitude and kinetics of release were determined. Morphine (100 μM) inhibited potassium-stimulated release of [^{3}H] dopamine from both striatal slices and synaptosomes. The kinetics of potassium-stimulated (20 mM) release from slices was unaffected by 100 μM morphine. In contrast, morphine (0.1, 1.0, 10, 100, and 500 μM) produced dose-dependent changes in both the magnitude and the kinetics of [^{3}H] dopamine release stimulated by 100 μM N-methyl-D-aspartate (NMDA). The results of control experiments demonstrated that 100 μM morphine did not have a significant direct effect on basal radiolabel efflux from slices. Pie-incubation of slices for 20 minutes at 37°C in the presence of 1.0 μM of calphostin C, a protein kinase C inhibitor, partially antagonized the effect of 100 μM morphine on both the magnitude ($p<0.01$) and kinetics ($p<0.001$) of [^{3}H] dopamine stimulated by 100 μM NMDA. These data indicate that NMDA receptor-mediated stimulation of dopamine release from striatum is potentiated by morphine via a mechanism involving protein phosphorylation by protein kinase C. These studies further suggest that the behavioral activating effects of morphine may be due to the modulation of glutamatergic influences on dopaminergic neurotransmission in striatum.

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BLOCKAGE OF THE BEHAVIORAL AND NEUROCHEMICAL EFFECTS OF HYDROCODONE BY QUININE ADMINISTRATION

B. Gomez-Mancilla, S. Cheung, S. V. Otton, E. M. Sellers

Several opiates of abuse are converted by cytochrome P450 2D6 (CYP2D6) to metabolites of much greater pharmacological potency than the parent compound e.g. hydrocodone to hydromorphone, codeine to morphine (Dayer 1988). The activity of human CYP2D6 is genetically variable (absent in about 7% of Caucasian), and can be inhibited by several compounds e.g. quinine, quinidine (Gonzalez 1991). Using Sprague-Dawley rats, we compared the behavioral (locomotor activity) and neurochemical effects (dopamine release in the n. accumbens) produced by hydrocodone given alone and in combination with quinine. The administration of hydrocodone at 0.01, 0.1, 1 mg/kg s.c., produced a dose-related increase in locomotor activity, the highest increase was observed at 1 mg/kg. The administration of hydrocodone at 1 mg/kg s.c., produced an increase in dopamine release of 38.8% (SEM 8.8%). These effects were reduced by quinine at 40 mg/kg ip. (given 1 hr. before hydrocodone), the locomotor activity was reduced 70%, and the release of dopamine was reduced at 11% (SEM 4.9%) in the n. accumbens when compared with the administration of hydrocodone given alone. Those results suggested that CYP2D6 activity may be an important determinant in the opiate abuse liability.

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PHENCYCLIDINE (PCP) PHARMACOKINETICS IN THE PRESENCE OF ANTI-PCP MONOCLONAL FAB FRAGMENTS

J. L. Valentine and S. M. Owens

Successful treatment strategies to reverse PCP toxicities are presently unavailable. As a consequence, supportive care is the mainstay of overdose management. Drug-specific high affinity antibodies are used clinically to treat digoxin overdoses. A similar immunotherapeutic approach is being studied to reverse PCP-induced toxicity.

High affinity (Kd=1.8 nM) anti-PCP monoclonal Fab fragments were purified from papain digested anti-PCP IgG produced in mouse ascites. For the pharmacokinetic studies, the right femoral and right jugular veins were cannulated in male SD rats for drug administration and blood sampling, respectively. Control animals (n=5) received an intravenous bolus dose of 1 mg/kg PCP, along with a tracer dose of [^{3}H]PCP. Fab-treated rats (n=5) also received this initial PCP regimen, followed two hours later by an equimolar dose of anti-PCP Fab (about 50 mg). Serum and urine were analyzed for total radioactivity by liquid scintillation spectrometry (LSC). Unchanged [^{3}H]PCP concentrations were determined by LSC following hexane extraction from serum and urine.

Within 5 minutes after the Fab administration, serum [^{3}H]PCP concentrations increased approximately dramatically. Volume of distribution (Vd) and systemic clearance (Cls) decreased to 14% and 10% of control values, respectively. Because both Vd and Cls decreased to a similar degree, half-life ($t_{1/2}$) did not change *(i.e.,* $t_{1/2}$ = 0.7 x Vd/Cls). While renal clearance decreased to 34% of control, a significant increase in amount of [^{3}H]PCP was found in the urine. These dramatic changes in PCP pharmacokinetics after anti-PCP Fab administration suggest anti-PCP Fab fragments could reverse PCP toxicities in overdose situations.

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SEX IS A MAJOR DETERMINANT OF PHENCYCLIDINE (PCP) METABOLISM AND METABOLITE COVALENT BINDING IN RATS

S. M. Owens, M. G. Gunnell, and S. L. Sorrels

The purpose of these studies was to determine the role of sex in PCP metabolism and covalent binding to liver microsomal proteins. Microsomal enzymes were prepared from male and female Sprague-Dawley, Fischer 344 and Dark Agouti rats by standard techniques. Unlabeled PCP (100 M) and [^{3}H]PCP (as a tracer) were incubated with microsomal enzymes in a complete NADPH regenerating system (or without the addition of $NADP^+$ for controls). Aliquots were removed for determination of PCP metabolite covalent binding by TCA precipitation or for determination of metabolite concentrations by C_{18} HPLC. The mean (SD) covalent binding for male Fischer 344, Sprague-Dawley and Dark Agouti rats were 0.078 (0.0074), 0.051 (±0.0060) and 0.054 (±0.0084) PCP nmol-eq./mg/min, respectively, with the Fischer 344 rats showing a statistically significantly greater amount of covalent binding of PCP metabolites. By comparison, the female rats of all strains showed essentially no covalently bound PCP metabolites (<5% of male values). PCP metabolite formation also showed significant sex-related differences, with the female rats showing lower amounts of metabolite formation.

Pharmacokinetics studies of PCP in the same three strains of rats did not show these sex-related differences. In these studies, animals were chronically treated with PCP for three days and steady state PCP pharmacokinetics were determined. Only the male Dark Agouti rats showed significantly different value for systemic clearance at steady state.

These data suggest sex-related differences in rats are a major determinant of PCP metabolism and the formation of irreversibly bound PCP metabolite adducts. Although whole body clearance of PCP is not affected in the same sex related manner, these large differences in PCP metabolism suggest potential adverse and sex-specific sensitivities to this drug.

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STRAIN DIFFERENCES IN MOTOR ACTIVITY RESPONSE TO PHENCYCLIDINE (PCP) IN MICE: RELATIONSHIP TO PCP RECEPTOR BINDING AND PHARMACOKINETICS

S. R. Shelnutt, S. M. Owens, W. C. Hardwick, S. E. Rodgers, and D. E. McMillan

DBA, C57/BL (C57) and a cross strain 2NB6D2Fl (BDF) mice were given i.p. doses of PCP (1-56 mg/kg) or MK801 (0.1-17 mg/kg) and placed on an Automex activity monitor (n = 4-6). Activity was recorded in 10 min intervals for 60 min. All of the dose-response curves had an "inverted U" shape, indicating that motor activity increased after low doses and decreased after higher doses (PCP max effect was at about 10 mg/kg). The DBA strain showed significantly greater increases in motor activity after PCP or MK801 than the other two strains.

To investigate the underlying mechanism(s) for these differences, [^{3}H]TCP receptor binding studies and two PCP pharmacokinetic studies were performed. The receptor binding studies revealed no differences in B_{max}, and K_d values between strains. In the first pharmacokinetic experiment, the three strains were dosed with 10 mg/kg PCP i.p. and a single blood level was obtained at the time of maximal effect. The average serum concentration of PCP in the DBA strain (1035 ng/ml) was significantly greater (ANOVA, followed by Newman-Keuls' test, $p<.05$) than the BDF strain (640 ng/ml) and the C57 strains (600 ng/ml). In the second experiment, mice were infused with PCP (18 mg/kg/day) to steady-state using subcutaneous osmotic minipumps. Average plasma concentrations at steady-state (Css) were 167 ng/ml (DBA), 99 ng/ml (BDF), and 139 ng/ml (C57). All strains were significantly different from each other ($p<.05$).

These data suggest that differences in motor activity response to PCP in these strains of mice could be due to underlying differences in PCP pharmacokinetics, since increased motor activity correlated with increased PCP concentrations. However, the large differences in pharmacokinetics between the DBA strain and the other two strains may not entirely explain the large difference in response of the DBA strain, as there is no apparent "shift to the right" in the dose-response curves of the C57 and BDF strains compared to the DBA strain.

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INHERENT DIFFERENCES IN BRAIN REGIONAL CONTENT OF DOPAMINE AND SEROTONIN IN TWO INBRED MOUSE STRAINS WHICH ARE DIFFERENTIALLY RESPONSIVE TO PHENCYCLIDINE (PCP)

A. L. Jewell, J. M. Carney, and L. P. Dwoskin

Two inbred mouse strains (C57BL/6ByJ and DBA/2J) have been identified which exhibit a robust difference in PCP-induced locomotor activity (Carney *et al.,* 1992). This strain-related difference in PCP-induced behavior was correlated positively with *in vitro* PCP-induced endogenous dopamine (DA) release from slices of striatum, frontal cortex and nucleus accumbens, but not olfactory tubercle (Dwoskin and Carney 1992). In both behavioral and neurochemical assays, the DBA/2J strain exhibited a greater responsiveness to PCP compared to the C57BL/6ByJ strain. Therefore. to examine if an intrinsic difference in brain DA content is correlated with PCP-induced responsiveness, regional content of DA and metabolites (dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)) were determined. Additionally, serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) regional content were examined to determine the specificity of observed strain differences. Frozen (-70°C) tissues were sonicated and centrifuged at 30,000 x g for 10 min at 4°C, supernatant filtered, and 50 µl injected onto the HPLC-EC. The HFLC-EC system consisted of a Beckman Model 116 pump and model 504 autosampler, ESA 3 micron (4.6 x 75 mm) ODS ultrasphere reverse phase column, and 5100 A electrochemical detector with a model 5011 analytical cell (E1 and E2; +0.05 and +0.32 V, respectively). The eluent was 0.03 M citric acid/0.05 M sodium phosphate containing 0.1 mM EDTA, 150 mg/L l-octane-sulfonic acid and 15-25% methanol. Dihydroxybenzylamine was used as an internal standard. Analysis revealed that DA content was greater in the olfactory tubercle from the DBA/2J strain compared to the C57BL/6ByJ strain. DOPAC and HVA content were also greater in the nucleus accumbens from the DBA/2J strain. No strain-related differences were observed for 5-HT content. However, 5-HIAA content in the nucleus accumbens was greater in the DBA/2J strain. Therefore, inherent strain differences in regional content of DA and its metabolites in nucleus accumbens were positively correlated with strain-related differences in PCP responsiveness. In contrast, in striatum, frontal cortex and olfactory tubercle, DA regional content and *in vivo* and *in vitro* PCP-induced responsiveness were not correlated.

References available from Senior Author.

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NORNICOTINE-INDUCED DOPAMINE (DA) RELEASE FROM RAT STRIATAL SLICES IS CONCENTRATION-DEPENDENT, CALCIUM-DEPENDENT AND STEREOSELECTIVE

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

INTRODUCTION:

Relatively little is known about the pharmacology of nicotine metabolite, nornicotine, in contrast to the wealth of information on the effects of nicotine. Both enantiomers of nornicotine appear to have qualitatively similar inhibition of high affinity binding of [^{3}H]S(-)nicotine to rat membranes (Reavill *et al.,* 1988; Copeland *et al.,* 1991) and behavioral activity (Risner *et al.,* 1985, 1988). The current studies characterize the effect of nornicotine on dopamine (DA) release from superfused rat striatal slices.

METHODS:

Male Sprague-Dawley rat striatal slices (500 μm) were incubated in Krebs' buffer at 34°C for 1 hr. Slices were transferred to chambers and supcrfused (1 ml/min) with Krebs' buffer. For low Ca^{++} experiments, $CaCl_2$ was omitted and 0.5 mM EGTA was added. After 60 min of superfusion, two 1-min samples were collected to determine basal outflow of endogenous DA and dihydroxyphenylacetic acid (DOPAC). S(-)nor-nicotine was added to the buffer after second sample and 15 1-min samples were collected. After the experiment, slices were weighed and overflow during each minute normalized for slice wt. The concentration of DA and DOPAC in superfusate were determined by a previously published method (Gerhardt *et al.,* 1989) using HPLC-EC.

RESULTS AND DISCUSSION:

S(-)Nornicotine (0.1 – 100 μM) evoked a concentration-dependent increase in superfusate DOPAC. DA was not detected. Low concentrations (1, 10 and 100 μM) produced a 2.1, 7.4 and 55-fold, respectively, increase in DOPAC overflow. Even at high concentrations (100 μM), a maximal effect was not observed. The time course of the effect of S(-)nornicotine revealed an immediate increase in response a plateau after 10 min of exposure, and no tachyphylaxis. Superfusion with a low-Ca^{++} buffer completely inhibited the S(-)nornicotine-induced increase in DOPAC overflow. Comparing equimolar concentrations of nornicotine, the S(-)isomer produced a greater increase DA release than did the R(+)isomer. Therefore, the concentration-dependency, calcium-dependency and stereoselectivity indicate that nornicotine may be activating a nicotinic receptor site. In conclusion, nornicotine possesses significant pharmacologic activity within the nigrostriatal dopaminergic system.

References available from senior author.

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CORRELATION BETWEEN EXTRACELLULAR FREE COCAINE CONCENTRATIONS AND DOPAMINE LEVELS INDUCED BY A "BINGEING" COCAINE CHALLENGE: AN *IN VIVO* MICRODIALYSIS STUDY

I. M. Maisonneuve, A. D. Saravia, and M. J. Kreek

Extending our investigations of the neurochemical effects of a cocaine "binge" administration paradigm that approximates the temporal pattern in which cocaine is used by humans, we determined, in rats, the extracellular concentrations of cocaine and assessed whether these levels correlate with the dopaminergic changes that they induced. Cocaine (10 or 15 mg/kg, i.p.) was administered three or five times at one hour intervals. Extracellular cocaine and dopamine (DA) levels were measured in the striatum using an *in vivo* microdialysis technique in freely moving rats. DA levels were also measured in the nucleus accumbens.

In the three regimens of cocaine injections studied, the total levels of cocaine in striatal dialysates increased with each injection (3 or 5) and in a dose dependent manner. The half-life of cocaine in the rat striatum was 28.6 ± 2.2 min (n=14). In the nucleus accumbens and striatum, cocaine produced an immediate increase in extracellular DA levels associated with a decrease in DA metabolites levels. In the nucleus accumbens, acute "binge" administration of cocaine, (10 or 15 mg/kg per injection) resulted in an increase in extracellular DA levels that plateaued immediately, or after the second injection. This plateau effect persisted even after increasing the dose or number of injections. In the striatum, a similar plateau was found in the 3 x 10 mg/kg series. Increasing the dose or the number of injections led to a slight increase of striatal DA levels. In all series, the absolute levels of cocaine and DA diverged with repeated injections (analysis of variance with two repeated measures: molecule x time, $p<0.05$, n=5 for the 3 x 10 mg/kg series; $p<0.018$, n=4 for the 3 x 15 mg/kg series; $p<0.023$, n=5 for 5 x 10 mg/kg series).

These results suggest the development of a rapid decrease in DA responsivity to cocaine in the nucleus accumbens and in the striatum. They are in concordance with the earlier findings of acute tolerance to cardiovascular and subjective effects of cocaine (Fischman *et al.,* 1985) and match what cocaine users, interviewed in our clinical research setting, have described: repeated cocaine administrations often do not reproduce the magnitude of the initial euphoric effect.

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ACKNOWLEDGEMENTS:

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CHRONIC COCAINE AND ITS WITHDRAWAL ALTER [^{3}H]PAROXETINE BINDING IN RAT BRAIN

L. G. Sharpe, E. Ambrosio, W. M. Mitchell, and N. S. Pilotte

We previously showed that withdrawal from cocaine down-regulates the dopamine transporter in the nucleus accumbens, an area also innervated by serotonin (5-HT). As cocaine also inhibits 5-HT uptake, we infused male Lewis rats IV with cocaine or saline for 10 days and measured [^{3}H]paroxetine binding (with or without citalopram) to 5-HT uptake sites immediately (0 Days) or 10 days after the last infusion session. [^{3}H]Paroxetine binding was significantly decreased at 0 days but recovered by 10 days in the nucleus accumbens (53%), olfactory tubercles (47%), and piriform cortex (37%). Binding was significantly increased only at 10 days of cocaine withdrawal in the medial prefrontal cortex (47%). linear nucleus raphe (50%) and the entorhinal cortex (23%). The ventral tegmental area showed significant up-regulation in the 5-HT transporter at 0 days (46%) which persisted up to 10 days (24%) of cocaine withdrawal. There were no changes in 31 other sites measured for [^{3}H]paroxetine binding. It appears that cocaine and its withdrawal can have separate and opposite effects on the 5HT and dopamine transporter.

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CHRONIC COCAINE ENHANCES [^{125}I] RTI-55-LABELED DOPAMINE UPTAKE SITES IN THE STRIATUM

P. Sheng, C. M. Dersch, B. Emilien, R. B. Rothman, and J. L. Cadet

Repeated administration of cocaine results in behavioral sensitization in rodents. The development of some of these behavioral phenomena have been attributed to changes in the mesolimbic dopamine system. It is known that cocaine inhibits the reuptake of dopamine, serotonin, and norepinephrine. Cocaine has high-affinity binding sites in all mammalian species including rodent, nonhuman primate and human brain. These binding sites show several properties that are associated with biologically relevant receptors, but the results of biochemical studies focusing on the determination of the effects of chronic administration of cocaine have not been consistent. These differences might be due to the possibility that the ligands used in these binding studies may interact at sites that are different from where cocaine has its main actions. In order to deal with some of these issues. a number of cocaine analogs were synthesized, labeled and are now being used in binding studies. A recent addition-to this list of ligands is [^{125}I] RTI55 which binds to the striatal DA uptake sites. We thus sought to determine if chronic treatment with cocaine induces changes in [^{125}I] RTI55-labeled striatal DA uptake sites. Male Sprague-Dawley rats weighing 200-250g were given injections of cocaine (ip, bid) twice a day. Group 1: equivalent volume of saline, Group 2: 2.5 mg/kg cocaine HCL, Group 3: 7.5 mg/kg cocaine HCL, Group 4: 15 mg/kg cocaine HCL. All injections were for 2 weeks. The rats were sacrificed 24 hours after the last injection. Their brains were removed quickly and the caudate regions were dissected and stored at -70° C until the Bmax and Kd for DA uptake sites were determined using [^{125}I] RTI55. All ligand binding experiments were conducted in assay tubes containing 1 ml buffer (55.2 mM sodium phosphate pH 7.4) at 4° C, each assay tube contained 50,000 cpm [^{125}I] RTI55 and 750 µl of tissue. GBR 12909 (10 µM) was added in order to determine nonspecific binding. The following table shows the effects of cocaine on [^{125}I] RTI55 binding in the caudate putamen.

Groups	B_{max} (fmol/mg protein)	K_d (nM)	r2
Group 1	6541±165	1.08±0.02	0.99
Group 2	6972±19.3	1.19±0.02*	0.99
Group 3	8489±152*	1.20±0.017*	0.99
Group 4	7740±329*	1.41±0.006*	0.98

Each value is ±SD. *P < 0.05

These data show that chronic cocaine administration produces dose-dependent increases in both the K_d and the B_{max} of the RTI-55 binding site on the dopamine transporter in caudate membranes. The different results observed by different labs may depend of which radioligand is used to label the DA transporter. One speculative possibility is that cocaine may be interacting at a number of sites on the DA transporter, some of which are upregulated while other sites might not be. These results point to the importance of developing ligands that are specific to binding subsites on the DA transporter.

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QUANTITATIVE AUTORADIOGRAPHIC EVALUATION OF THE EFFECT OF 6-OH-DOPAMINE LESIONS ON BINDING SITE LABELED WITH THE COCAINE ANALOG [^{125}I] RTI-55

S. Ordinez, J. L. Cadet, C. M. Dersch, A. Brockington, K. M. Becketts, J. S. Partilla, B. R. de Costa, K. C. Rice, F. I. Carroll, H. C. Akunne, and R. B. Rothman

Cocaine is thought to produce its reinforcing properties through the potentiation of the DA on postsynaptic DA receptors at the levels of the caudate-putamen (CPu), the nucleus accumbens (NAc), or of the cortex. This occurs through the blockade of DA uptake sites. Although a number of studies have been done to characterize the specific effects of cocaine on the brain, these studies have used ligands which bind at more than the DA uptake sites. Thus, a substantial effort has been underway to develop a ligand which has high affinity and selectivity for DA uptake sites. As a first step towards developing these ligands, a number of cocaine analogs have been synthesized and have been used in homogenate binding studies. One if these ligands is [^{125}I] RTI-55. Dersch *et al.* (this volume) has determined that this ligand binds to DA and 5-HT transporters in the caudate-putamen. It was important to determine the anatomical distribution of these sites in the rat central nervous system in order to determine the specific loci of action of these cocaine analogs. In addition, we evaluated the effects of 6-OHDA lesions on these sites in the nigrostriatal DAergic pathway. Male Sprague-Dawley rats weighing 220-250 g were used. Unilateral lesions of the nigrostriatal DAergic pathway were performed by the stereotaxic application of 6-OHDA in the CPu. The animals were sacrificed about two weeks after the 6-OHDA lesions. Sections were taken at the levels of the NAc, CPu, and the substantia nigra pars compacta (SNpc). The sections were labeled with [^{125}I] RTI-55 according to the following protocol. Autoradiographic distribution of total [^{125}I] RTI-55 binding (no blocking agents) showed high binding densities in the NAc, the olfactory tubercle, the CPu, and in the SNpc. Binding showed a laminar distribution in the cortex. 6-OHDA caused marked decreases in [^{125}I] RTI-55 binding sites in the NAc and the CPu. The sections incubated in the presence of paroxetine, which blocks binding to 5-HT uptake sites, caused a total disappearance of binding in the cortex. There were marked decreases in paroxetine-insensitive [^{125}I] RTI-55 binding sites in the CPu and in the SNpc on the side of 6-OHDA lesions. The NAc still had some DA uptake sites remaining. The ventral tegmental area was spared in these animals due to the fact that 6-OHDA was injected within the striatum. Sections labeled with [^{125}I] RTI-55 in the presence of LR1111, which blocks binding of the ligand to DA uptake sites, showed marked decreases in [^{125}I] RTI55 binding in the CPu. Them was substantial binding left in the olfactory tubercle. The laminar pattern of the distribution [^{125}I] RTI-55 in the cortex was still apparent even in the presence of LR1111. There were no differences between the two sides of the brains of animals that had gotten 6-OHDA lesions. These results provide additional evidence that [^{125}I] RTI-55 binds to both striatal DA and 5-HT transporters. In the cortex, the binding is mostly serotonergic. In the presence of paroxetine, [^{125}I] RTI-55 is a good ligand for labeling the DA uptake site in the striatum.

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COCAINE AND SIGMA LIGANDS INHIBIT DOPAMINE UPTAKE VIA A COMMON SITE IN RAT CAUDATE-PUTAMEN

A. H. Newman, J. L. Katz, and S. Izenwasser

Recent studies have implicated compounds that selectively bind to sigma receptors as potential therapeutic targets in the treatment of cocaine abuse. Sigma ligands including rimcazole, BMY 14802 and NPC16377 have been shown to block cocaine-induced locomotor stimulant activity in mice, at behaviorally inactive doses (Menkel, *et al.,* 1991. Witkin, *et al.,* 1993). Another selective sigma ligand, DuP 734, attenuates the locomotor stimulant as well as discriminative stimulus effects of cocaine in rats (Cook, et al, 1992). Biochemical studies using the photoaffinity label [^{125}I]iodoazidococaine demonstrated that this ligand binds to high and low affinity cocaine binding sites; however, when photoactivated, it derivatizes a 26 kD polypeptide that has the pharmacology of a sigma receptor (Kahoun and Ruoho, 1992). From these behavioral and biochemical studies, a relationship between sigma ligands and the cocaine recognition sites is apparent. Although it is unlikely that a high affinity binding site is shared, a common low affinity site that both cocaine and these sigma ligands recognize may be present and might play a role in the pharmacology of these two classes of drugs. In light of these studies, we were interested in determining whether sigma ligands recognize cocaine binding sites and furthermore whether a functional relationship exists between the binding of these ligands and their ability to block [^{3}H]dopamine uptake.

A series of structurally unrelated sigma ligands displaced [^{3}H]WIN 35,428 binding in a concentration-dependent manner in rat caudate-putamen. The order of potency was rimcazole > ifenprodil > (+)3PPP > carbetapentane > (-)-3PPP > NPC16377 > caramiphen > haloperidol > PRE-084. Affinities of most of these compounds were relatively low, but approached that of cocaine, and in some cases were higher than their reported affinities for binding to sigma receptors. The highest affinity was obtained with rimcazole (K_i=103 nM). In addition, these compounds inhibited dopamine uptake in a chopped tissue slice preparation of caudate-putamen. None of these sigma ligands have been reported to exhibit cocaine-like stimulation of locomotor activity, or discriminative stimulus effects. These results suggest that inhibition of dopamine uptake does not universally result in cocaine-like behavioral effects. Furthermore, the site at which these compounds exert their actions may be related to their ability to attenuate behavioral effects of cocaine and thus serve as a target for the development of cocaine abuse medical treatments.

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COMPARISON OF [^{3}H]WIN 35428 BINDING IN HUMAN COCAINE USERS AND A RAT NEUROCHEMICAL MODEL OF HIGH DOSE COCAINE EFFECTS

K. Y. Little, F. I. Carroll, C. Joyner, and E. Ellinwood

Chronic cocaine exposure may regulate the expression and function of the dopamine transporter (DAT), an important cocaine site of action. A complex animal literature exists addressing this issue. Three factors appear to explain differing experimental outcomes: 1) cumulative cocaine dose (higher doses appear more likely to lead to increased transporter binding and/or function); 2) interval since last cocaine exposure (induced increases tend to dissipate over days to weeks after the last cocaine exposure, and may even become subnormal with time); and 3) the radioligand used in binding studies (increased binding appears more likely with [^{3}H]cocaine or analogs than with structurally dissimilar radioligands).

Earlier work in this laboratory found that striatal [^{3}H]WIN 35420 binding was increased in human cocaine users (Little *et al.).* Although [^{3}H]WIN 35428 and [^{125}I]RTI-55 differ only in their 3ß *para*-phenyl substituent, preliminary studies have suggested that [^{125}I]RTI-55 binding is less effected by cocaine exposure (Little *et al.).* The present experiments were designed to model in the rat the neurochemical alterations found in human cocaine users. [^{125}I] RTI-55 and [^{3}H]WIN 35420 binding was compared in striatal specimens from rats treated with high doses of cocaine (40 mg/kg b.w./day) via osmotic minipumps for two weeks. DAT binding sites in the striatum were assessed employing *in vitro* quantitative autoradiography. Twelve rats received cocaine and twelve only saline vehicle. Half of each treatment group were then sacrificed at the end of the two week treatment period. The other half were sacrificed following a further one week withdrawal period.

Cocaine-treated animals displayed increased [^{3}H]WIN 35420 binding at both time points: 1.25±.18 nCi/mg vs .54±.09 nCi/mg ($p<.01$, no withdrawal) and 1.41±.23 vs .56±.06 ($p<.005$, one week withdrawal). However, [^{125}I]RTI-55 binding was not increased at either time point: 413±48 nCi/mg vs 437±70 nCi/mg (no withdrawal) and 341±48 vs 362±41 (one week withdrawal). Based on the present and previous results, it appears that human and rat DAT binding sites are fairly plastic, and sensitive to cocaine dosing regimes and radioligand structure. Adaptations induced by cocaine in the human DAT could contribute to bingeing, withdrawal depression, and/or craving.

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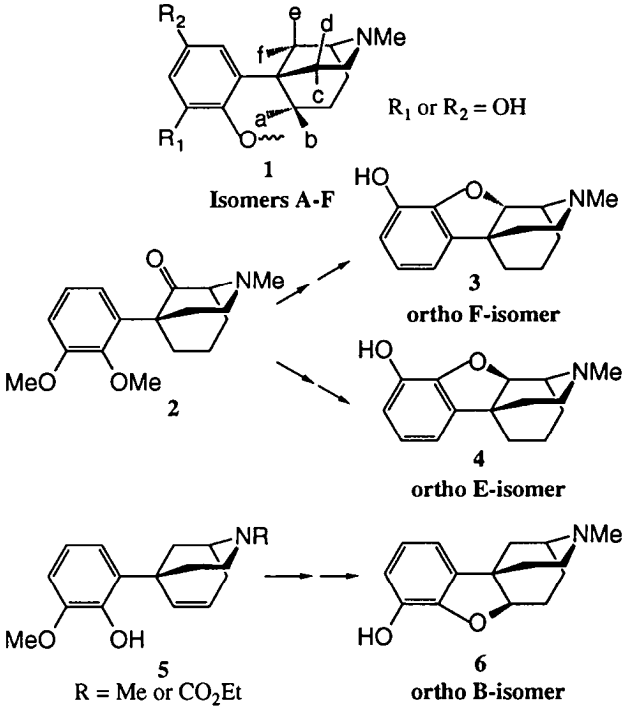
OXIDE-BRIDGED 5-(3-HYDROXYPHENYL)-2-METHYLMORPHANS AS PROBES FOR NARCOTIC RECEPTOR MEDIATED PHENOMENA

S. Kodato, J. T. M. Linders, K. Yamada, 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** (R_1 or R_2 = OH). 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 and convenient synthesis of **3** ("ortho F- isomer") from the intermediate **2** via stereoselective reduction of the carbonyl, stereoselective substitution to the chloride, O-demethylation, and base-mediated ring closure. Also, we report the the synthetic approach to **4** and **6** ("ortho E- and B-isomers") from the intermediate **2** and **5,** respectively.



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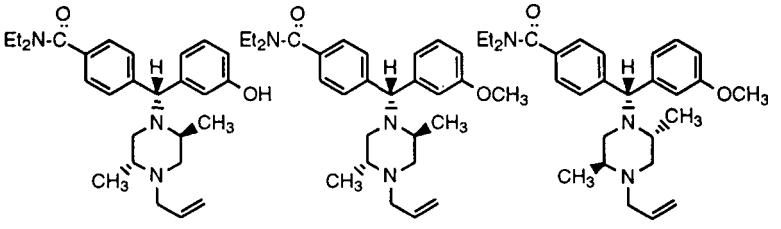
SYNTHESIS AND ABSOLUTE CONFIGURATION OF OPTICALLY PURE ENANTIOMERS OF (±)-BW373U86. DEVELOPMENT OF SNC80, A POTENT AND SELECTIVE NONPEPTIDIC δ-OPIOID RECEPTOR AGONIST

S. N. Calderon, C. George, H. Xu, X. Y. Cha, R. B. Rothman, K. D. Wild, E. J. Bilsky, F. Porreca, A. E. Jacobson, and K. C. Rice

The synthesis of potent non-peptide agonists and antagonists and affinity labels with high selectivity for δ opioid receptor subtypes would provide valuable research tools for gaining further insight into the structure and function of the δ opioid receptor system. A novel nonpeptidic δ-opioid receptor agonist, ((±)-BW373U86), was recently reported (Lee et al, 1992). This potent racemic compound was shown to have a high degree of selectivity for d opioid receptors in both *in vitro* receptor binding studies and in *ex vivo* functional assays.



(±)-BW373U86 SNC80 SNC83

Since it is well established that drug enantiomers can show distinctly different, and in some cases opposite, pharmacological effects (Ariëns 1986), we thought that it would be of interest to study the optically pure enantiomers of BW373U86. We have developed a practical synthesis of the enantiomers of (±)-BW373U86 and its diastereoisomer, which retains the *trans* dimethyl piperazine moiety, and have synthesized related compounds as well. Our synthetic approach involves assembly of the molecule from two components: a) the chiral N-allyl-*trans*-2,5-dimethyl-1,4-piperazine and b) the appropriate benzhydryl chloride. The absolute configuration of an intermediate was determined by single-crystal X-ray diffraction. We evaluated the affinity of these isomers and their immediate precursors for δ and μ receptors through displacement studies. Opioid activity was studied in isolated mouse-vas deferens (MVD) and guinea pig ileum (GPI). The phenolic enantiomers of BW373U86 and their benzylic epimers show high affinity for δ and μ receptors, but the methyl ethers of two of these compounds (SNC80 and SNC83) show about 2000-fold δ selectivity in binding assays. Displacement studies of the methyl ether isomers of BW373U86, immediate precursors in our synthetic route, revealed that methylation of the phenolic group virtually eliminates the affinity of these compounds for μ receptors. Our results in the MVD and in GPI suggest that SNC80 is a highly selective and potent nonpeptidic δ agonist which will be of value for further elucidation of δ1 receptor function. Additional work with SNC80 as a template is being carried out to provide highly selective affinity labels, imaging agents and other research tools.

REFERENCES: Available upon request.

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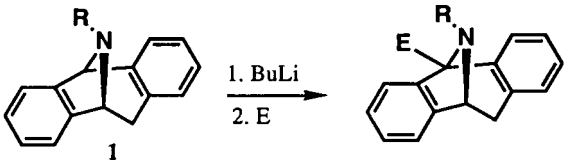
APPROACHES TO THE C5-LITHIATION OF 10,11-DIHYDRO-5H-DIBENZO[a,d]CYCLOHEPTEN-5,10-IMINE (DESMETHYL-MK-801)

T. H. Jones, K. C. Rice, and A. Thurkauf

The interesting pharmacological properties of certain C-5 substituted analogues of 10,11-dibenzo[a,d]cyclohepten-5,10-imine (desmethyl MK-801) prompted us to seek a more expedient route to these compounds. Previously, the t-butylformamidine group (1, R= -CH=N-t-butyl) has been used to protect the secondary amine function and stabilize the C-5 lithiated derivative prior to treatment with a suitable electrophile. A number of protecting groups have been reported for the elaboration of amines adjacent to nitrogen bv electrophilic addition to a metallated intermediate. Since the practicality of this transformation depends on the ease of protection and deprotection of the amine as much as the efficiency of the electrophilic addition, we have examined a series of protecting groups including carbamates, cyclic formamidines, and oxazolines.



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The most promising of these derivatives is N-(2-oxazolinyl)-desmethyl MK-801 (R= 2-oxazoline), since them is ample precedent for the metallation adjacent to nitrogen of the amine function of 2-aminooxazolines. To this end, we have developed practical methodology for the formation and removal of the oxazoline ring from the secondary amine function of desmethyl MK-801.

REFERENCES:

Available upon request.

AFFILIATIONS:

LMC, NIDDK, NIH, Bethesda, MD; Neurogen Inc., Branford CT.

SYNTHESIS AND EVALUATION OF THE FIRST CHIRAL "GBR" DERIVATIVES AS POTENT AND ENANTIOSELECTIVE INHIBITORS OF DOPAMINE REUPTAKE

D. Matecka, B. R. de Costa, R. B. Rothman, M. L. Silverthorn, L. Radesca, C. M. Dersch, K. M. Becketts, A. Pert, J. Glowa and K. C. Rice

The continuing status of cocaine as a major drug of abuse in the United States has prompted considerable investigation into its mode of action. Cocaine exhibits a variety of pharmacological effects on the central nervous system, the cardiovascular system, the sympathetic nervous system and nerve conduction. The addictive and reinforcing effects of cocaine are thought to be mediated through its inhibition of dopamine (DA) reuptake into dopaminergic nerve terminals. Other compounds including certain arylcyclohexylamines and the disubstituted piperazines such as GBR12935 (1-[(2-diphenylmethoxy)ethyl]-4-(3-phenylpropyl)piperazine and GBR12909 (l-{2-[bis(4-fluorophenyl)methoxy]ethy1}-4-(3-phenylpropyl)piperazine) are also potent and selective ligands at DA-uptake sites.

We are pursuing a systematic structure-activity study of compounds related to GBR12935 to probe its mode of action at DA-reuptake sites and also to identify clinically useful cocaine antagonists or substitutes. We synthesized and tested a series of symmetrically and asymmetrically disubstituted GBR analogs where the piperazine moiety was replaced by another diamine moiety. Several of the asymmetrically substituted derivatives were obtained in enantiomeric form and the absolute configuration was established by single crystal X-ray analysis. Most of these compounds displayed low-nanomolar affinity for sites labeled by [^{3}H]GBR12935 and also revealed a spectrum of activity and selectivity for inhibition of [^{3}H]DA uptake. Within the chiral GBR series of compounds 35-fold and 10-fold enantioselectivity ratios for binding to the DA transporter labeled by [^{125}I]RTI-55 and inhibition of [^{3}H]DA-reuptake, respectively, was observed. This is the first example of enantioselective binding with chiral "GBR" derivatives. This enantioselectivity offers support for the DA-reuptake inhibition as being a receptor mediated event. Several compounds, moreover, displayed significantly improved selectivities (vs. [^{3}H]5HT-reuptake) and ratios of IC_{50} for [^{3}H]DA reuptake inhibition to [^{3}H]GBR12935 displacement *(e.g.* 2.44 and 1.23) compared with GBR12935 (0.34). It would be of interest to examine the effects of these compounds on cocaine self-administration in primates.

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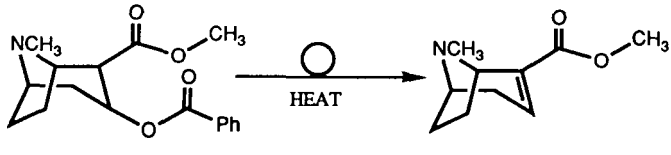
SYNTHESIS AND PHARMACOLOGICAL CHARACTERIZATION OF PYROLYSIS PRODUCTS OF COCAINE AND RELATED ANALOGS

A.C. Allen, J.M. Witkin, J.L. Katz, S. Izenwasser, and A.H. Newman

Anhydroecogonine methyl ester (AEME) has been determined to be the major pyrolysis product of cocaine and has been detected in high concentration in the urine of subjects who have smoked cocaine, "Crack". AEME, its ethyl analog (AEEE, the metabolic consequence of co-consumption of ethyl alcohol and smoking "crack") and the desmethyl analog (Nor-AEME, a cocaine processing artifact followed by thermal decomposition) were synthesized and evaluated in (1) radiolabeled ligand displacement assays using [^{3}H]WIN 35,428, (2) a locomotor-activity arena for mice, (3) a drug discrimination paradigm, where rats were trained to discriminate cocaine from saline, and (4) for overt toxicity. These studies have demonstrated that AEME and its prepared analogs do not appear to be cocaine-like and do not produce signs of toxicity characteristic of dopamine uptake inhibitors or cholinergic agonists. Thus, AEME probably does not contribute to the stimulant and subjective effects or the toxicity of "Crack".



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METHYLECGONIDINE, A COCAINE PYROLYSIS PRODUCT, IS A POTENT ANTICHOLINERGIC AGENT *IN VITRO* THAT MAY AGGRAVATE THE ADVERSE EFFECTS OF CRACK SMOKING

H. A. N. El-Fawal and R. W. Wood

Methylecgonidine (anhydroecgonine methylester, MEG) has been detected in the urine of crack smokers, but not when cocaine is taken by other routes. Pulmonary toxicity and a structure similar to cholinergic agonists led us to characterize the actions of MEG and cocaine on isolated guinea pig tracheal rings.

Cumulative response curves were established to acetylcholine (Ach: 10^{-10}- $2x10^{-3}$M), then MEG fumarate or cocaine HCl were put in the bath and Ach cumulative curves determined. Cocaine sensitized tracheal rings to Ach, increasing both its potency and efficacy; cocaine may thus aggravate bronchoconstriction.

MEG given before or after Ach, antagonized contraction noncompetitively. These effects occurred at a small fraction of the cocaine blood concentration associated with euphoria. Furthermore, Meg noncompetitively antagonized the sensitization produced by cocaine at 1:50 ratio, a pyrolyzate ratio encountered in crack smoking.

This nonequilibrium antagonism of acetylcholine could not be surmounted, and could not be reversed after prolonged washing of the rings. Methylecgonidine also produced non-equilibrium antagonism of histamine, which was also not reversible with prolonged washing. These surprising findings leads us to speculate that quatenary derivatives of methylecgonidine administered by inhalation may be useful in the management of asthma or cystic fibrosis.

If MEG displays anticholinergic activity *in vivo,* it could increase the abuse potential of cocaine base and aggravate the behavioral disruption and cardiovascular toxicity associated with crack smoking.

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MEMBRANE-RELATED CONFORMATIONAL CHANGES IN CANNABINOID SIDE-CHAINS AS STUDIED BY SMALL-ANGLE X-BAY DIFFRACTION

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In this study, small angle X-ray diffraction was used to study the topography of (-)-Δ^8-tetrahydrocannabinol (Δ^8-THC) and the conformation of its pentyl side-chain in different membrane preparations, which included synaptosomal plasma membrane as well as model membranes of hydrated phospholipids ranging from synthetic lipids (saturated and unsaturated) to extracted lipids from bovine sources. X-ray diffraction experiments provided us with an electron density profile for each membrane preparation in the trans-bilayer dimension. When a cannabinoid molecule is incorporated in the membrane, the electron density is increased in the region of cannabinoid presence. By comparing electron density profiles from the corresponding drug-containing and drug-free membranes, we have determined the location of the tricyclic ring system of Δ^8-THC in these different membranes. In addition, the cannabinoid molecule Δ^8-THC was labeled with an iodine at the S-position (5'-iodo-Δ^8-THC), which has an enhanced electron density at the terminal methyl group of the pentyl side chain. By comparing the electron density of a membrane containing the labeled Δ^8-THC with that of the same membrane containing the non-labeled Δ^8-THC, we detected the location of the iodine atom in the bilayer. Using both the location of the ring system and the location of the side-chain terminal, we have determined the topography of this cannabinoid in these membranes as well as the preferred conformations of the side chain in different lipid bilayer environments. Our results showed that the side-chain assumes an all-*trans* conformation and extends towards the hydrophobic center of the bilayer when the membrane is made from a saturated lipid and the bilayer is in the gel phase. However, when the membrane is from unsaturated lipids or brain synaptosomal preparations, the cannabinoid is located deeper in the bilayer and the side-chain does not any longer adopt the all-*trans* conformation but forms a more compact structure involving 2 to 3 *gauche* conformers. This new conformation can be related to the fact that the membrane is in the liquid crystalline phase. The results are also congruent with recent neutron diffraction experiments. This membrane-related conformational change in the cannabinoid side-chains may determine a preferential incorporation of the drug in certain membranes and their abilities to better interact with the cannabinoid receptor or its sub-types. These results may provide useful information towards an understanding of the preferred distribution of cannabinoids in different regions in the brain.

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SIGMA LIGANDS AFFECT MORPHOLOGY, DIVISION, AND VIABILITY OF C6 GLIOMA CELLS IN CULTURE

B. J. Vilner, B. R. de Costa, and W. D. Bowen

Several neuroleptics which are active at sigma receptors produced marked changes in the morphology and viability of C6 glioma cells in culture (Vilner and Bowen, Eur J Pharmacol 244:199-201, 1993). We have now extended these studies to additional neuroleptics as well as to other novel and prototypic sigma ligands. Over 90 compounds were routinely screened at a concentration of 100 uM by addition directly to culture medium. Sigma ligands caused withdrawal of processes, "rounding up", and cessation of cell division. Continued exposure to sigma compounds ultimately resulted in cell death. The potency of compounds to produce these effects generally correlated with binding affinity at sigma receptors labeled with [^{3}H](+)-pentazocine. Haloperidol, reduced haloperidol, fluphenazine, perphenazine, trifluperazine, BD737, LR172, BD1008, and SH344 produced significant effects in 3-6 hours of exposure. Other compounds, such as trifluperidol, thioridazine, and (-)-butaclamol, produced significant effects by 24 hours of exposure. Neuroleptics lacking potent sigma binding affinity (eg. (-)-sulperide and (+)-butaclamol) and other compounds which lack significant sigma affinity but which are agonists or antagonists at dopamine, serotonin, -adrenergic, ß-adrenergic, glutamate, GABA, PCP, opiate, or muscarinic cholinergic receptors were without effect at concentrations up to 300 uM over a period of 72 hours. lnterestingly, DTG, (+)-3-PPP, (+)-pentazocine, (+)-cyclazocine and other sigma-active benzomorphans and morphinans appeared *inactive* in up to 72 hours of culture. However, these compounds interacted synergistically with a sub-effective dose of BD737 (30 uM) to produce effects usually in 6 hours or less. Also, the pH of the incubation medium had a profound effect on the activity of sigma compounds. Normal pH was 7.2 - 7.4. Increasing the pH (> 7.6) shifted the dose curves for all sigma compounds to the left. Under these conditions, DTG. (+)-3-PPP and benzomorphans produced effects in 24 hours or less. Decreasing the medium pH (< 7.0) reduced the activity of sigma ligands. Importantly, compounds which lacked sigma affinity neither showed synergism with 30 uM BD737 nor an increase in activity at higher pH. These results confirm the sigma specificity of this effect. These findings are consistent with a possible role of sigma receptors in cell growth and development and/or in neurodegeneration and neuroprotection. There are also important implications for chronic treatment with neuroleptics, if these compounds can cause cell loss *in vivo.* For example, since brainstem motor nuclei are rich in sigma receptors, it is feasible that irreversible tardive dyskinesia is related to neuroleptic-induced cell loss in these regions. More investigation will be needed to determine the mechanism of this effect and the clinical implications.

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CHARACTERIZATION OF [^{3}H](+)-AZIDO-PHENAZOCINE AS A SELECTIVE PHOTOAFFINITY PROBE FOR SIGMA-1 RECEPTORS

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Heterogeneity of sigma binding sites has been demonstrated on the basis of differences in ligand selectivity profiles using various radioligands and tissues (for reviews, Walker *et al.,* Pharmacol Rev 42:355-402, 1990; Quirion *et al.,* Trends Pharmacol Sci 13:85-86, 1992). Sigma-1 and sigma-2 receptors differ in their affinity for (+)-benzomorphans, with sigma-1 receptors having much higher affinity for these compounds than sigma-2. These two subtypes have also been differentiated on the basis of photoaffinity labeling using [^{3}H]azido-DTG ([^{3}H]Az-DTG) and determination of molecular weight by SDS polyacrylamide gel electrophoresis (Hellewell and Bowen, Brain Res 527:244-253, 1990). Sigma-1 receptors have an apparent molecular weight of 25 kDa, whereas sigma-2 receptors have a molecular weight of 18-21 kDa. Since [^{3}H]Az-DTG labels both sigma-1 and sigma-2 sites, we attempted to design a selective photoaffmity probe for sigma-1 sites. The benzomorphan, (+)-phenazocine was found to be highly selective for sigma-1 receptors (sigma-1 K_i = 3.90 nM; sigma-2 K_i = 1,269 nM) (Di Paolo *et al.,* Soc Neurosci Abstr 17:814, 1991). On this basis, we synthesized unlabeled and radiolabeled (+)-azido-phenazocine. Unlabeled (+)-azido-phenazocine exhibited a sigma-1 K_i = 1.34 ± 0.21 vs. the selective sigma-1 probe, [^{3}H](+)-pentazocine in guinea pig brain. Competition studies (carried out in the dark) revealed that 5 nM [^{3}H](+)-azido-phenazocine ([^{3}H](+)-Az-PHEN) labeled a site in guinea pig brain with a typical sigma-1 profile, similar to that labeled by [^{3}H](+)-pentazocine and [^{3}H](+)-3-PPP: (+)-pentazocine > haloperidol = DTG > (+)-3-PPP > (+)-SKF 10,047 > (-)-pentazocine > (-)-SKF 10,047. Ligands for other receptors were inactive. Thus, [^{3}H](+)-Az-PHEN appears to selectively label sigma-1 receptors, as predicted. Guinea pig brain membranes were incubated in the dark with 150 nM [^{3}H](+)-Az-PHEN in 50 mM HEPES, pH 8.0 followed by irradiation with light of 254 nm and analysis of proteins by SDS-PAGE and gel slicing. Non-specific binding was subtracted from total binding to reveal specifically labeled peaks. When non-specific binding was determined in the presence of 10 uM haloperidol, [^{3}H](+)-Az-PHEN predominantly labeled a polypeptide of 26 kDa, with much lower labeling of a 17-18 kDa polypeptide. However, when 10 uM (+)-pentazocine was used to determine specific incorporation, only the 26 kDa polypeptide was observed. These molecular weights are in good a reement with sigma-1 and sigma-2 polypeptides, respectively, as described above using [^{3}H]Az-DTG. Also, the failure of (+)-pentazocine to effectively block labeling of the 17-18 kDa polypeptide is consistent with a sigma-2 profile. Some labeling of sigma-2 receptors most likely results from the relatively high concentration of [^{3}H](+)-Az-PHEN used here. [^{3}H](+)-Az-PHEN will be a useful tool for further molecular characterization of sigma-1 receptor sites.

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CHARACTERIZATION OF NOVEL AGENTS FOR SIGMA RECEPTOR AGONIST AND ANTAGONIST ACTIVITY IN MODULATION OF THE MUSCARINIC PHOSPHOINOSITIDE RESPONSE

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We have developed an extensive series of novel compounds based on N-[arylethyl]-N-alkyl-2-(1-pyrrolidinyl)ethylamine which exhibit high affinity and selectivity for sigma sites (Radesca *et al.,* 1991; de Costa *et al.,* 1992; de Costa *et al.,* in press; Dominguez *et al.,* this meeting). These compounds can be divided into four major classes: 1) aryl ethyl(pyrrolidinyl)cyclohexylamines, 2) aryl ethylene diamines, 3) aryl alkyl piperazines, and 4) aryl poly-alkylamines. Previous work has demonstrated that sigma ligands non-competitively inhibit the muscarinic phosphoinositide response in rat brain synaptoneurosomes (Bowen *et al.,* 1988). This effect is mediated by sigma-1 receptors (Bowen *et al.,* 1992). Several of these novel sigma agents (as well as some more prototypic compounds) were investigated using non-competitive inhibition of oxotremorine-M stimulated PPI turnover as a measure of sigma-1 agonist activity. Most compounds with high sigma-1 affinity produced the expected inhibition *(e.g.* (+)-pentazocine, DTG, haloperidol), suggesting that these are sigma agonists. The aryl ethyl (pyrrolidinyl)cyclohexylamine, BD737 is in this category. However, despite high sigma-1 affinity, several of the novel compounds inhibited with less than the expected efficacy, suggesting potential antagonist-like properties. The aryl ethylene diamine, BD1139 (K_i = 5.78 nM) produced dose-dependent, non-competitive inhibition of oxotremorine-M (oxo-M) stimulated PPI turnover at concentrations above 50 uM. However, at 50 uM and below, BD1139 had little or no effect on oxo-M-stimulated PPI turnover. BD1139 at 10, 30, and 50 uM significantly attenuated the ability of 30 uM *(+)-pentazocine to* inhibit oxo-M-stimulated PPI turnover. These data suggest that BD1139 is a partial agonist at sigma-1 sites. Alone at a concentration of 30 uM, the aryl ethylene diamine, BD1047 (K_i = 1.26 nM) and the aryl alkyl piperazine, BD1063 (K_i = 9.15 nM) had little effect on oxo-M-stimulated PPI turnover. However, both compounds attenuated the inhibition produced by 30 uM (+)-pentazocine. This suggests that these compounds are also sigma-1 antagonists. BD1139, BD1047, and BD1063 will be important tools for further studies of sigma receptor function.

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NEUROCHEMICAL AND PHARMACOLOGICAL EXAMINATION OF THE INVOLVEMENT OF [MET]ENKEPHALIN IN MEMORY FOR AVOIDANCE TRAINING IN TWO REGIONS OF THE CHICK BRAIN

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Enkephalins are involved in the formation of memory for aversively motivated tasks in a variety of vertebrate species. In the chick, two brain regions have been implicated strongly in memory formation; these are the medial hyperstriatum ventrale (MHV), a homologue to mammalian visual cortex, and lobus parolfactorius (LPO), a homologue to mammalian nucleus accumbens. Administration of [Leu]enkephalin in the MHV impairs memory for one-trial peck-avoidance (PA) training, but it is not known whether [Met]enkephalin (ME) administration produces impairment. Other researchers demonstrated that PA training produces changes in the chick brain that are related to learning including increased glucose metabolism, focal elevation of bursting activity, increased spine density, and induction of c-*fos*. We examined the role of ME in memory formation using two different methods. First, two-day-old chicks were injected with ME in half log increments from 0.01 to 1.0 mM in either the MHV or the LPO. trained on a one-trial peck-avoidance task, and tested 24 hours later for retention. The 0.3 mM dose of ME produced amnesia when injected in the LPO, however, none of the doses of ME produced amnesia when injected in the MHV. Second, non-injected chicks were trained on the peck-avoidance task, their brains were removed either 5 or 45 minutes after training, and ME was quantified in the left and right MHV and LPO by radioimmunoassay. Basal concentrations of ME in non-injected chicks were approximately 95 pmol/mg protein in the LPO and 4 pmol/mg protein in the MHV. These concentrations are consistent with values we reported previously for larger areas of the chick brain, and similar to values reported by other laboratories for homologous brain regions in mammals. There was a significant decrease (= 25%) in ME in the LPO of trained vs control chicks at both 5 and 45 minutes after training. No change in ME was detected in the MHV as a result of training, and no difference in ME was found between the left and right hemispheres in either brain region. The data from both methods used in these experiments support a role of ME in formation of memory for aversive training in the LPO but not in the MHV.

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CAN NEONATAL ABSTINENCE BE DEMONSTRATED IN THE SEVEN DAY OLD RAT?

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To determine the behavioral components of abstinence in the young rat, 14 day osmotic minipumps were implanted in dams on gestational day 16 to deliver an average dose of either 9 or 14 m&/kg/day methadone hydrochloride (METH-9, METH-14). Pair-fed (PF) and nontreated (NT) control groups were run simultaneously. All pups were reared by their biological mothers, therefore the pups of the methadone exposed dams continued to receive methadone postnatally via maternal milk. On postnatal day (PND) 7, pups were administered either 1 mg/kg naltrexone ip or an equal volume of saline and compared on the following tests: 1) Ultrasonic vocalization (USV) testing: The number of USV emitted during 6 minutes of isolation, 15 minute post-injection 2) Activity testing: Animals administered naltrexone and saline were immediately placed in separate cages, balanced for number of pups and sex, and tested on activity monitors for 30 minutes.

An increased rate of ultrasonic vocalization over the 6 minute test session was seen in the METH-14 pups administered naltrexone compared to their littermates administered saline (paired $t=2.562$, $df=10$, $p<0.029$). This increase was not seen in the METH-9, PF, or NT pups. For the first 15 min of the activity test, the METH-9 and the METH-14 pups had increased activity counts when administered naltrexone compared to their littermates administered saline (METH-9: paired $t=2.165$, $df=11$, $p<0.054$; METH-14: paired $t=2.280$, $df=11$, $p<0.045$). Neither control group showed this increase. During the last 15 min this trend continued but the differences were not significant.

Due to the immaturity of the central nervous system of the newborn rat. physical dependence has been difficult to demonstrate. Similarly, opiate-exposed human neonates born preterm *(i.e.* immature) also show diminished abstinence symptoms. On PND 7, methadone exposed pups administered naltrexone have an increased rate of ultrasonic vocalization, as well as an increase in locomotor activity when compared to their littermates administered saline. We interpret these behavioral changes to represent precipitated abstinence, thus increased activity and ultrasonic vocalizations may serve as useful behavioral indicators of abstinence in the young rat.

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THE EFFECTS OF U50,488 ON ULTRASONIC VOCALIZATIONS IN RAT PUPS

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Rat pups, like the young of many mammals, cry when isolated in an unfamiliar milieu. These ultrasonic vocalizations (USV) are widely accepted as a metric for distress. Administered centrally, μ and δ opiate receptor agonists DAMGO and DPDPE quiet 10- and 14-day old isolated pups; the κ agonist U50,488 increases USV. In the current study of peripheral effects, 243 Wistar pups (3-, 10-, and 18-days old) were injected intraperitoneally with saline or U50,488 (0.1 - 30.0 mg/kg) and tested either in isolation or with littermates in the homecage. (Preweanling rats seldom emit USV *in the homecage* in the absence of a physical disturbance.) The number of USV and level of activity were recorded for isolates. In the homecage experiments an additional "snapshot" observation was made every 15 seconds. Pups were "in contact" with littermates or "separate"; they were "active" or "quiet".

There were significant USV increases for all age groups, in isolation and homecage, with the highest doses producing submaximal rates of calling. Linear increases in activity were seen in isolated 3- and 10-day olds, but there was a significant decrease in 18-day old activity, presaging the transition to sedation seen in adults rats. In the homecage, U50,488 increased activity of 3- and 10-day olds, but, although the drug boosted activity in 18-day olds, higher doses diminished this effect. The percent of time pups spent separate from all littermates in the homecage increased in a linear, dose-dependent manner. For 3- and 10-day olds, the microenvironment formed by the odors of the homecage, bedding, warmth, and the presence of littermates offered partial protection against the anxiogenic properties of U50,488. Higher doses were required to elicit USV from these pups in the homecage than in isolation. For 18-day olds, close to weaning and independence, there was no shift in threshold.

U50,488 raised USV rates in isolated pups. Effects were age-related (10>3>18) and at 18 days we saw the beginning of the torpor U50,488 produces in adult rats. That the drug elicited USV in the homecage and disrupted species typical huddling is evidence of its surprisingly powerful ability to disrupt normal patterns of behavior. It is tempting to speculate that there is some incentive value normally associated with littermate contact that is changed by the drug - possibly modification of sensory control. U50,488 may act directly on the κ 1receptor or may precipitate activity downstream in some other neurochemical system that modifies normal patterns of companion contact.

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STRAIN DIFFERENCES IN THE REWARDING AND DOPAMINE-RELEASING EFFECTS OF MORPHINE IN RATS

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Pharmacogenetic studies have demonstrated that strains of rodents can differ in their sensitivity to psychoactive drugs. Thus gcnotypic differences may contribute to the aetiology of the certain addictions. A number of studies have evaluated the addictive properties of narcotics within inbred strains of mice (Belknap 1990; Cunningham *et al.,* 1991). However, these studies have concentrated on behavioural differences (*e.g.* oral consumption of fluids) and neurochemical bases for such differences have not been examined. The present study sought to evaluate this issue in the rat using *in vivo* microdialysis and the conditioned place preference paradigm. Specifically, we have characterised and compared the dopamine-releasing and conditioned rewarding effects of morphine in two outbred rat strains.

In counterbalanced conditioning designs (3 drug and 3 vehicle trials for 50 min each), increasing doses of morphine (1.0-10.0 mg/kg S.C.) produced significant CPPs in both Sprague Dawley and Wistar strains of rat. However, a significantly greater dose of morphine (5.0 mg/kg) was required to produce a significant CPP in Wistar rats than in the Sprague Dawley strain which showed a CPP at 3.0 mg/kg morphine dose. Both strains produced similar maximal magnitudes of CPP with the largest dose of morphine (10.0 mg/kg). In parallel microdialysis experiments, both strains showed significant dose-related increases in dopamine release in the nucleus accumbens following an acute challenge of morphine (1.0-10.0 mg/kg S.C.). Again in Wistar rats, a larger dose of morphine was necessary to produce a significant increase in comparison to Sprague Dawley which showed an increase with 3.0 mg/kg morphine. These results indicate differential sensitivity to morphine between the two strains at both behavioural and neurochemical levels. These data suggest that genetic factors can govern both the bchavioural and ncurochemical aspects of opiate addiction.

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MODULATOIN OF MORPHINE-INDUCED SENSITIZATION BY ENDOGENOUS κ-OPIOID SYSTEMS

R. Spanagel and T. S. Shippenberg

The biphasic effects of morphine upon locomotor activity are well documented. However, during chronic administration. tolerance to the sedative effects of morphine and an enhancement of the stimulatory actions of this drug are seen (behavioral sensitization). There is increasing evidence that the mesolimbic dopaminergic (DA) system is critically involved in the initiation and mediation of morphine-induced behavioral sensitization. It was recently shown that mesolimbic DA neurons are modulated by two opposing tonically active endogenous opioid systems (Spanagel *et al.,* 1992). A stimulatory μ opioid system is located in the ventral tegmental area (VTA), the origin of mesolimbic dopaminergic neurons, whereas an inhibitory ***k*** system is located in the nucleus accumbens (NAC). It is suggested that the tonic activity of both opioid systems is necessary for the maintenance of basal DA release in the NAC. Given that these opioid systems modulate mesolimbic neuronal activity and it is these same neurons which have been implicated in the process of sensitization, we examined the influence of ***k*** opioid ligands upon mesolimbic and behavioral sensitization. Male Sprague Dawley rats (Charles River, Sulzfeld, Germany) weighing 250-270 g were implanted with a microdialysis guide cannula (Carnegie Medicine, Stockholm) in the NAC (relative to interaural: A: 9,9, L: +1.4, V: -6.0) and an i.c.v. guide cannula into the lateral ventricle (relative to bregma: A: -0.9, L: +1.5, V: -3.0). Following one week of handling and recovery, rats were pretreated with either sterile water or a single injection of nor-BNI (30 μg/3 μl, i.c.v.) 30 minutes prior to the first morphine injection. Rats were then injected twice daily at 8 am. and 8 p.m. for 10 days with either saline or ascending doses (10-120 mg/kg s.c.) of morphine hydrochloride. In another set of experiments, rats received 30 minutes prior to each morphine injection, the ***k***-agonist U69593. Three and 30 days after me last morphine injection microdialysis experiments were conducted according to Spanagel *et al.,* (1992). After DA output was stablized, three consecutive samples were collected at 20 minute intervals for the determination of basal levels. Rats were men injected with 10 mg/kg morphine s.c. and dialysates were collected for 180 minutes and immediately analyzed using a reverse phase HPLC system with electrochemical detection. The effects of the morphine challenge on locomotor activity were assessed by measuring horizontal cage crosses and vertical movements.

Morphine produced a biphasic effect on motor activity in drug naive animals. Thus, depression of activity occurred during the first two hours which was followed by an increase in activity (3-4 hours post-morphine injection). However, in rats which were chronically treated with morphine only a stimulation of activity was seen, which was significantly greater than in controls, indicating the occurrence of behavioral sensitization. In animals which received the nor-BNI pretreatment the stimulant effect of morphine was significantly potentiated. However, the U69593 pretreatment (0.16 and 0.32 mg/kg s.c.) prevented the development of tolerance to the sedative effects to morphine. On the neurochemical level, similar effects were observed: Morphine (10 mg/kg s.c.), given 3 and 30 days after the chronic exposure to morphine, produced a greater increase in DA release in the NAC in the morphine experienced rats compared to naive rats. In nor-BNI pretreated rats, DA release was even further enhanced compared to animals which received only the chronic morphine treatment.

The present study confirms that chronic injections of morphine enhances both the motor stimulatory and mesolimbic DA-releasing effects of morphine. Such sensitization was apparent 3 as well as 30 days after chronic morphine treatment. In animals pretreated with the ***k*** opioid antagonist nor-BNI an even greater sensitized response to morphine was seen. The ***k*** agonist U69593 prevented tolerance to the sedative effect but did not affect morphine-induced behavioral sensitization. These data and those demonstrating marked effects of ***k*** opioid receptor ligands upon morpbine tolerance and dependence suggest that pharmacological manipulations of endogenous ***k*** opioid systems may represent a new direction in the management of opioid addiction, craving and relapse.

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INDIVIDUAL DIFFERENCES FOLLOWING INTRACRANIAL INFUSIONS OF DOPAMINERGIC, GLUTAMATERGIC AND OPIOID AGONISTS

M. S. Hooks and P. W. Kalivas

High (HR) and low (LR) responding rats to a novel environment show differences in their vulnerability to drugs of abuse, such as amphetamine and cocaine, when administered systemically. To assess the role of the dopaminergic. glutamatergic and opioid systems in producing behavioral activation in HR and LR, specific agonists were infused into local brain regions. This study analyzed the effects of various compounds that produced behavioral activation when infused into the nucleus accumbens (NACC), ventral tegmental area (VTA) and ventral palladium (VP) in HR and LR. Male Sprague-Dawley rats were stereotaxically implanted with permanent stainless steel cannulae in the NACC, VTA and VP. After recovery and screening for locomotor response to a novel environment, subjects were infused four times at three day intervals with the appropriate drug in a volume of 0.5 µl. Infusions of the direct dopamine agonist, dopamine (0, 3, 10, and 30 µg/side), into the NACC ($p<<0.05$) and the VP $p<<0.0025$) produced dose-dependent differences between HR and LR in horizontal counts, distance travelled and vertical activity. The glutamatergic agonist, AMPA (0.0.03,0.l, and 0.3 µg/side), infused into the NACC ($p<<0.05$) and VP ($p<<0.00l$) produced behavioral differences between HR and LR in horizontal counts and distance travelled. In addition, infusions of AMPA (0, 0.01, 0.03, and 0.1 µg/side) into the VTA also produced differences between HR and LR in horizontal counts ($p<<0.10$) and distance travelled ($p<<0.05$). Infusions of the mu opioid agonist, DAMGO, into the NACC, VP (0, 0.03, 0.1, and 0.3 nmol/side) or the VTA (0, 0.01, 0.03, and 0.1 nmol/side) produced behavioral activation but no differences between HR and LR. Infusions of dopamine, AMPA and DAMGO into these selected regions produced dose dependent changes in activity for horizontal counts, distance travelled, and vertical activity in all cases. These results indicate that activation of either the dopaminergic or glutamatergic systems in the NACC or VP can produce individual differences in behavioral activation as predicted by response to novelty. However, activation of the opioid system in the VTA, VP or NACC does not produce differences between HR and LR. The involvement of the dopaminergic and glutamatergic systems in the NACC or VP is not surprising since both have been implicated in sensitization and reinforcement of cocaine and amphetamine. These results indicate that variation in the dopaminergic and/or the excitatory amino acid systems contribute to the differences observed between HR and LR in the level of behavioral activation induced by novelty and drugs of abuse. The circuitry involving the NACC, VP and VTA appears to be of great importance in producing differences in responsiveness between subjects.

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RESPONSE RATE-DECREASING EFFECTS OF MU, KAPPA, AND MIXED-ACTION OPIOIDS: DIFFERENTIAL SENSITIVITY TO ANTAGONISM BY NALTREXONE

R. C. Pitts, L. A. Dykstra, and M. J. Picker

Lever pressing by rats was maintained under a fixed-ratio 30 (FR 30) schedule of food presentation. Using a cumulative-dosing regimen, effects of various doses of the mu-agonists morphine and fentanyl, the kappa-agonists bremazocine and U50,488 and the mixed-agonists butorphanol, nalbuphine, nalorphine, and (-)-pentazocine were tested alone and in combination with various doses of naltrexone. When given alone, each of these drugs produced dose-dependent decreases in response rates. The dose-effect curves for morphine, fentanyl, butorphanol, and nalbuphine were shifted to the right in a dose-dependent manner. Apparent pA_2 values for naltrexone against these opioids were consistent with those of mu agonists. In contrast, although the dose-effect curves of nalorphine, (-)-pentazocine, bremazocine, and U50,488 were shifted to the right by one or more doses of naltrexone, these effects were not an orderly function of dose. Thus, the rate-decreasing effects of morphine, fentanyl, butorphanol and nalbuphine in the present study appear to be mu-mediated. Although the rate-decreasing effects of nalorphine, (-)-pentazocine, bremazocine, and U50,488 obtained in the present study appear to be, at least in part, opioid mediated, the data for naltrexone suggest that these rate-decreasing effects may reflect actions in other receptor systems.

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OPIOID AND SEROTONIN INTERACTIONS IN SQUIRREL MONKEYS RESPONDING UNDER A SHOCK TITRATION SCHEDULE

K. R. Powell and L. A. Dykstra

The role of serotonin (5HT) in the antinociceptive effects of the kappa opioid, U50,488, and the mu opioid, morphine, was examined in squirrel monkeys responding under a shock titration procedure. Under this procedure, shock was scheduled to increase once every 15 seconds from 0.01 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 and morphine were examined alone and in combination with the $5HT_2$ antagonists, ketanserin and pirenperone, and the $5HT_{1A}$ agonists, 8-OH-DPAT and ipsapirone. When administered alone, U50,488 and morphine increased median shock level in a dose-dependent manner, whereas 8-OH-DPAT, ipsapirone, ketanserin and pirenperone generally did not alter responding. When administered in combination with U50,488, high doses ketanserin and pirenperone shifted the U50,488 dose-effect curve to the left, whereas 8-OH-DPAT did not alter the U50,488 dose-effect curve. In contrast, when administered in combination with morphine, 8-OH-DPAT and ipsapirone dose-dependently antagonized the highest dose of morphine in most squirrel monkeys, whereas ketanserin did not alter the morphine dose-effect curve. Taken together, these data suggest a role for the $5HT_2$ receptor system in kappa-induced antinociception and for the $5HT_{1A}$ receptor system in mu-induced antinociception.

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THE INDIRECT 5-HT AGONIST D-FENFLURAMINE REDUCES HEROIN SELF-ADMINISTRATION IN RATS

Y. Wang, G. A. Higgins, P. J. Fletcher, and E. M. Sellers

The 5-HT reuptake inhibitor and releaser d-fenfluramine (d-FENF) has been previously reported to diminish feeding and alcohol self-administration in rats (e.g. Higgins et al. 1992). The purpose of the present study was to examine the effect of d-FENF on heroin self-administration and morphine drug discrimination.

Separate squads of rats (male Wistar strain, 300g starting wt.) were trained to intravenously self-administer heroin made available under 2 schedules of reinforcement: a) 0.03mg/kg/infusion, FR5TO1min, 1h/day; and b) 0.1mg/kg/infusion, FR1TO1min, 2h/day. Following acquisition of stable rates of responding, rats self-administered approximately 10-13 infusions under each schedule. Pretreatment with d-FENF (1-2.5mg/kg ip, 1h pre session), significantly suppressed this behaviour in both groups (e.g., 0.03mg/kg/infusion: veh = 10.3 ± 1.2; d-FENF 1mg/kg = 5.9 ± 1.0. $p<0.05$). This suppressant effect of d-FENF (1mg/kg) was blocked by metergoline and attenuated by ritanserin pretreatment (both 1mg/kg, sc). Similar doses of d-FENF had only moderate effects against food maintained responding under a similar schedule of reinforcement.

A different group of rats was trained to discriminate morphine (3mg/kg) from saline using a food motivated operant paradigm. In generalization tests, d-FENF (0.5-2.5mg/kg ip) produced negligible (<33%) morphine lever responding. Furthermore, d-FENF (1mg/kg) did not modify a heroin generalization to morphine. We conclude that d-FENF reduces: heroin self-administration by a mechanism unrelated to malaise or substitution/potentiation of the heroin stimulus. Furthermore, an involvement of 5-$HT_{1c/2}$ receptors in this effect seem most likely.

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AGONIST AND ANTAGONIST EFFECTS OF MIXED ACTION OPIOIDS IN THE PIGEON DRUG DISCRIMINATION PROCEDURE: INFLUENCE OF TRAINING DOSE, INTRINSIC EFFICACY AND INTER-ANIMAL DIFFERENCES

M. A. Smith, D. Morgan, C. E. Hughes, L. A. Dykstra, and M. J. Picker

This study examined the stimulus effects of selective, high efficacy mu opioids with varying degrees of efficacy at the mu receptor. In a drug discrimination procedure, pigeons were trained to discriminate between saline and either 0.056 (low) or 0.18 (high) mg/kg fentanyl. The stimulus profiles produced by the various opioids could be separated into three groups: (1) Opioids that substituted completely for both training doses of fentanyl, with steep slopes and little inter-animal differences in the lowest dose (lowest discriminable dose) that produced complete substitution (fentanyl, morphine, LAAM). (2) Opioids that substituted completely for the low training dose and produced intermediate levels of substitution for the high training dose, with relatively shallow slopes and inter-animal differences in the lowest discriminable dose (butorphanol, buprenorphine, EKC, ketocyclazocine, proxorphan, (-)-pentazocine, (-)-metazocine). (3) Opioids that substituted completely for the low training dose, with relatively shallow slopes and large inter-animal differences in the lowest discriminahle dose (nalbuphine, nalorpine, (-)-cyclorphan, (-)-cyclazocine, (-)-NANM, levallorphan). These patterns of substitution and antagonism most likely reflect differences in the intrinsic efficacy of these drugs at the mu receptor, with low intrinsic efficacy associated with shallow dose-effect functions, large inter-animal differences in a drug's lowest discriminahle dose and low levels of substitution for the high-dose fentanyl stimulus. The present findings emphasize the importance of training dose, intrinsic efficacy and inter-animal differences when analyzing drug discrimination data.

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ASSESSMENT OF RELATIVE INTRINSIC EFFICACY OF PROFADOL AND MEPERIDINE IN THE PIGEON DRUG DISCRIMINATION PROCEDURE: RELEVANCE TO PARTIAL SUBSTITUTION PATTERNS

D. Morgan, M. A. Smith, and M. J. Picker

The stimulus effects of meperidine and profadol were examined in pigeons trained to discriminate between saline and either 0.056 or 0.18 mg/kg fentanyl. In the low-dose group, fentanyl, meperidine. profadol and butorphanol substituted completely (≥ 8 5 % fentanyl-appropriate responding) for the fentanyl stimulus. For fentanyl and butorphanol, the lowest dose that substituted completely for the low-dose fentanyl stimulus had little effect on rates of responding, whereas profadol substituted at doses that moderately decreased rates and meperidine substituted at doses that substantially decreased rates. Although naloxone antagonized the stimulus effects of meperidine and profadol, it failed to alter their rate-decreasing effects. In the high-dose group, fentanyl and butorphanol substituted completely and meperidine and profadol partially for the fentanyl stimulus. Meperidine and profadol failed to antagonize (≤85% fentanyl-appropriate responding) the fentanyl stimulus, Analysis of individual data indicated three patterns of substitution and antagonism in the high-dose group. In one group, meperidine and profadol substituted completely for hut failed to antagonize the fentanyl stimulus, in another, these opioids failed to substitute for but antagonized the fentanyl stimulus, and in another, these opioids failed to substitute for or antagonize the fentanyl stimulus. In this latter group, meperidine and profadol potentiated the stimulus effects of fentanyl and butrorphanol, shifting their dose-effect functions to the left. The present findings suggest that the failure of meperidine and profadol to substitute completely for the high-dose fentanyl stimulus was a direct consequence of their rate-decreasing effects and not low or intermediate efficacy at the mu receptor.

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ASSESSMENT OF NORADRENERGIC INVOLVEMENT IN THE DISCRIMINATIVE-STIMULUS EFFECTS OF MORPHINE IN RATS

C. E. Hughes, T. Habash, L. A. Dykstra, and M. J. Picker

Numerous studies have shown that the noradrenergic system is involved in the analgesic effects of opioids. In the present experiment, a discrimination between 5.6 mg/kg morphine and water was established in rats, and then the discriminative-stimulus effects of various noradrcnergic compounds were examined. Substitution of a range of doses of morphine (0.3-17.5 mg/kg) produced dose-dependent increases in morphine-appropriate responding and decreases in response rate. Substitution of a range of doses of the a_2-agonist clonidine (0.003-0.01 mg/kg), the a_2-antagonist yohimhine (1.0-10.0 mg/kg), and the a_1-antagonist prazosin (0.3-10.0 mg/kg) produced little morphine-lever appropriate responding. When doses of these drugs were combined with several doses of morphine, there was essentially no shift in the morphine dose-effect curve for drug-appropriate responding. These data suggest that the noradrenergic system may not be involved in the discriminative-stimulus effects of morphine when the training dose is high. Other studies have shown that clonidine partially substituted for morphine when the training dose of morphine was low (1.0, 2.0, or 4.0 mg/kg). When non-rate-decreasing doses of clonidine and morphine were administered in combination, response rates were substantially decreased. These data suggest that the rate-decreasing effects of clonidine and morphine interact in an additive manner. When non-rate-decreasing doses of yohimbine were administered with the larger doses of morphine (5.6 mg/kg and 10.0 mg/kg), response rates were further decreased. These data suggest that these effects may reflect actions in other neurotransmitter systems, *e.g.,* serotonin. They also may reflect nonselective effects.

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DISCRIMINATION OF A DRUG MIXTURE UNDER THREE DIFFERENT TRAINING PROCEDURES IN RATS

E. A. Mariathasan and I. P. Stolerman

Previous studies on the discrimination of drug mixtures have not probed the role of different training procedures in depth (Stolerman *et al.* 1991). Two-lever discriminations based on mixtures of (+)-amphetamine (0.4 mg/kg) plus pentobarbitone (10 mg/kg) have been compared in three groups of rats (n=8) trained to discriminate: (1) mixture from saline - AND-discrimination; (2) either mixture, amphetamine or pentobarbitone from saline - **OR-discrimination;** (3) mixture from either amphetamine or pentobarbitone **-AND/OR-discrimination.** After 60 training sessions, all discriminations were performed with similar (90-94%) accuracy. In rats trained under **AND-** and **OR- discrimination** procedures, there was full generalization from the mixture to the largest doses used of either amphetamine or pentobarbitone. In contrast, in rats trained under the **AND/OR** procedure, there was no generalization from the mixture to any dose of either drug separately. The effects of the different procedures persisted for a prolonged period after training conditions were equated across groups, confirming and extending earlier findings (Stolerman and Mariathasan 1990). The results show in a direct comparison that varying the training procedure can very substantially alter the major characteristics of a discrimination based on a mixture of drugs.

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COCAINE SELF-ADMINISTRATION UNDER A PROGRESSIVE-RATIO SCHEDULE IN RATS: POTENTIATION BY AMPHETAMINE BUT NOT BY BUPRENORPHINE

D. Li, R. Y. Depoortere, and M. W. Emmett-Oglesby

The effects of pretreatment with the partial mu-agonist buprenorphine (SUP) or the dopamine releaser amphetamine (AMPH) were investigated in F-344 rats trained to self-administer cocaine (0.25 mg/injection of 100 ml) under a progressive-ratio (PR) schedule of reinforcement. BUP (0.01, 0.032, or 0.1 mg/kg) or saline was tested against a cocaine dose of 0.083 mg/inj. AMPH (0.32, 1.0, or 1.8 mg/kg) or saline was tested against cocaine-vehicle or three doses of cocaine (0.028, 0.083, or 0.25 mg/inj.). The effects of saline, BUP, or AMPH pretreatments (s.c. 30 minutes presession) were assessed on the number of reinforcers (cocaine infusions) obtained. BUP pretreatment did not modify the number of reinforcers obtained as compared to saline, AMPH pretreatment, on the other hand, significantly increased the number of reinforcers obtained for all three doses of cocaine and for cocaine-vehicle. This set of data supports the hypothesis that in rats, BUP does not modify the reinforcing effects of cocaine. In addition BUP (0.01 or 0.1 mg/kg) does not modify the dose-effect curve for cocaine in rats trained to discriminative cocaine, 10 mg/kg i.p. The absence of effects of BUP pretreatment does not appear to be due to a lack of sensitivity of this PR schedule to pretreatments that can potentiate cocaine self-administration, since AMPH pretreatment was shown to increase the number of reinforcers obtained.

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D-AMPHETAMINE PRODUCES CROSS-TOLERANCE TO COCAINE IN A SELF-ADMINISTRATION PARADIGM

R. L. Peltier and M. W. Emmett-Oglesby

The experiment determined whether the chronic administration of d-amphetamine would result in cross-tolerance to cocaine in a 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 employees an FR2 schedule with a maximum of 24 reinforcers. The reinforcers are 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 was obtained, rats then received injections of d-amphetamine (3.2 mg/kg, s.c.) three times daily for seven days. During this chronic regimen, the rats were not allowed to self-administer cocaine. Twenty-four hours following the last d-amphetamine injection, a cocaine dose-response curve was then obtained, this dose-response curve was shifted approximately two-fold to the right. 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 cross-tolerance to cocaine in a self-administration paradigm.

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EFFECTS OF BEHAVIORAL HISTORY ON COCAINE SELF-ADMINISTRATION BY RHESUS MONKEYS

M. A. Nader

Research with animals has shown that behavioral or environmental factors such as reinforcement schedule, can influence the rate and pattern of drug self-administration. In addition, when non-drug reinforcers are maintaining responding, prior training under certain reinforcement schedules can produce long-lasting changes in behavior and in the behavioral effects of drugs. **However, there is no data on how sensitive drug self-administration would be to reinforcement schedule histories.** The purpose of this study was to examine the effects of behavioral history on cocaine self-administration. Experimentally naive rhesus monkeys (N=8) were surgically prepared with chronic indwelling intravenous catheters and trained to respond under a fixed-interval (FI) 5 minute schedule of cocaine (0.03 mg/kg/inj, i.v.) presentation. After 100 sessions, and following completion of a cocaine dose-response curve (0.01-0.3 mg/kg/inj), the monkeys were randomly assigned to one of two groups (N=4/group) and trained to respond on another lever under either a fixed-ratio (FR) 50 or an interresponse times (IRT) > 30-sec schedule of cocaine (0.03 mg/kg/inj) presentation. After 65 sessions responding was again maintained under the FI 5 minute schedule of 0.03 mg/kg/inj cocaine. The mean rate of responding under the FI 5 minute schedule of 0.03 mg/kg/inj cocaine, prior to interpolated training under other schedules, was 3.47 (± 1.04) r/min and the cocaine dose-response curve was characterized as an inverted-U shaped function, with peak responding at 0.03 mg/kg/inj. Response rates under the FR 50 schedule were significantly higher (66.80 ± 5.6 r/min), while rates under the IRT>30-set schedule were iower (2.62 ± 0.2 r/min), than pre-history FI rates. Following an FR history, responding under the FI 5-min schedule was higher ($p<0.05$) than pre-history rates in 3 of 4 monkeys, that persisted for at least 60 consecutive sessions. The cocaine dose-response curves for these subjects were shifted up and/or to the right. Following an IRT history, 2 of 4 monkeys had lower ($p<0.05$) response rates under the FI 5 minute schedule compared to pre-history FI rates, that persisted for at least 60 sessions; their cocaine dose-response curves were flat and shifted down. The other two IRT-history monkeys were retrained under an IRT>40-sec schedule for 27-30 sessions and when returned to the FI 5 minute schedule responding was below baseline ($p<0.05$) for at least 30 sessions. Thus, in all four subjects, an IRT history produced long-lasting reductions in cocaine self-administration under an FI schedule. When saline was substituted for cocaine responding persisted at higher rates in IRT-history monkeys compared to FR-history subjects, indicating that behavioral history can influence resistance to extinction. After completion of the post-history dose-response curves, responding was again maintained by 0.03 mg/kg/inj cocaine and the effects of changing the FI value (2.5, 10, 20, 40, 60, 80 and 120 min) were assessed for single sessions on Tuesdays and Fridays in three IRT-history monkeys and one FR-history subject. For the IRT-history monkeys, increases in the FI schedule (20-120 min) resulted in decreases in response rates (<50% of control at FI 120 min). In contrast, increases in the FI value resulted in increases in response rates in the FR-history subject. These preliminarv results suggest that further differences between groups, as a function of behavioral history, may be observed when the availability of cocaine is changed *(e.g.,* under leaner FI schedules). Taken together, these results indicate that cocaine self-administration can be modified by behavioral history and that these changes are persistent. Knowledge of such historical variables may be important in understanding the maintenance and treatment of drug abuse.

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EFFECT OF CHRONIC MORPHINE ON COCAINE SELF-ADMINISTRATION

M. W. Emmett-Oglesby and Y. Gong

The primary purpose of this experiment was to determine whether the chronic administration of morphine would result in cross-tolerance to cocaine in a self-administration paradigm. Rats were allowed to self-administer cocaine (0.25 mg/injection) through an indwelling i.v. catheter. After stable baseline responding was established, a cocaine dose-effect curve (0.125, 0.25 and 0.5 mg/injection) was determined in a single session. In addition, the effect of morphine, 1.0, 3.2 and 5.6 mg/kg, on the cocaine dose-effect curve was also determined. Increasing doses of cocaine resulted in significantly longer times between successive injections of cocaine; morphine given immediately prior to cocaine testing further increased the times between successive injections of cocaine. Subsequently, rats were withheld from all cocaine training or testing and morphine was administered for one-week in an escalating dosing regimen that terminated with 10 mg/kg, given every 12-hr, for 5 days. At 24 hr after the last dose of morphine, the cocaine dose-effect was redetermined. The cocaine dose-effect curve was essentially identical to that obtained prior to chronic morphine administration, and these data can be contrasted to those obtained with chronic administration of CNS stimulants, which produce cross-tolerance in this paradigm. Thus, chronic administration of morphine does not confer cross-tolerance to self-administration of cocaine.

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EFFECTS OF SACCHARIN AND BUPRENORPHINE ON COCAINE BASE SMOKING IN RHESUS MONKEYS

S. D. Comer, V. R. Hunt, and M. E. Carroll

The purpose of this study was to examine the effect of behavioral and pharmacological treatments on the demand for cocaine base smoking. Four male rhesus monkeys were trained to press a lever under FR schedules (FR 32-1024) and then to make inhalations (FR 5) on a smoking spout to gain access to vaporized cocaine base (1.0 mg/kg/smoke). The demand for cocaine was evaluated by varying the fixed-ratio (FR) value for lever pressing. Within behavioral economic principles, this procedure allowed the generation of a demand curve which is a measure of drug consumption (mg) as a function of unit price (responses/mg).

In the first experiment, water or saccharin was concurrently available contingent upon lip-contact responses (FR 1) on a drinking spout. More saccharin than water was consumed during the experimental session, which indicated that saccharin was serving as a reinforcer. At a baseline lever FR value each monkey received the maximum number of smoke deliveries. As lever FR values were increased, the number of smoke deliveries decreased. The elasticity of demand for cocaine, which is a measure of the rate of change in consumption with increasing unit price, was increased slightly at higher unit prices in the presence of saccharin. Cocaine and saccharin were also substitutable reinforcers under these conditions since saccharin intake increased as cocaine intake decreased.

In the second experiment, buprenorphine (0.01 and 0.1 mg/kg) was administered intramuscularly 30 minutes prior to the start of the experimental session. Overall, pretreatment with the lower dose of buprenorphine (0.01 mg/kg) had no effect on demand for cocaine. Individual monkeys showed either an increase, decrease or no change in cocaine intake when pretreated with 0.01 mg/kg buprenorphine. A higher dose of buprenorphine (0.1 mg/kg) reduced cocaine intake and produced an increase in the elasticity of demand for cocaine.

Thus, while the presence of an alternative reinforcer (saccharin) produced only a small increase in the elasticity of demand for cocaine, pretreatment with buprenorphine (0.1 mg/kg) substantially increased the elasticity of demand for smoked cocaine.

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THE EFFECTS OF COCAINE ALONE AND IN COMBINATION WITH SEROTONERGIC ANTAGONISTS ON SQUIRREL MONKEYS' MULTIPLE FIXED-INTERVAL, FIXED-RATIO SCHEDULE PERFORMANCE

S. L. Serdikoff, C. W. Schindler, S. R. Goldberg, and C. A. Sannerud

Recent findings have established that there is a serotonergic (5-HT) component involved in the behavioral effects of psychomotor stimulants. Additionally, it has been shown that cocaine (CCC) potently inhibits 5-HT reuptake as well as depresses the spontaneous activity of the dorsal raphe. In the present study, the effects of acute pretreatments of cocaine alone (0.032, 0.10, 0.32, 1.0, and 3.2 mg/kg, i.m.), cocaine together with the 5-HT_1 antagonist Nan-190 Hydrobromide (NAN) (0.1, 1.0, and 3.2 mg/kg, i.m.). and cocaine together wih the 5-$HT_{1/2}$ antagonist 1-(1-Naphthyl)piperazine HCl (1-NP) (0.32, 1.0, and 3.2 mg/kg, i.m.) were evaluated in 4 squirrel monkeys responding under a multiple FI 5 min - FR 30 schedule of food reinforcement. For each of three squirrel monkeys, experimental sessions were preceded by a 15 minute pre-session during which no stimulus lights were illuminated and lever pressing was not consequated. During the fixed-interval (FI) component, two red stimulus lights were illuminated and lever pressing was reinforced according to a FI 5-minute schedule of food reinforcement. During the fixed-ratio (FR) component, two green stimulus lights were illuminated and lever pressing was reinforced according to a an FR 30 schedule of food reinforcement. For Subject 1890, both NAN and 1-NP appear to have antagonized the rate-decreasing effect of high cocaine doses during the FI and FR components. These results are comparable to those obtained following COC and KET administration. For Subject 1990, who showed a rate-increasing effect of lower cocaine doses during the FI component, the lower doses of both NAN and 1-NP appear to have potentiated that rate-increasing effect in a manner similar to that observed following COC and MDL 72222 (a 5-HT_3 antagonist) administration. This finding can be contrasted, however, with the attenuation of COC's FI-rate increasing effect that was obtained following concomitant COC and KET administration. For Subject 3090, both NAN and 1-NP appear to have antagonized the rate increasing effect observed the rate increasing effect observed during the FI component following administration of the intermediate COC dose. However, there were no other consistent effects of COC in combination with either NAN or 1-NP on this subject's responding under this multiple FI-FR schedule. The present results support the assertion that there is a serotonergic component involved in the behavioral effects of COC. Changes in COC's effects on food maintained responding as a function of NAN and 1-NP administration suggest that the involvement of 5-HT in the psychomotor effects of COC may be mediated by the 5-HT_1 and/or 5-HT_2 systems. This conclusion is consistent with previous findings showing changes in COC's effects on food maintained responding as a function of KET administration. However, the consistency of the current findings regarding potentiation of COC's FI-rate increasing effects in Subject 1990 with the findings regarding concomitant COC and MDL 72222 administration suggest that other 5-HT systems may be involved in mediating COC's psychomotor effects.

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COMPARISON OF THE BEHAVIORAL EFFECTS OF SKF 81297, SKF 82958, AND COCAINE IN SQUIRREL MONKEYS

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The D_1 agonists SKF 82958 and SKF 81297 have been reported to maintain self-administration in rats and rhesus monkeys, respectively (Self and Stein 1992; Weed et al. 1992). The present studies were conducted to examine the generality of these findings and to further compare the behavioral effects of D_1 agonists with cocaine in squirrel monkeys. In observational studied, all three drugs produced dose-related increases in the frequency of stationary postures and visual scanning. In monkeys responding under 3-min fixed-interval (FI) schedule of stimulus shock termination, SKF 82958 and cocaine, but not SKF 81297, produced dose-related increases in FI responding. In monkeys trained to discriminate SKF 81297 from saline, SKF 81297 and SKF 82958, but not cocaine, produced dose-related increases in the percentage of responses on the drug-associated lever. In monkeys trained to discriminate methamphetamine from saline, all three drugs produced dose-related increases in the percentage of responses on the drug-associated lever. In monkeys responding under a 30-response fixed-ratio (FR) schedule of stimulus-shock termination, all three drugs produced dose-dependent decreases in response rate that were surmountably antagonized by the selective D_1 antagonist SCH 39166. Under this schedule, only the effects of cocaine were also surmountably antagonized by the selective D_2 antagonist eticlopride. Preliminary results indicate that SKF 82958 and cocaine, but not SKF 81297, maintain self-administration under both second-order FI and FR schedules in squirrel monkeys. Additionally, in radioligand binding experiments both SKF 81297 and SKF 82958 are selective for D_1 over D_2 receptors (appoximately 340-fold and 18-fold, respectively, in monkey caudate-putamen). These results indicate that, although D_1 mechanisms likely play a prominent role in cocaine's behavioral effects, the actions of cocaine and D_1 agonists are not identical.

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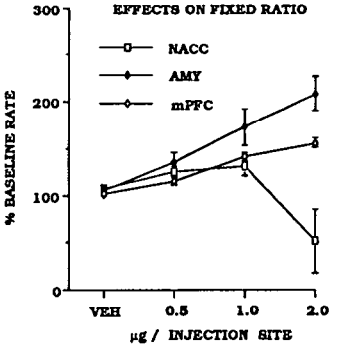
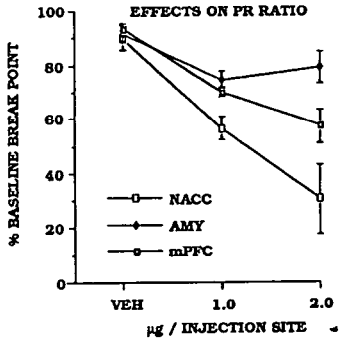
DIFFERENTIAL EFFECTS OF SCH 23390 INJECTION INTO VARIOUS MESOCORTICOLIMBIC TERMINAL AREAS ON COCAINE SELF-ADMINISTRATION

A. McGregor and D.C.S. Roberts

A role for the ventral tegmental area (VTA) and its dopaminergic (DAergic) innervation of the nucleus accumbens (NACC) in reinforcement mechanisms is now evident. The contribution of the DAergic innervation of the amygdala (AMY) and the medial prefrontal cortex (mPFC) is less well studied. The experiments reported here set out to compare the involvement of these three VTA terminal areas in cocaine reinforcement mechanisms.

Rats were trained to self-administer intravenous cocaine (1.5 mg/kg iv) either under a fixed ratio (FR1) or a progressive ratio (PR) schedule of reinforcement. Bilateral stainless steel cannulae were then implanted above the NACC, AMY or mPFC (N = 8 in all groups). Injections of the Dl receptor antagonist, SCH 23390, were given to animals immediately prior to a cocaine self-administration session. The effects of these injections within the three different neural sites were examined under both types of schedule (FR and PR). The figures below illustrate the results.





These results indicate that in addition to the NACC, the AMY and the mPFC also have significant roles to play in cocaine reinforcement. Furthermore, the dissociation between FR and PR data suggests that these schedules may measure different aspects of cocaine CNS action and that distinct neural areas may underlie these different aspects of action.

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COCAINE-LIKE EFFECTS OF DOPAMINE D2 RECEPTOR SELECTIVE AGONISTS IN SQUIRREL MONKEYS (SAIMIRI SCIUREUS)

J. L. Katz and J. M. Witkin

The present study investigated the role of D2 receptors in mediating the behavioral effects of cocaine in primates. The psychomotor stimulant and cocaine-like discriminative stimulus effects of D2 agonists were compared in squirrel monkeys to establish the relationship between these behavioral effects and D2 receptor agonism. One group of squirrel monkeys was trained to press a lever under a fixed-interval schedule of electric-shock presentation. Another group was deprived of food and trained to press either of two levers under a cocaine (0.3 mg/kg) discrimination procedure.

Several of the dopaminergic agonists stimulated rates of responding in squirrel monkeys under the fixed-interval schedule. There were distinct variations in the efficacy of these drugs, with the indirect agonist d-amphetamine most efficacious followed by cocaine and the D2 agonist Ru 24213. Other D2 agonists were not very effective as stimulants of fixed-interval responding. Each of the dopaminergic agonists produced some effects similar to those of cocaine in monkeys trained to discriminate cocaine injections. The exceptions to this were the partial D2 agonist, SDZ 208-912 and the D1 agonist, SKF 38393. There was no relationship between the stimulant effectiveness of various D2 agonists under the fixed-interval schedule and the effectiveness in substituting for cocaine in monkeys trained to discriminate cocaine from saline.

These results suggest that agonist actions at D2 receptors alone may contribute to some of the behavioral effects of cocaine, but that D2 agonist effects alone are not sufficient to fully reproduce those effects. Further, the efficacy of D2 agonists as psychomotor stimulants did not appear to be related to efficacy in substitution for the discriminative effects of cocaine. These results suggest a difference in the mechanisms underlying each of these behavioral effects, and further that the discriminative stimulus effects of cocaine are not based exclusively on the psychomotor stimulation that is produced by agonist actions at D2 receptors.

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EFFECTS OF DOPAMINE AGONISTS ON THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE AND METHAMPHETAMINE

J. M. Witkin and J. L. Katz

Several pieces of evidence suggest that partial agonists of Dl or D2 dopamine receptors may function as antagonists of the discriminative stimulus effects of indirect-acting dopamine agonists like cocaine (COC) or amphetamines. The present study examined the potential of some partial D1 and D2 agonists to antagonize the discriminative stimulus effects of COC or methamphetamine (MA) in rats. The benzazepine D1 partial agonists SKF 75670 and SKF 38393 were studied. The aminoergolines, SDZ 208-911 and SDZ 208-912, have been characterized as partial D_2 receptor agonists with different degrees of intrinsic activity. The (-)-isomer of the n-propylpiperidine derivative, 3-PPP, has been characterized as a D2 receptor partial agonist with antagonist actions at postsynaptic D2 receptors. Male Sprague-Dawley rats maintained at 350 g were trained to discriminate 10 mg/kg (-)-CCC HCl from saline or 1 mg/kg (+)-MA HCl from saline using standard operant conditioning methods.

The D1 receptor partial agonist SKF 38393 did not attenuate the discriminative stimulus effects of COC or MA. SKF 75670, a D1 recęptor partial aeonist with lower intrinsic efficacy than SKF 38393, produced small attenuations (30-50%) of the discriminative stimulus effects of COC and MA at moderate doses. Higher doses of SKF 75670 produced less of an attenuation. D2 partial agonists with different degrees of intrinsic efficacy (terguride, SDZ 208-911, SDZ 208-912) did not substitute for COC or METH. Nonetheless, SDZ 208-912 produced a dose-dependent attenuation of the discriminative stimulus effects of COC and METH to about 50%. Whereas, the non-selective dopamine receptor ligand, (+)-3-PPP, did not block the discriminative stimulus effects of COC or MA, the dopamine autoreceptor agonist, (-)-3-PPP, blocked the effects of MA but not those of COC.

In conclusion, some D1 and D2 dopamine receptor partial agonists can be effective in blocking the discriminative stimulus effects of cocaine and methamphetamine. Antagonist effects of these compounds may be related to their intrinsic activity (as suggested by the differences in effects of SKF 38393 and SKF 75670). The D1 partial agonist SKF 75670 blocks discriminative stimulus effects of cocaine in rats despite producing partial cocaine-like discriminative stimulus effects of its own. Certain dopamine agonists may block important behavioral and subjective effects of psychomotor stimulants in human drug abusers and be useful in the treatment of psychomotor stimulant dependence.

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INHERENT BIOCHEMISTRY AND BEHAVIORAL RESPONSE TO COCAINE DISTINGUISH SUBGROUPS OF OUTBRED SPRAGUE-DAWLEY RATS

M. J. D. Miserendino, T. A. Kosten, X. Guitart, S. Chi, and E. J. Nestler

Individual differences in behavioral responses to drugs of abuse have been documented both between inbred rat strains and among animals within a single outbred strain. We have previously shown inherent biochemical differences in the ventral tegmental area (VTA), a part of the mesolimbic dopamine system implicated in drug reward, between drug "preferring" Lewis and "non-preferring" Fischer 344 rats; relative to Fischers, Lewis rats showed higher levels of tyrosine hydroxylase (TH) and glial fibrillary acidic protein (GFAP) and lower levels of neurofilament (NF) proteins. We have extended these findings in the present studies by examining Sprague-Dawley rats that show differential locomotor activity in a novel environment with respect to both levels of these proteins in the VTA, and response to cocaine in a number of behavioral assays.

Groups of animals were assessed for locomotor activity level during initial exposure to a novel environment, and the highest (1° High N=4) and lowest (1° Low N=4) activity animals from each group were selected. Brain areas were analyzed for TH and NF immunoreactivity by immunoblotting procedures. It was found that relative to High rats, the VTA of Low rats exhibit higher levels of TH and GFAP and lower levels of NF-200, NF-160, NF-68. Further, relative to High rats, Low rats showed smaller increases in locomotor activity to acute cocaine administration but larger differences between initial and subsequent cocaine exposure *(e.g.,* behavioral sensitization). Further, compared to High rats, Low rats developed greater cocaine-induced conditioned place preference, and preliminary data suggests that Low rats may more readily acquire intravenous cocaine self-administration behavior.

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COCAINE-REINFORCED RESPONDING OF RHESUS MONKEYS: EFFECTS OF COCAINE CONCENTRATION AND RESPONSE REQUIREMENT

M. J. Macenski and R. A. Meisch

Cocaine has been shown to function as an orally delivered reinforcer for the rhesus monkey. The ability of cocaine to maintain responding was examined by systematically varying the cocaine concentration and fixed-ratio (FR) size.. These parametric manipulations allow for data analysis in terms of: 1) dose response relationships, 2) behavioral persistence over time, and 3) behavioral economics among others. Four adult male rhesus monkeys (Macaca mulatta) maintained at 80-90% of their free feeding weight served as subjects. Sessions were held in each monkey's home cage. Cages were equipped with a work panel which contained two solenoid-operated brass drinking spouts. These spouts were activated by mouth contacts (the operant) and were independently controlled via solid-state programming equipment located in an adjacent room. Cocaine concentrations (mg/ml) of: 0.8, 0.57, 0.4, 0.2, 0.1, 0.05, and 0.025 were used. Sessions were conducted 7 days a week beginning at 11:00 hrs and ending at 14:00 hrs. Initially 0.8 mg/ml cocaine and vehicle were concurrently available under FR 8 reinforcement schedules. Thus, eight responses on a spout was immediately followed by the delivery of 0.65 ml of the appropriate solution. During sessions conditions across spouts were identical with the exception that one spout delivered a cocaine solution and one spout delivered vehicle. Side position of cocaine was alternated each session. Conditions were changed after six stable sessions of behavior. Across blocks of sessions, descending cocaine concentrations were presented until cocaine no longer maintained greater responding than vehicle. Cocaine (0.8) was retested, and the FR size was doubled. Within a FR size cocaine deliveries and response rate were inverted-U shaped functions of cocaine concentration. At larger FR sizes this was an increasing monotonic function. Generally, as FR size increased, the peak of the dose response function shifted to the right and smaller doses no longer maintained responding. Both within and across FR sizes, larger cocaine doses were better able to maintain responding. As FR size increased, the decline in behavior relative to FR 8 values was inversely re1ated to cocaine concentration. Cocaine intake (mg/kg) was a monotonically increasing function of cocaine concentration for all FR sizes and an inverse function of ratio size within concentrations. The demand curve for cocaine was a monotonic positively decelerating function of unit price over a 100 fold range. Orally delivered cocaine in an effective reinforcer for rhesus monkeys. Use of orally delivered cocaine allows orderly relations to emerge as a function of FR size, dose, and their interactions. Despite cocaine intakes of up to 10 mg/kg/session, only one animal showed gross behavioral changes. Thus, delivering cocaine orally appears to be. an efficient administration route with minimal potential for toxicity. The current data show that over a range of FR sizes and doses a typical demand curve is obtained. This is consistent with a behavioral economic analysis suggesting that manipulations of concentration and FR size may be functionally equivalent. The current data show that reinforcing effects increase with cocaine amount despite lower response rates over the descending portion of the dose response function. This conclusion is evidenced by the ability of larger cocaine doses to maintain behavior as FR size is increased and is consistent with studies using other behavioral measures *(e.g.,* concurrent drug-drug choice; concurrent drug-alternative nondrug choice). It appears that relative rate measures are more accurate in assessing reinforcing effects than absolute rate measures.

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EVALUATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF MIDAZOLAM (MDZ) AND MORPHINE (MOR) ALONE AND IN COMBINATION USING 2- AND 3-LEVER DRUG DISCRIMINATION PROCEDURES IN RATS

C. A. Sannerud, J. A. White, S. R. Goldberg, and I. P. Stolerman

In the present studies, male Hooded rats were trained to discriminate 3.2 mg/kg MOR from saline (SAL) using a 2-lever procedure and 0.32 mg/kg MDZ and 3.2 mg/kg MOR from SAL using a 3-lever procedure. SAL and MOR were given 30 min and MDZ was given 15 minutes prior to 15 minute daily sessions during which rats responded under an FR 30 schedule for food. Test sessions were conducted in extinction and were terminated after 30 consecutive responses were made on one lever or after 5 minutes. In the 2-lever study, MOR (v, 0.4-3.2 mg/kg) produced dose-dependent increases in MOR-lever responding. MDZ (v, 0.1, 0.2 mg/kg) in combination with MOR did not shift the MOR generalization gradient or alter response rates. In the 3-lever study, MOR (v, 0.4-3.2 mg/kg) and MDZ (v, 0.1-3.2) produced dose-dependent increases in the MOR- and MDZ-levers, respectively. MDZ (0.1, 0.32, 1.0 mg/kg) in combination with MOR attenuated MOR's discriminative stimulus effects. Taken together, these data show the lack of pharmacological interaction between MDZ and MOR in the 2-lever study and may suggest the involvement of behavioral processes in the MDZ-MOR interactions in the 3-lever study.

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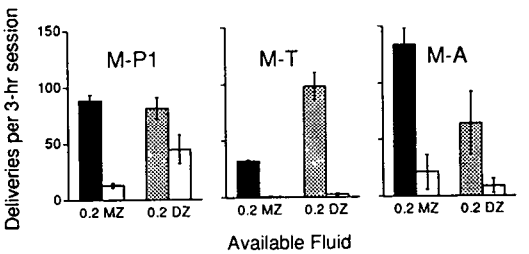
REINFORCING EFFECTS OF ORALLY DELIVERED DIAZEPAM AND MIDAZOLAM IN RHESUS MONKEYS

R. B. Stewart, R. A. Meisdh, and J. D. Roache

Midazolam, a benzodiazepine with a relatively-short duration of action, was established as an orally-delivered reinforcer in three adult male rhesus monkeys (see Meisch et al., this volume). Drug intake consistently exceeded that of drug vehicle and orderly relationships were observed between drug intake and concentration, and between drug intake and fixed ratio size. In the present investigation, the self-administration of diazepam, a benzodiazepine with a relatively long duration of action, was examined in the same three monkeys following a lengthy period of' oral midazolam-reinforced responding. Drug solutions and drug vehicle were concurrently available for three-hr each day under fixed-ratio (FR) reinforcement schedules.

Diazepam (0.2 mg/ml) maintained drug self-administration behavior upon direct substitution for 0.2 mg/ml midazolam. Shown below are the mean (±sem) number of 0.65 ml liquid deliveries per three-hr session for each monkey (M-P1, M-T, M-A), averaged over six consecutive stable sessions. Filled bars: midazolam; Shaded bars: diazepam; Open bars: water.



Subsequently, the diazepam concentration was varied (0.0125-0.8 mg/ml). The resultant concentration-response functions showed the characteristic inverted-U shape and were generally similar to curves generated using midazolam as the reinforcer. Midazolam and diazepam were approximately equipotent in maintaining behavior and response rates were greatest at 0.1 or 0.2 mg/ml for both drugs. These data demonstrate robust reinforcing effects of both "short-" and "long-" acting benzodiazepines delivered by the oral route of administration.

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ORALLY DELIVERED MIDAZOLAM AS A REINFORCER FOR RHESUS MONKEYS: DEMONSTRATION OF REINFORCING EFFECTS

R. A. Meisch, J. D. Roache, G. A. Lemaire, and R. B. Stewart

The introduction of new short-acting benzodiazcpines and of partial agonists has led to an increased interest in the reinforcing effects of this class of drugs. However, rigorous study of these reinforcing effects has been limited by the lack of success in establishing benzodiazepines as orally-delivered reinforcers in laboratory animals (Woods *et al.* 1992).

In the present investigation, oral midazolam self-administration was examined in adult male rhesus monkeys with histories of ethanol- and pentobarbital-reinforced behavior. Drug solutions and drug vehicle were concurrently available for three-hr each day under fixed-ratio (FR) reinforcement schedules. The discriminative stimulus lights for each fluid were identical. Initially, the monkeys rejected a midazolam solution (0.1 mg/ml) following direct substitution of the drug for an 8% ethanol solution. However, midazolam self-administration was subsequently established by using a fading procedure in which increasing amounts of drug (0.0125-0.2 mg/ml) were gradually (over several weeks) added to an 8% ethanol solution, followed by the gradual reduction of the ethanol concentration to zero. This acquisition procedure established midazolam as a reinforcer in three of four monkeys tested, *i.e.,* drug solution intake exceeded that of the drug vehicle. The fourth monkey also self-administered midazolam but drug intake was not consistently greater than vehicle.

The monkeys 'tracked' the drug solution from side to side as the the drug and vehicle positions were reversed. An orderly inverse relationship was observed between FR size (varied from FR 8 to FR 32) and the amount self-administered. Midazolam concentrations from 0.00625 to 0.8 mg/ml were tested and the concentration-response function showed an "inverted-U" shape which is commonly observed with drug reinforcers. On the other hand, the midazolam intake (mg/kg) increased as a function of increases in the drug concentration. At the higher concentrations, marked sedative intoxication was observed. This animal model of oral midazolam self-administration may prove to be useful in the investigation of factors underlying benzodiazepine reinforcement.

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TOLERANCE, CROSS-TOLERANCE AND DEPENDENCE MEASURED BY OPERANT RESPONDING IN RATS TREATED WITH TRIAZOLAM VIA OSMOTIC PUMPS

C. Cohen and D. J. Sanger

Previous research has found that drugs with affinity for w (benzodiazepine) sites differ in their abilities to produce tolerance and dependence (Haigh and Feely 1988; Perrault *et al,* 1992; Sanger and Zivkovic 1992). The purpose of the present study was to extend these observations by investigating the effects of several w site ligands (triazolam, lorazepam, zopiclone, CL 218,872, zolpidem, alpidem, bretazenil and flumazenil) in rats chronically treated with triazolam.

After lever-press training on a fixed ratio 10 schedule of food presentation, male Wistar rats were implanted with osmotic pumps (Alzet 2ML2) delivering subcutaneously either the vehicle, propylene glycol, or a dose of 3 mg/kg/day of triazolam. On day 14, pumps were removed and daily sessions continued. Two experiments were carried out in separate groups of rats. Test drugs were administered using a cumulative dosing method. When flumazenil (3.0-10-30 mg/kg) was administered on day 11 of chronic treatment it greatly decreased rates of responding in triazolam treated rats whereas only the highest dose had a significant effect in control rats. This pattern of effects may therefore represent a precipitated withdrawal syndrome. In contrast, chronic infusion of triazolam did not affect the sensitivity of rats to alpidem (10 - 30 - 100 mg/kg) on day 11 whereas it abolished the stimulant effect of bretazenil (0.1 - 1.0 mg/kg).

Three days after pump removal, triazolam suppressed response rates at doses of 1.0 and 3.0 mg/kg in control rats. In contrast these doses did not decrease rates in triazolam pretreated animals indicating that chronic infusion of triazolam rendered animals tolerant to the depressant effect of triazolam. Rats were still tolerant to acute doses of triazolam 14 days after pump removal. When tested 3-14 days after pump removal, triazolam treated rats were tolerant to the effects of lorazepam (0.3-1.0-3.0 mg/kg) and to those of 10 mg/kg of zopiclone. The dose effect curve of zolpidem was flattened in triazolam treated rats but responding did not differ significantly between groups at any doses tested. Control and triazolam pretreated rats did not differ in their sensitivity to CL 218,872 (3.0-10-30 mg/kg).

Differences between compounds highlighted in this model of tolerance are in agreement with previous observations that these agents possess different pharmacological profiles and different potentials to induce tolerance.

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ETHANOL STRESS INTERACTION AS MEASURED BY CONDITIONED FREEZING IN THE MOUSE

M. F. Stromberg

Ethanol has traditionally been assumed to have anxiolytic properties. This basic assumption was formalized in the Tension Reduction Hypothesis (TRH) (Conger 1956). Despite the failure of experimental tests of the TRH to provide consistent support for its predictions, its assumptions continue to guide much of the research into the interaction of ethanol and stress. Another view of ethanol's interaction with stress has been suggested by Volpicelli (1987) as the Opioid Compensation Hypothesis (OCH). This view suggests that it is ethanol's agonist action at endogenous opioid receptors following, not during, stress that underlie its reinforcing properties.

A novel way of testing the predictions of these two theoretical accounts is to utilize a behavior that is both maintained by "fear" and mediated by endogcnous opioid activity. One such behavior is the freezing response seen in rodents when exposed to a context that has been associated with an aversive environmental stimulus. The Perceptual-Defensive-Recuperative (PDR) model of fear and pain (Belles and Fanselow 1980) suggests that the endogenous opioid system has adaptive significance because it can function to reduce the probability of recuperative behavior in contexts where defensive behaviors, like freezing, would increase the probabilitv of survival. Therefore, if ethanol is administered in a situation where an animal is likely to freeze, it could potentially produce two quite different effects. If it works to reduce context fear, the amount of freezing otherwise seen should be reduced. On the other hand, if it binds to the same endogenous opioid sites that mediate freezing, it should actually increase the amount of freezing seen.

Two groups of mice were exposed to three sessions of a single 1.0 mA, 2 second inescapable footshock. On an extinction test day, one group was injected with ethanol, 1.2 g/kg ip, while the second group was injected with a comparable volume of saline. This dose of ethanol was chosen because it has been demonstrated to increase locomotor activity in mice. Ethanol, however, significantly potentiated the freezing response compared to saline (+34.9% versus +13.5%). These data suggest that ethanol's interaction with stress may be mediated by the endogenous opioid systems which are also thought to mediate the expression of the freezing response and are consistent with the OCH (Volpicelli 1987) which suggests that ethanol's reinforcing properties are mediated by the endogenous opioid system.

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DIFFERENTIAL CONTROL OF RESPONDING BY DRUG AND VISUAL CUES IN A TWO-CHOICE DISCRIMINATION TASK FOR RATS

T. U. C. Järbe, M. Kujansuu, and D. A. Mathis

Drug discrimination learning (DDL) refers to the process whereby one or more drugs acquire the capacity to differentially control the emission of responses. For example, when affected by drug A, a rat has to turn left in a T-maze to escape aversive foot stimulation; when trained nondrugged (or with drug B), a right hand turn is required to escape the maze. Most DDL research has been devoted to characterizing and categorizing drugs in terms of their pharmacological stimulus attributes. A neglected area of research concerns the possible interaction between drug stimuli and external events. Here. we examined composites of visual (light and dark) and drug stimuli [ethanol (ETOH) and pentobarbital (PB)] in controlling the choice behavior of rats. Animals discriminated between ETOH and PB in combination with light and dark (High and Low dose experimental groups), or when the visual stimuli did not co-vary with the drug stimuli (High and Low dose controls); thus, 4 groups were used. The High-dose groups discriminated between 1750 mg/kg ETOH and 17.5 mg/kg PB and the doses for the Low-dose animals were 1000 mg/kg ETOH and 10 mg/kg PB. As an example, an experimental rat had to turn left when trained with ETOH when the maze was illuminated by a 60W bulb. When trained with PB the experimental room was completely dark and escape was possible only through the right-hand side of the maze. Once discriminative control was established, mis-match tests with different doses of the two drugs were conducted in order to generate dose-generalization gradients. Two gradients were established for each compound, one for the illuminated and one for the dark maze condition. The doses ranged between 0 to 17500 mg/kg ETOH. and between 0 to 17.5 mg/kg PB for the High-dose animals. The doses for Low-dose animals ranged between 0 to 1000 mg/kg (ETOH), and between 0 to 10 mg/kg (PB). The major result was that the control over choice behavior was a function of both sets of stimuli, the control by the visual cues being less with higher as compared to lower drug training doses. The performance of the controls did not differ between the lighted as compared to the dark maze condition. Thus, these data help delineate the interaction between interoceptive and exteroceptive stimuli in the control of behavior.

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INCOME AND DRUG VS NONDRUG CHOICE IN MONKEYS

J. S. Rodefer and M. E. Carroll

The purpose of the present experiment was to examine the effects of an alternative nondrug reinforcer on drug consumption under conditions of varied income (session length). Six rhesus monkeys self-administered orally-delivered PCP (0.25 mg/ml) and saccharin (0.03% or 0.3% wt/vol) or water under concurrent fixed-ratio (FR) schedules under three income conditions (20.60 or 180 min). The FR requirement for PCP was changed nonsystematically from 4 to 8, 16, 32.64 and 128, while the FR value for water and saccharin remained at 32.

Changes in income level had a greater effect on saccharin than on PCP deliveries. As income decreased from 180 to 20 min, saccharin deliveries decreased by approximately 90%. while PCP deliveries decreased by approximately 54%. These differential changes resulted in differences in relative preference for PCP vs. saccharin. At intermediate PCP FRs (16 and 32). preference for PCP vs. saccharin was reversed at the high and low income conditions.

Demand for PCP was evaluated by plotting PCP consumption (mg) as a function of unit price (responses/mg). When the PCP FR was increased, deliveries decreased in a positively decelerating fashion. This decrease in demand for PCP was enhanced from 20% to 70% when saccharin (vs. water) was concurrently available. The decrease in PCP due to saccharin was enhanced at the two highest PCP FRs; however, the effect of saccharin was not altered by changes in income. The present results indicate that income level and the availability of nondrug alternative reinforcers independently alter the demand for drug.

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TOLERANCE TO THE DISCRIMINATIVE STIMULUS EFFECTS Δ^9-THC

J. L. Wiley, R. L. Barrett, R. L. Balster, and B. R. Martin

Although tolerance to a variety of behavioral and physiological effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) has been demonstrated previous studies have reported that tolerance to the discriminative stimulus effects of Δ^9-THC does not develop when discrimination training is continued during repeated administration. The present study investigated development of tolerance to the discriminative stimulus effects of Δ^9-THC under conditions of supplemental administration during suspended training. Rats, trained to discriminate Δ^9-THC (3 mg/kg) from vehicle in a two-lever drug discrimination procedure under a fixed-ratio 10 schedule of food reinforcement, were tested with cumulative doses of Δ^9-THC before and after repeated administration of vehicle and of high doses of Δ^9-THC. Following suspended training with repeated vehicle injection, the Δ^9-THC dose-effect curve for percentage of drug-lever responding showed little change from the pre-vehicle curve. After supplemental administration of Δ^9-THC, the degree of rightward shift in the post-THC dose-effect curve was 40-fold. Recovery to pre-THC levels of percentage of drug-lever responding was observed during a second post-THC dose-effect curve administered twenty-three days later. The reversible large shift in the dose-effect curve following supplemental administration of Δ^9-THC suggests that tolerance developed to the discriminative stimulus effects of Δ^9-THC under suspended training conditions.

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AVAILABILITY OF INTRAVENOUS Δ^9-TETRAHYDRO/ CANNABINOL UNDER A FIXED-INTERVAL SCHEDULE IN MONKEYS

R. S. Mansbach, K. Nicholson, and **R. L.** Balster

The lack of procedures which can unequivocally demonstrate cannabinoid self-administration in animals has been an obstacle to the study of the neural basis for the reinforcing effects of this drug class. Because Δ^9-tetrahydrocannabinol (Δ^9-THC) produces a relatively slow-onset, long-lasting behavioral effect, a self-administration procedure with widely spaced drug deliveries was evaluated as an alternative to fixed-ratio schedules which typically require frequent, closely spaced injections to demonstrate reinforcing effects. Three adult male rhesus monkeys were surgically implanted with intravenous catheters and trained to self-administer phencyclidine (PCP) under a 10-mm fixed-interval schedule of reinforcement. Three injections were available each day, separated by 2-h periods during which responding had no programmed consequences. In an attempt to link the effect of the drug with the response which produced it, each 20-s injection was paired with a red light which remained illuminated for 10 min. PCP (100 mg/kg/injection) maintained steady rates of responding during each availability period, ranging from approximately 0.2 to 0.7 responses/s. During 7-day substitution periods, Δ^9-THC (17-100 mg/kg/injection) maintained low rates of responding which occasionally surpassed those during vehicle substitutions, but fell far below rates maintained by PCP. Substitution tests with the potent Δ^9-THC analog CP 55,940 also resulted in low rates of responding. These results demonstrate that Δ^9-THC is a poor reinforcer in animals, even under conditions where some of its unfavorable biodispositional properties are taken into consideration.

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ABUSED ANABOLIC STEROIDS INDUCE RAPID ONSET OF ANXIOLYTIC-LIKE BEHAVIORS IN MICE

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The small body of evidence for the behavioral and neurochemical effects of abused anabolic steroids stresses the necessity for further investigation of both acute and chronic administration studies to elucidate their actions. We have observed anxiolytic-like effects for an acute administration of nandrolone (N), fluoxymesterone (F), and boldenone (B), 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 min. after IP injection of the steroid. There were large dose dependent reductions in aversive behaviors with no changes in locomotor activity. The estimated ED50 values for F, N, and B were 0.04, 0.47, 1.8 and µg/kg respectively (0.15, 1.40 and 6.28 nmoles/kg). Effects of N and F were more potent when compared to testosterone (T), dihydrotestosterone (DHT), estradiol (E), dexamethasone (DEX), and androsterone (A). The ED50 values for T and DHT were 0.032 and 0.06 mg/kg respectively (110 and 210 nmoles/kg). A, a metabolite of T that has no virilizing capacity, was inactive in this assay. The non-anabolic steroids E, an estrogen, and DEX, a glucocorticoid, did demonstrate some activity. The E and DEX ED50 values were respectively 0.3 and 0.25 mg/kg (1100 and 637 nmole/kg). Progesterone, a progestin, and aldosterone, the mineralocorticoid, were found to be inactive in this assay. The action of DHT implicates an androgen binding site due to the fact that it cannot be metabolized to estrogen. The typical androgenic effects are mediated by changes in gene expression which takes hours or days to occur. The rapid behavioral changes that we have observed indicate the presence of an androgen binding site in the brain that modulates non-sexual behaviors.

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THE USE OF A SUBCUTANEOUS INTRAVENOUS PORT SYSTEM IN RHESUS MONKEYS TO STUDY THE REINFORCING EFFECTS OF DRUGS OF ABUSE

F. H. Wojnicki, J. D. Bacher, and J. R. Glowa

Self-administration studies in monkeys are facilitated by using chronic indwelling venous catheters. Often these catheters are exteriorized through the skin. Complications of exteriorized chronic catheter implants include accidental trauma to the catheter, as well local or systemic infections. We have developed the use of a chronic indwelling catheter system placed in the internal jugular vein and connected to a subcutaneously implanted vascular access port for use in self-administration studies. The port is commercially available, and can be attached to several different catheter materials. Our current system employs the use of a 5 French polyurethane catheter with a hydromer coating. This Hydrocath catheter system reduces platelet adhesion and bacterial clustering. Polyurethane, while firm for insertion, quickly softens at body temperature to enhance compliance. The average life of the catheter is yet to be determined. With daily use, some have been in operation for well over a year without problems. We have not yet experienced loss through clotting within the catheter, although one monkey developed a thrombus at the tip. The catheter permits blood draws, and can be used arterially. In chaired monkeys, the catheter can be effectively used without jackets. With home cage tethering systems and jackets, the port can be accessed continuously, if the line is protected. This method is a potential advance over previous intravenous catheter systems because it extends the life of the catheter, minimizes the potential health risks to the monkeys, thus reduces the number of experimental animals required for a particular study.

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REINFORCING DRUGS PRODUCE TASTE AVOIDANCE, BUT NOT TASTE AVERSION

L. A. Parker

The nature of flavor-drug associations produced by rewarding and nonrewarding drugs were assessed in taste reactivity (TR) test, as well as the conditioned taste avoidance (CTA) test. The TR test serves as a direct measure of palatability. Although both rewarding and nonrewarding drugs produce avoidance of a flavor as assessed by the CTA test, only nonrewarding drugs produce an hedonic shift in the palatability of the flavor that reflects a taste aversion.

An analysis was presented that included various groups of rats that had received an intraoral infusion of .5 M sucrose solution followed on each of 5-6 trials with one of various doses of a variety of agents including: Amphetamine (1-10 mg/kg. ip), cocaine (5-40 mg/kg, sc), methamphetamine (1-10 mg/kg, ip), methylphenidate (5-30 mg/kg, ip), morphine (2-80 mg/kg, ip), nicotine (.4-2 mg/kg, sc), phencyclidine (.5-20 mg/kg, sc) and lithium (12-50 mg/kg, ip). At doses that produced equivalent strength CTAs, rewarding drugs (as assessed by place conditioning) did not produce aversive taste reactions (which reflect unpalatability), but nonrewarding drugs did produce aversive taste reactions. The CTA produced by nonrewarding drugs, but not rewarding drugs, may thus be motivated by a shift in the palatability of the drug-paired flavor. The TR test may provide an alternative means of assessing the rewarding properties of drug agents.

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CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY (CANTAB): APPLICATION TO NEUROPSYCHOLOGICAL ASSESSMENT IN RHESUS MONKEYS

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A computerized, neuropsychological testing battery is being developed to be used for detecting changes in cognitive performance in rhesus monkeys produced by various manipulations thought to improve or impair memory. The apparatus consists of a microcomputer installed with a touch sensitive screen and CANTAB Software package (Paul Fray Ltd., Cambridge, UK) featuring tasks designed to probe different aspects of cognitive function and enabling the construction of performance profiles. The monkeys are tested in a transport cage and respond by touching the computer screen to obtain food reinforcement. Attentional set-shifting is measured using an intra-dimensional (ID)/extra-dimensional (ED) shift paradigm consisting of 4 stages which include a simple discrimination, compound discrimination, ID shift and ED shift. Rhesus monkeys (N=5) exhibit improved performance across learning sets as reflected by progressively fewer trials to criterion on each successive stage. Superior performance on the ID shift compared to previous stages is interpreted as selective attention to the relevant dimension of the stimuli which was not disrupted by introduction of novel exemplars. Short-term memory as well as visual discrimination ability are measured using a delayed non-matching to sample task. Task difficulty is manipulated by varying the delay between the offset of the sample stimulus and the presentation of the choice stimuli from 0 to 16 seconds. A simultaneous condition is also included to control for perceptual/attentional and performance difficulties. The two monkeys trained in this task perform in the range of 70% to 90% correct for the shorter delays, dropping below 60% correct for the longest delay. Working memory is evaluated using a spatial working memory task. In this task a number of boxes is displayed on the screen and the monkey must select each box only once within a trial. Blanking the screen (0.5 seconds) after each response within a trial, and increasing the number of boxes (2-7) between trials are used to place an increasing demand on memory processes. On the two box condition, performance is consistently 90-100% correct, and as the number of boxes increases, performance progressively declines. Motor coordination is assessed with a bimanual motor task in which the monkey has to use both hands to retrieve raisins from a holeboard mounted perpendicular to the door of the transport cage. Experienced monkeys routinely retrieve all of the raisins in under 2 minutes. Motivational state will be assessed using a progressive-ratio schedule for food reinforcement. Advantages of such a test battery are ease of administration, flexibility in terms of tests that can be developed, and repeatability. Rhesus monkeys are able to be trained on multiple tasks within the battery and perform at a level intermediate to that of marmosets and humans. Rhesus monkey performance profiles generated using this battery can be used to study the CNS changes associated with acute and chronic exposure to drugs of abuse and drug abstinence, as well as providing a model for testing potential psychotherapeutic agents. Direct comparison of data collected in rhesus monkeys with performance profiles collected in patient populations and marmosets with site-specific lesions will aid in the interpretation of results on a neuroanatomical level.

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INDIVIDUAL DIFFERENCES IN THE EFFICACY OF MORPHINE-INDUCED ANALGESIA ARE MEDIATED BY DELTA-SENSITIVE MECHANISMS

G. I. Elmer and S. R. Goldberg

Individual differences in the potency and efficacy of morphine-induced analgesia are, in part, related to genetic factors. The purpose of the current study was to investigate the possible pharmacological mechanisms underlying genetic differences in the efficacy of opioid-induced analgesia.

Genetic differences in the efficacy of morphine were determined via three methods in eight inbred mouse strains; **1)** administration of an equi-active dose of morphine for each respective strain at increasing stimulus intensities, **2)** determination of ED_{50} values at 51, 55 and 57 °C via full dose-response analysis and subsequent linear interpolation of the slope of the ED_{50} values from 51 to 57 °C and **3)** construction of stimulus-effect functions using an *in vivo* method of partial irreversible receptor blockade. The mechanisms underlying the observed genetic variation in efficacy were determined via analysis of dose-ratios for antagonism of morphine-induced analgesia. Yohimbine, nor-BNI and cinanserin antagonism of morphine-induced analgesia was determined in three of the strains and naltrindole in all eight. The dose-ratios for yohimbine, nor-BNI, cinanserin and naltrindole were correlated with efficacy values as determined by methods one and two and were used as fitting parameters for stimulus effect functions generated in method three.

The results suggest that relative sensitivity to naltrindole antagonism of morphine-induced analgesia was significantly correlated with the efficacy of morphine-induced analgesia as determined by all three methods. Dose-ratios for adrenergic, kappa and serotonergic antagonists did not correlate with efficacy values determined by the three methods. Further studies investigating the pharmacological and biochemical mechanisms important in the efficacy of opioids may be useful in determining the role of delta mechanisms in an individuals response to additional opiate-mediated phenotypes such as respiratory depression and addiction.

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THE EFFECTS OF TRIMU5, A μ2-OPIOID AGONIST ON PLASMA CORTICOSTERONE

R. M. Eisenberg

Previous work in our laboratory has shown that DAMGO (i.c.v.) will cause an elevation in plasma corticosterone (CS). The effect was blocked by pretreatment with ßFNA but not by naloxonazine, suggesting indirectly that DAMGO's effect was via a μ2-opioid receptor. TRIMU5, a μ2-agonist/μ1-antagonist, was tested in a similar series of experiments to show more directly that the effect of DAMGO to increase plasma CS was via the μ2- receptor. 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. TRIMU5, 50μg, produced a sustained increase in plasma CS for a 3 hr period. The response peaked at 30 min showing a plasma CS level of 19.7 ± 1.4 μg/dl. A lower dose, 10μg, did not produce a significant response. A higher dose, 100μg, produced an elevated hormone response in a pilot study but was lethal in half the animals. The plasma CS increase was blocked by pretreatment with ßFNA, 20μg i.c.v., given 18 hrs before TRIMU5 but unaffected by naloxonazine pretreatment, 20mg/kg i.v. These data confirm our earlier conclusion that the effect of DAMGO to elevate plasma CS was through a μ2-opioid receptor.

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INTERACTION BETWEEN KAPPA-SELECTIVE OPIOID AGONISTS AND NEUROTENSIN MODULATES BODY TEMPERATURE IN THE RAT

C. M. Handler, E. A. Bradley, E. B. Geller, and M. W. Adler

Previous work has demonstrated that hypothermia may be induced by either κ-selective opioid agonists or neurotensin (NT). We injected dynorphin A_{1-17} (DY), U50,488H (U50) and NT alone and in combination to see if the interaction between κ-selective opioid agonists and the neuromodulator would have a synergistic effect on body temperature (Tb) similar to that seen when U50 is given in combination with chlorpromazine (Adler & Geller, Eur J Pharmacol., 140, 1987). DY, U50 and NT were injected into unrestrained, male S-D rats, and Tb was monitored for 3 hr post-injection at 20° C ambient. NT, DY and U50 induced dose-dependent hypothermia (max ΔTb: NT -2.81° C, 0.125-100 µg, icv; DY -1.99° C, 0.1-50 µg, icv; U50 -3.82° C, 2.5-160 mg/kg, sc). In the combination experiments, a single dose of the κ-selective agonist was tested over a range of NT doses. DY/NT (10 µg/0.125-2.5 µg) failed to induce hypothermia that differed significantly from either NT- or DY-induced hypothermia. U50/NT (40 mg/kg/0.125-5.0 µg) significantly increased the hypothermia seen with either NT or U50 alone. Pretreatment with the κ-selective antagonist, nor-BNI (25 nmol, 30 min), partially blocked the combination-induced hypothermia while naloxone (10mg/kg, sc, 15 min pre-treatment) completely blocked the κ-mediated component of the combination hypothermia. The small number of centrally located κ receptors may account for the ineffectiveness of the DY/NT combination on Tb. The synergistic hypothermia induced by U50/NT may be due to the combination of central and peripheral mechanisms brought into play through sc administration of U50.

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MODULATION OF OPIOID MU RECEPTOR DENSITY BY THE ENDOGENOUS ANTI-OPIOID PEPTIDE, NPFF

C. B. Goodman, J. L. Cadet, M. H. Baumann, H.-Y. T. Yang, C.-H. Lee, and R. B. Rothman

A variety of data support the hypothesis that endogenous anti-opioid peptides function as modulators of opioid activity, Previous studies from our laboratory indicated that whereas chronic i.c.v. infusion of NPFF down-regulated, chronic i.c.v. infusion of purified polyclonal anti-NPFF 1gG up-regulated mu opioid receptors. The present study used purified mouse monoclonal anti-NPFF 1gG which selectively binds NPFF. Rats were administered control 1gG (1μg/μl) or monoclonal 1gG diluted with control mouse lgG (1μg/μl) via i.c.v. cannula placed in the left lateral ventricle and attached to ALZET 2002 osmotic minipumps (0.5 μl/hr for 13 days). The doses of monoclonal 1gG used were 0.1 μg/μl, 0.01 μg/μl, and 0.001 μg/μl. On day #13 of the infusion, the rats were sacrificed, the brains removed, and then kept frozen at -70°C. On the day of the assay, membranes were prepared from whole brain, and the Bmax and Kd of mu receptors were determined using [^{3}H]DAMGO. The data indicated that chronic i.c.v. infusion of mouse monoclonal anti-NPFF lgG produced a dose-dependent up-regulation of mu receptors to 102%. 128%. and 172% of control at the 0.001, 0.01, and 0.1 μg/μl dose, respectively. Viewed collectively with other information, these data suggest that the density of mu opioid receptors in rat brain is tonically controlled by NPFF.

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ISOLATION OF OPIATE AND "ANTI-OPIATE" PEPTIDES FROM HUMAN PLASMA

J. S. Partilla, J. You and R. B. Rothman

According to the anti-opioid peptide model of tolerance and dependence, the CNS secretes certain peptides which attenuate the effects of morphine and endogenous opioids. Evidence from several laboratories indicate that these anti-opioid peptides (AOPs) may be involved in the development of opioid tolerance and dependence. In order to assess whether opiate abuse alters plasma and CSF levels of AOPs and endogenous opiates (OPs), an assay system which couples reverse-phase HPLC resolution of AOPs and OPs with RIA quantitation was undertaken, with the goal being to be able to quantitate several peptides from one sample. Initial experiments involved spiking aliquots of pooled HCl-acidified (0.1N final) plasma with UV-detectable amounts of selected AOPs and OPs in order to verify HPLC retention time consistency and to determine recovery. Retention time consistency was maintained with high levels of AOP and OP recovery: **1)** by diluting 1 ml plasma aliquots to 10 ml with 4% acetic acid prior to loading onto a C-18 Sep-Pak; **2)** by eluting the Sep-Pak and redissolving dried samples with ethanol:acetic acid:water 90:6:4; **3)** by controlling the flow rate through the Sep-Pak (10 ml/min), and 4) by using only polypropylene tubes throughout the procedure. Peptide recovery values are: met-enkephalin 98%, dynorphin A 81%, big dynorphin 33%, big dynorphin$_{1\text{-}24}$ 81%, ß-endorphin 80%, ß-endorphin$_{1\text{-}27}$ 88%, NPFF 58%, and dynorphin B 92%. CCK-8 and substance P had low recoveries, indicating that further modifications will be required. We are currently using this method in conjunction with RIA to determine the effect of drug abuse and chronic pain on the levels of AOPs and OPs in plasma and CSF.

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DISPOSITION OF [^{3}H]IBOGAINE IN THE RAT

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Ibogaine, a psychotropic indole alkaloid, is of interest due to the reported ability of a single oral treatment to eliminate the desire for opiate and stimulant drugs for extended periods (US Pat 4,499,096 and 4,587,243). To better understand the disposition of this potential treatment drug, we gave single doses of [^{3}H]ibogaine at dose levels of 5 and 50 mg/kg po and 5 mg/kg iv to 4 young adult CD rats of each sex. A total of 10 blood samples of ca. 0.15 g each were collected over 24 h from an indwelling jugular cannula implanted the day prior to dosing. Animals were then sacrificed and selected tissues were removed. Approximately 60-70% of the dose was excreted in urine and feces during the 24 h duration of each study. Similar values had been obtained for 24 h excretion in pilot studies, with total excretion over 6 days averaging 78% dose. Highest concentrations of radiolabel at sacrifice were in liver (0.5-1% dose), spleen, kidney and in the gastrointestinal tract (ca. 10% dose).

The systemic clearance of intravenously administered ibogaine was extremely rapid (7-10 L/h/kg), exceeding hepatic plasma flow by a factor of 3-4 and suggesting that extra hepatic clearance of this compound may be significant. Terminal half-life was estimated at 2.8±0.5 (SD) h. Differences in kinetic parameters between male and female rats were not statistically significant.

After the 5 mg/kg oral dose, peak plasma levels of ibogaine were ca. 30 ng/g plasma in females and 10 ng/g plasma in males. Areas under the concentration-time profiles (AUC) in females were more than twice those for males. Much higher plasma concentrations of ibogaine were found after the 50 mg/kg dose. Peak plasma levels were 180-430 ng/g plasma and AUC values were 45-59 times the corresponding values for the 5 mg/kg dose. Oral bioavailabilities after the 50 mg/kg dose were 43% in males and 71% in females. Gender differences were also apparent at the 5 mg/kg oral dose, with bioavailabilities of 7% in males and 16% in females. This dose-dependent bioavailability suggests that ibogaine absorption and/or first pass loss is nonlinear. Moreover, the mean residence time was increased markedly at the high dose in female, but not male, rats suggesting that the kinetics of absorption may be different between genders.

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CARDIOVASCULAR EFFECTS OF PHENCYCLIDINE IN PREWEANLING AND WEANLING RATS

F. M. Scalzo and L. J. Burge

Developmental exposure to phencyclidine (PCP) has been shown to have adverse neurobehavioral effects, however the cardiovascular effects of such exposure are poorly understood. To assess the adverse effects of PCP on cardiovascular and autonomic development, we examined the effects of PCP on blood pressure (BP) and heart rate (HR) in rats at four stages of autonomic development. Rats were instrumented with a carotid and jugularcannula on postnatal day (PND) 14-15, 16-17, 18-19 or 20-21. Twenty-four hours later, 0.625, 1.25, 2.50 or 5.00 mg/kg PCP was administered (iv) and BP, HR and locomotor activity were recorded for one hour. On PNDs 15-18, PCP had inconsistent effects on BP and HR at the lowest dose tested, whereas on PND 21-22, a 20 mm Hg BP increase and a brief bradycardia, followed by a 60 bpm HR increase, were observed. At 1.25 mg/kg and above, PCP increased BP (10-40 mm Hg), with PND 21-22 rats exhibiting the largest BP increases (approx. 40 mm Hg) with the longest durations (approx. 45 min.). PCP produced transient bradycardia at all ages at doses of 1.25 mg/kg and above. This HR decrease was 125 bpm at some ages and lasted 5-7 min on PNDs 15-16. This bradycardia was followed by a return to baseline or tachycardia, depending on the dose and age tested. The data demonstrate ontogenetic and dose-dependent changes in the cardiovascular response to PCP that parallel the maturation of autonomic regulation of cardiovascular function. This change in responsiveness might indicate periods of differential susceptibility to the adverse effects of PCP on cardiovascular and autonomic function.

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RTI4793-14, A NEW LIGAND WITH HIGH AFFINITY AND SELECTIVITY FOR PCP SITE 2

B. Emilien, C. B. Goodman, F. I. Carroll, B. E. Blough, M. A. Rogawski, S. Subramaniam, and R. B. Rothman

[^{3}H]TCP, an analog of the dissociative anesthetic phencyclidine (PCP). binds with high affinity to two sites in guinea pig brain membranes, one which is MK-801 sensitive and one which is not. The MK-801-sensitive site (PCP site 1) is associated with NMDA receptors whereas the MK-801-insensitive site (PCP site 2) may be associated with biogenic amine transporters (BAT). Although several "BAT ligands" are known which bind selectively to PCP site 2 and not to PCP site 1 (such as indatraline), these compounds have low affinity for site 2 (Ki values > 1 μM). Here we demonstrate that the novel RTI-4793-14 is a selective, high affinity ligand for PCP site 2. We determined the IC_{50} values of RTI-4793-14 and several reference compounds [PCP, (+)-MK801 and indatraline] for PCP site 1 (assayed with [^{3}H](+)-MK801), PCP site 2 (assayed with [^{3}H]TCP in the presence of 500 nM (+)-MK801) and a variety of BAT-related measures ([3H]CFI binding to the DA transporter, [^{3}H]nisoxetine binding to the norepinephrine transporter, [^{3}H]dopamine uptake, [^{3}H]serotonin uptake). In addition, we determined the ability of RTI-4793-14 to block NMDA responses in cultured hippocampal neurons under voltage clamp. (+)-MK801 had high affinity for PCP site 1 (4.6 nM), potently inhibited NMDA-induced responses, but was much less potent in BAT-related measures (IC_{50}s > 10 μM). PCP had high affinity at PCP site 1 (IC_{50} = 92 nM) and PCP site 2 (IC_{50} = 117 nM), and was moderately potent in all BAT-related measures except [^{3}H]nisoxetine binding. Indatraline was potent in BAT-related measures (IC_{50}s, 3 to 5 nM), but weak in other measures (IC_{50}s > 1 μM). In contrast, RTI-4793-14 had high affinity for PCP site 2 (38 nM), low affinity for PCP site 1 (>36 μM), moderate IC_{50}s for all BAT-related measures, and negligible activity at NMDA receptors. Viewed collectively, these data indicate that RTI-4793-14 binds with high affinity and selectivity to PCP site 2 and provides further support for an association between PCP site 2 and the BATs.

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Δ^9-TETRAHYDROCANNABINOL'S ENHANCEMENT OF NUCLEUS ACCUMBENS DOPAMINE RESEMBLES THAT OF REUPTAKE BLOCKERS RATHER THAN RELEASERS - EVIDENCE FROM *IN VIVO* MICRODIALYSIS EXPERIMENTS WITH 3-METHOXYTYRAMINE

J. Chen, W. Paredes, and E. L. Gardner

We previously reported that Δ^9-tetrahydrocannabinol (Δ^9-THC), marijuana's psychoactive constituent, enhances electrical brain-stimulation reward in the medial forebrain bundle and enhances extracellular dopamine (DA) efflux in the reward-relevant nucleus accumbens (NAcc), actions presumably related to marijuana's abuse potential (Gardner and Lowinson 1991). We also previously reported that Δ^9-THC's DA-enhancing effect appears to resemble that produced by DA reuptake blockade rather than enhanced DA release (Ng Cheong Ton *et al.* 1988; Gardner *et al.* 1990). The DA metabolite 3-methoxytyramine (3-MT) has been suggested as a biochemical index of enhanced extracellular DA (Wood and Altar, 1988) and as a sensitive marker for distinguishing between DA releasing agents and reuptake blockers (Heal *et al.* 1990). We now report the effects on NAcc extracellular 3-MT of Δ^9-THC as compared to well-characterized DA releasers and reuptake blockers, using *in vivo* brain microdialysis in freely moving rats. Amphetamine (0.5 mg/kg) significantly increased both DA and 3-MT in NAcc, while the DA reuptake blockers cocaine (10 mg/kg) and nomifensine (1.0 mg/kg) increased only DA. Δ^9-THC increased only DA, resembling the pattern of the DA reuptake blockers.

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POSSIBLE CONDITIONING EFFECTS OF INTRAVENOUS COCAINE ON PUPILLARY DIAMETER

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Stimuli paired with cocaine injections acquire incentive motivational properties. Classical conditioning using cocaine as the unconditioned stimulus is readily found in humans. Some studies suggest that conditioned drug effects play a critical role in the relapse of opiate as well as cocaine addicts. Understanding the neurochemical mechanisms which mediate the acquisition of the unconditioned stimulus properties of cocaine, as well as their expression, may be a crucial first step in the process of developing medications to facilitate abstinence in a clinical setting.

Weiss, Post and Pert (Pharmacol. Biochem. Behav. 34:655-661; 1989) introduced a simple and powerful one-session conditioning paradigm with cocaine to characterize the unconditioned stimulus properties of cocaine in rodents. Their results indicate that conditioning plays a major role in the development of behavioral sensitization. A clinical research protocol similar to that used in rodent studies was designed to determine if context-dependent cocaine-conditioning could be demonstrated in humans. End-point measures included subjective-effect scales, vital signs, EEG, motor activity as measured by wrist activity meters, pupil-responses and plasma prolactin. The physiological data and limited subjective effects data are presented in this volume by Rothman *et al.* The pupil-response data are presented here.

Details on subject characteristics and experimental design can be found in the Rothman *et al.* paper in this volume. Pupillary diametere was measured using a pupillometry system. To mimic the rodent studies, injections were given in two locations: a home room (mimics the 'home cage') and a test chamber. On the conditioning day (day #1) subjects received two injections: one in the home room and the other in the test chamber. Three groups of subjects received either saline/saline, cocaine/saline, or saline/cocaine in this respective order. Thus, for one group the cocaine injection was PAIRED with the test chamber and for the other group the cocaine injection was UNPAIRED. The dose of cocaine was 40 mg. given intravenously. On the test day (day #2), either cocaine (25 mg, IV) or saline was given in the test chamber. Pupillary diameter was measured at time baseline, 10 and 60 minutes after drug or saline administration.

Cocaine caused a small transient increase in pupillary size which was dose-dependent. There was some evidence for sensitization in the pupillary diameter response in the UNPAIRED group when cocaine was administered in the morning, but not in the afternoon. This result tentatively suggests a role for diurnal changes in the neurotransmitters which affect pupil diameter. These preliminary findings should be replicated with a greater number of subjects than used in this analysis (n=3-4).

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COMPARATIVE STUDY OF THE EFFECTS OF COCAINE ON EXTRACELLULAR NOREPINEPHRINE IN THE ANESTHETIZED VERSUS AWAKE RAT

D. N. Thomas, R. M. Post and A. Pert

Cocaine prevents the neuronal uptake of catecholamines and indoleamines. There is extensive literature to suggest that alterations in dopaminergic function underlie the majority of the behavioral effects of psychomotor stimulants. However considerably less is known about the actions of cocaine on the norepinephrine (NE) system. In the present study using the technique of *in vivo* microdialysis we have characterized the effects of systemic and focal administration of cocaine on extracellular NE in the frontal cortex. hippocampus and the region of the locus coeruleus.

Systemically applied cocaine (20mg/kg) appears to have no effect on NE in either the frontal cortex or the hippocampus of the anesthetized rat. However, in the region of the locus coeruleus systemic cocaine increased the extracellular NE by 170% above the baseline. This increase in locus coeruleus NE may explain the lack of effect in the terminal regions, since increasing the extracellular concentration of NE at the cell bodies would reduce the cell firing and hence the tonic overflow in the terminal regions. Focal application of cocaine via the dialysis probe in these animals showed differential effects in the two regions. In the hippocampus, cocaine (1 - 100μM) produced a concentration dependent increase in extracellular NE in of 34%, 86% and 110% respectively. However, in the frontal cortex only the highest concentration (100μM) produced any significant increase in extracellular NE (69%).

In the awake freely moving animal systemic cocaine (20mg/kg) increased extracellular NE in the frontal cortex by 150% above basal with the effect lasting for 75 mins post injection. Cocaine methiodide which is unable to cross the blood brain barrier had no effect on extracellular NE at a equimolar dose of 26 mg/kg. The disparity between the awake and anesthetized animal may be due to the presence of anesthesia which suppresses the response to cocaine in the terminal regions. A hypothesis for the mechanism of this suppression may have its origins in the animals stress axis, in particular the involvement of the corticosteroids. Our present data shows that cocaine elevates the plasma corticosterone levels 250% above resting levels, whilst the peripherally acting analogue cocaine methiodide merely increases the plasma corticosterones by 60%.

In an attempt to elucidate whether corticosterone may be involved in the cocaine induced increase in extracellular NE in the awake freely moving animal we have administered corticosterone (5mg/kg, s.c). The present data shows a slight increase (20%) in the extracellular NE in the frontal cortex. Although this increase is significantly less than that observed with cocaine it may provide an explanation for the disparity between the awake and the anesthetized animal preparation.

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MICROINJECTION OF IDAZOXAN INTO ROSTRAL VENTROLATERAL MEDULLA ATTENUATES THE SYMPATHOINHIBITORY RESPONSE ELICTED BY COCAINE

T. P. Abrahams, M. Cuntapay, and K. J. Varner

Recent reports have shown that cocaine decreases, rather than increases sympathetic nerve discharge. The central or perioheral mechanism(s) responsible for this sympathoinhibitory (SI) response are unknown. The purpose of the present study was to determine whether neurons in rostral ventrolateral medulla (RVLM) are involved in the SI response elicited by cocaine. Pentobarbital-anesthetized; mechanically-ventilated male Sprague-Dawley rats were used in all studies. Renal-(RSND) or splanchnic sympathetic nerve discharge (SSND) were recorded using bipolar platinum electrodes. RVLM was functionally identified by the microinjection of glutamate (30 nl of 10 mM). Idazoxan, an α_2-adrenoceptor antagonist with nanomolar affinity for imidazoline receptors was bilaterally microinjected (3.0 nmol/50 nl) into RVLM in an effort to block the SI responses elicited by cocaine (1 mg/kg, i.v.). The bilateral microinjection of saline (50 nl, 0.9%) was used in control experiments. After microinjection of saline, cocaine increased mean arterial pressure (MAP) 21±2 mmHg (n=5) and decreased SSND 59±8% (n=5) and RSND 56±14% (n=5). After bilateral microinjection of idazoxan, the pressor response elicited by cocaine (24±2, n=5) was not different from control, nor was the peak decrease in SSND (46±5%, n=5) different. However, the peak decrease in RSND (22±16%, n=5) was attenuated. After saline microinjection, the duration of the SI responses were 35±4 (SSND) and 24±6 min. (RSND). After microinjection of idazoxan the duration of the SI responses were significantly reduced to 11±2 min. (SSND) and 8±2 min. (RSND). We conclude that neurons in RVLM play a major role in mediating the magnitude and duration of the SI responses elicited by cocaine via an α_2-adrenoceptor mechanism.

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CORONARY VASCULAR EFFECTS OF COCAINE IN CONSCIOUS AND ANESTHETIZED RATS

P. J. Mueller and M. M. Knuepfer

The coronary vascular effects of cocaine (COC) are not clearly understood. COC has been shown to increase (Lange *et al.,* 1989) and have no effect (Majid *et al.,* 1992) on coronary vascular resistance (CVR) in humans. Therefore, we examined the effects of COC (5 mg/kg, *i.v.)* on coronary blood flow (CBF) and other cardiovascular parameters in anesthetized rats. Prazosin (0.1 mg/kg) was used in some experiments to determine the role of α_1-adrenergic receptors in these responses. COC elicited a decrease in heart rate (HR), rate-pressure product (RPP), cardiac output (CO), and CBF. Cocaine administration also resulted in an increase in CVR and a biphasic presser/depressor response. Decreases in CO were correlated with decreases in CBF, but not with increases in CVR. CBF was correlated with RPP, suggesting that CBF was reduced as a result of a decrease in metabolic demand. Prazosin reduced the initial decrease in HR and CO, but had no effect on CBF or CVR responses.

Since anesthesia alters the coronary vascular effects of cocaine in dogs (Fraker *et al.,* 1990). we compared CBF responses in conscious and anesthetized rats. Unlike results found in anesthetized rats, cocaine elicited a sustained pressor response in conscious rats without affecting CBF. Cocaine administration produced similar increases in CVR and decreases in HR in conscious and anesthetized animals. Prazosin abolished the pressor response as well as the increase in CVR. The results of these studies suggest that coronary vascular responses to cocaine are altered by anesthesia. Furthermore, α_1-adrenoceptors appear to be involved in these responses in conscious, but not anesthetized rats. We speculate that the determinants of myocardial oxygen demand differ under anesthesia and may explain disparate responses to cocaine observed in conscious and anesthetized animals.

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IMPORTANCE OF CARDIAC OUTPUT MEASUREMENTS IN EVALUATING DRUG INTERACTIONS WITH COCAINE

Q. Gan and M. M. Knuepfer

Cocaine abuse has been associated with life-threatening cardiovascular responses in susceptible individuals. We reported (Branch and Knuepfer 1993) that cocaine (1 or 5 mg/kg, *i.v.)* elicited similar arterial pressure (AP) and heart rate responses in conscious rats but in only 1/2 of the rats studied cocaine produced a decrease in cardiac output (CO). This subset, named responders, also has an increased incidence of cocaine-induced cardiomyopathies and a decrease in CO in response to acute air jet stress (Knuepfer *et al.,* 1993). In previous studies, we observed the decrease in CO was reduced by prazosin, pentolinium, nifedipine or verapamil yet pressor responses were not reduced by the calcium channel antagonists (Knuepfer and Branch 1993; Branch and Knuepfer, unpublished data). Propranolol reduced the AP response but enhanced the decrease in CO in responders (Branch and Knuepfer, unpublished data).

In this study, we tested several agents to further characterize the pharmacological effects of cocaine in responders. Bromocryptine (1 mg/kg) or dcsipramine (1 mg/kg) pretreatment reduced the cocaine-induced decrease in CO and desipramine also reduced the pressor response. In contrast, ethanol (385 and 770 mg/kg) pretreatment reduced the AP response but enhanced the decrease in CO. In conclusion, several drugs affect the pressor and cardiac output responses differentially. We suggest that studies of potential treatments for cocaine addiction or potential drug interactions should not only examine pressor responses but also should consider cardiac output responses to cocaine and the possible enhancement of cardiomyopathies. We propose that the CO responses more closely reflect cardiotoxicity compared to AP responses.

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EFFECTS OF COCAINE, COCAETHYLENE AND NORCOCAINE ON CARDIORESPIRATORY CENTERS IN THE HINDBRAIN OF THE RABBIT

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One of the most serious complications resulting from the use of cocaine alone or together with alcohol is cardiorespiratory arrest. To investigate mechanisms underlying cardiorespiratory arrest after cocaine, we injected 1 mg of either cocaine (COC), cocaethylene (CE), norcocaine (NC) or benzyolecgonine (BE) into the vertebral artery (VA) or i.v., while monitoring arterial blood pressure (MBP), heart rate (HR) and respiratory rate (RR). The vertebral artery route is a standard method for studying drug effects on the cardiorespiratory centers of the hindbrain. When given by the i.v. route at a dose of 1 mg, all the drugs were either ineffective or had a little effect (see table). In contrast, when injected into the vertebral artery, cocaine and cocaethylene produced hypotension, bradycardia and respiratory arrest, while norcocaine had no significant effect on RR, but significantly decreased both MBP and HR. No tachyphylaxis was observed for any of the above effects. Benzoylecgonine had no significant effect on either MBP, HR or RR.

	INITIAL VALUES			PEAK CHANGES		
Drugs/route	MBP	HR	RR	MBP	HR	RR
CO VA	67±8	183±18	24±3	-25±4*	-28±6*	-24±3*
CO IV	80±8	181±4	20±3	1 ± 4	4±3	5±2
CE VA	56±6	176±10	26±2	-19±2*	-12±3*	-26±2*
CE IV	79±7	203±12	20±5	4 ± 3	28±3	6±1
NC VA	80±8	201±12	21±2	-15±4*	-6±3*	2±1
NC IV	82±5	204±4	23±2	6±4	9±5	3±1
BE VA	69±13	185±16	20±1.8	-3±4	3±4	1±1
BE IV	84±8	188±6	21±4	1±2	11±10	0±1

MBP=mean arterial blood pressure (mm Hg); HR=heart rate (beats/min); RR=respiratory rate (breaths/min), *P<.05, values are mean±S.E.M.

These data suggest that: 1) Cocaine, cocaethylene and norcocaine administered to the hindbrain had sympatholytic and parasympathomimetic effects as reflected by hypotension and bradycardia. 2) Cocaine and cocaethylene injected in the hindbrain can lead to cardiopulmonary collapse. 3) No tachyphylaxis was observed for the central cardiorespiratory effects of cocaine, cocaethylene and norcocaine. 4) As no tachyphylaxis occurred, repeated dose “bingeing,” which is a common practice among cocaine users, might lead to enhanced cardiorespiratory depression. 5) At the dose tested, neither norcocaine nor benzoylecgonine had significant effects on respiratory activity.

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CARDIOVASCULAR EFFECTS OF SMOKED COCAINE AND METHAMPHETAMINE IN SQUIRREL MONKEYS: PRELIMINARY DATA USING FORCED ADMINISTRATION

G. N. Carmona, R. M. Keenan, S. R. Goldberg and C. W. Schindler

Smoking of abused drugs has become more prevalent in recent years, primarily due to the advent of "crack" cocaine. As a result, it is important to analyze the physiological effects of drugs delivered via this route of administration. We report here preliminary data on the cardiovascular effects of cocaine base and methamphetamine smoking using a modification of the procedure originally described by Carroll *et al.,* (Psychopharm. 102: 443-450, 1990). In brief, a known amount of the drug is placed on a wire coil. The coil is placed in the middle of a chamber which consists of a small mouthpiece on one end and a larger respiration bag at the other. The mouthpiece is placed over the face of a squirrel monkey and the coil is heated rapidly to volatilize the drug while the respiration bag is gently squeezed, forcing the smoke into the mouthpiece. For control sessions, the mouthpiece was placed on the monkey's face for a comparable time, but no drug was administered. The monkeys adapted rapidly to this procedure, such that only small changes in blood pressure and heart rate were observed during control sessions. Both cocaine and methamphetamine produced increases in blood pressure and heart rate over a dose range of .3-10 mg/kg. However, dose-dependent effects were apparent only for blood pressure and methamphetamine's effect on heart was relatively small. No bradycardia was ever observed for either of the compound. Comparison to previous studies using i.v. administration of these compounds suggest that the bioavailability of drug using this procedure may be less than 50%. Nevertheless, these results do indicate that this procedure for delivering smoked drugs is effective.

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BRONCHOCONSTRICTION FOLLOWING EXPOSURE TO COCAINE TEST ATMOSPHERES

L. C. Chen, R. W. Wood, M. H. Zhong, J. F. Graefe, and J. Shojaie

Fatal bronchoconstriction can follow episodes of crack smoking. Crack smoke is an aerosol of cocaine base and its pyrolysis products. To study cardiopulmonary function in squirrel monkeys and guinea pigs, whole body plethysmographs were arranged so that respiratory flow could be measured when the animal was briefly sealed within the box. By recording the first derivative of the flow vs the first derivative of the box pressure, an index of respiratory conductance was obtained (SGaw; the Agrawal method). Reduction in SGaw occurs during bronchoconstriction. Heart rate and rectal temperature were recorded simultaneously.

Bronchoconstriction could be produced reliably by condensation aerosols of cocaine base or its pyrolysis product, methylecgonidine base. Exposure to methylecgonidine base alone was effective in producing bronchoconstriction, and was lethal to a guinea pig after 1 min x 13 mg/liter. Squirrel monkeys bronchoconstricted when administered either methylecgonidine or 5 mg/liter of cocaine. Methylecgonidine also produced decreases in body temperature and heart rate. Cocaine displayed a mixed pattern, sometimes resembling methylecgonidine, other times producing a pattern like cocaine administered intravenously; perhaps this was due to co-administration of methylecgonidine.

The mechanisms underlying bronchoconstriction and body temperature decreases following inhalation exposures arc not conclusively identified. Cocaine and its pyrolysis products may present an alkaline as well as a pharmacologic challenge to the lung. Exposure to high nebulized concentrations of the drug salts did not produce bronchoconstriction. Administration of 1.0 mg/kg of cocaine or 10 mg/kg of methylecgonidine intravenously also did not produce bronchoconstriction. This route-dependency is consistent with lung irritation. Furthermore, the body temperature decreases observed thus might be attributable to irritant elicitation of a $5HT_3$-dependent pulmonary vagal reflex that produces bradycardia and simultaneous peripheral vasodilation. Hence, the paradoxical decreases in rectal temperature observed after inhalation may result from an interaction of primary drug effects with reflex changes elicited by lung irritation.

Squirrel monkeys with a cumulative history of 22 to 24 mg/kg IV and a history of methylecgonidine inhalation exposure would not bronchoconstrict to either acetyl- or methacholine given by inhalation or intravenously, despite concurrent salivation and bradycardia. This surprising finding leads us to speculate that quatenary derivatives of methylecgonidine may be useful in the management of asthma or cystic fibrosis.

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LIQUID METHYLECGONIDINE COATS THE CRACK DROPLET

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Methylecgonidine, (anhydroecgonine methylester, MEG) is a cocaine pyrolysis product readily detected in smoke and urine. Cocaine base melts at 98°C, but its vapor pressure is not elevated below 160°C; pyrolysis occurs at only slightly higher temperatures. MEG, a liquid at 23°C, displays elevated vapor pressure at 90°C. Thus, when cocaine pyrolysis occurs, MEG flashes to vapor. As the "smoke" cools, the components supersaturate and the least volatile condense first. Cocaine condenses in milliseconds, forming a viscous droplet that solidifies slowly. As the stream cools further, MEG condenses on the large surface provided by the cocaine droplets.

Inertial impaction samples indicate that MEG and cocaine coexist as a single particle because they have the same aerodynamic diameter despite their varying airborne concentration. The pyrolysis products occur at concentrations below 10%, so the difference in diameters would be large if cocaine and methylecgonidine formed separate particles.

Upon dilution, MEG vapor pressure equilibrium is disturbed, and MEG begins to move back from the liquid to the vapor phase. We have observed that MEG is stripped from the cocaine particle when test atmospheres are diluted for optical particle sizing. To determine if cocaine and its pyrolysis products form a stable aerosol during simulated crack smoking, a pipe and screen were attached to the inlet of a 29 liter jar, a torch applied, and the atmosphere withdrawn through filters and charcoal tubes in series at 2.5 liters per minute. A fan stirring the atmosphere reduced the cocaine concentration by impaction, a single compartment elimination process that was more rapid than simple single compartment dilution. MEG followed a two-compartment elimination model. One compartment was similar to the cocaine particle component; the other was slower than would be predicted by simple dilution. This is consistent with MEG partitioning between the particle, the chamber wall, and the vapor phase. In this case, the chamber wall proved to be a significant secondary source of MEG vapor.

Crack smokers are thus likely to be inhaling MEG both as a vapor, and as MEG-coated cocaine droplets. If the airborne concentration is below saturation at a given temperature, MEG exists solely as vapor; above saturation, MEG coats the crack particle. The pharmacological interaction of MEG and cocaine await detailed characterization; because of its physical state as a vapor or as a coating on the crack particle, MEG may be more rapidly absorbed.

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COCAINE EFFECTS ON PULSATILE SECRETION OF ACTH IN COCAINE AND OPIOID DEPENDENT MEN

S. K. Teoh, Z. Sarnyai, J. H. Mendelson, N. K. Mello, S. A. Springer, W. Sholar, M. Wapler, and H. Gelles

Acute cocaine administration alters secretion of anterior pituitary hormones in humans, rhesus monkey and rats. This report describes the effects of cocaine on pulsatile secretion of ACTH in men studied under controlled research ward conditions. Seven subjects with DSM-III-R diagnosis of concurrent cocaine and opioid dependence were evaluated. Following an overnight fast, a challenge dose of cocaine (30 mg i.v.) or placebo was administered under single blind conditions in a randomized order on 2 study hays. Blood samples were collected at 2-minute interval for 76 min during the baseline and for an additional 76 minutes following challenge dose administration. The cluster analysis program originally described by Veldhuis and Johnson (1986) was used to identify ACTH pulse frequency (Iranmanesh 1990). Following cocaine administration, peak plasma cocaine levels of 271.8 ± 63.4 ng/ml were reached within 2 minutes. Acute cocaine administration significantly increased the mean peak amplitude ($P<0.02$), total area under the curve ($P<0.02$) and mean valley levels ($P<0.03$) of pulsatile ACTH episodes, without alteration of ACTH pulse frequency in cocaine-dependent men. The precise mechanisms of action of cocaine on ACTH secretion are unknown but we postulate that CRF may be responsible for the amplitude modulation of ACTH secretion since cocaine stimulates the hypothalamic-pituitaiy-adrenal axis through release of CRF. CRF activation of ACTH may also play a role in cocaine's rapid reinforcing effects in humans.

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COCAINE STIMULATES LH IN RHESUS MALES AND MID-LUTEAL FEMALES BUT NOT IN OVARIECTOMIZED FEMALES

J. M. Drieze, N. K. Mello, Z. Sarnyai, J. H. Mendelson, and M. Kelly

Cocaine significantly increased LH and enhanced LHRH-stimulated LH in early follicular phase rhesus females (Mello *et al.,* 1990a and b). We examined the acute effects of cocaine on gonadotropins in four males and six mid-luteal phase females to determine if the LH increase was gender or menstrual cycle phase specific. Cocaine (0.8 mg/kg) stimulated a significant increase in LH within 10 to 20 minutes ($P<0.01$) in both males and mid-luteal females. LH reached peak levels (59-60% above baseline) within 30 minutes after cocaine administration. FSH levels were unchanged in mid-luteal females but male testosterone increased by 50 percent above average baseline levels within 50 minutes after the LH peak (80 min post-cocaine). A lower dose of cocaine (0.4 mg/kg) did not change basal levels of LH and FSH in mid-luteal females or LH and testosterone in males. In contrast, cocaine did not stimulate basal LH levels in long-term ovariectomized females. Administration of synthetic LHRH following cocaine administration (0.4 and 0.8 mg/kg) did not significantly enhance or attenuate the magnitude or the duration of LHRH-stimulated increases in gonadotropins. Pituitary response to LHRH stimulation after placebo-cocaine was adequate and LH and FSH increased significantly. These data suggest that the gonadal steroid environment may be critically important for expression of cocaine's effect on LH.

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RESOLUTION OF TWO SEROTONIN TRANSPORTER-RELATED BINDING SITES WITH THE COCAINE ANALOG, [^{125}I]RTI-55

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Other laboratories showed that the cocaine analog [125I]RTI-55 labels DA and 5-HT biogenic amine transporters (BAT) with high affinity. Using the method of binding surface analysis, we characterized [125I]RTI-55 binding to membranes prepared from whole rat brain minus the caudate nuclei. We conducted quantitative binding studies of the interaction of selective DA (RTI-120) and 5-HT (paroxetine) BAT ligands with [125I]RTI-55 binding sites. The results indicated that [125I]RTI-55 labeled approximately equal numbers of DA (Bmax = 382±36 fmol/mg protein) and 5-HT (Bmax = 460±12 fmol/mg protein) transporters. The Kd/Ki values of RTI-55, RTI-120 and paroxetine for the DA and 5-HT transporter sites were: RTI-55 (1.75 nM, 0.42 nM), RTI-120 (33.7 nM, 11596 nM) and paroxetine (1164 nM, 0.26 nM). The ligand-selectivity pattern of the 5-HT transporter was determined by displacing 0.01 nM [125I]RTI-55 by various test agents under DA-transporter-blocked conditions. The results demonstrated a 5-HT transporter-like ligand selectivity pattern. Ketanserin and CFT had slope factors of about 0.7. Therefore, CFT and ketanserin binding surfaces were generated under DA-transporter-blocked conditions. The data were best-fit by a two site model (site A, site B): [Bmax (fmol/mg protein): 445±125, 240±150], [RTI-55 (Kd, nM): 0.66, 0.15], [CFT (Ki, nM): 337,42.5], [ketanserin (Ki, nM): 4341, 705]. The major finding of this study is that [125I]RTI-55 labels two binding sites related to the 5-HT transporter using non-caudate brain membranes.

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REGIONAL CEREBRAL BLOOD FLOW EFFECTS OF ACUTE COCAINE INFUSION

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Animal studies have demonstrated increases in local cerebral glucose utilization (LCGU) and cerebral blood flow (CBF) in striatal structures following acute cocaine. In humans, decreases in absolute whole brain and absolute striatal cerebral glucose utilization have been reported after IV cocaine using PET and the FDG method, which averages glucose metabolism over an approximate 30 minute period. Decreases in relative striatal CBF have been reported using Tc-99m-HMPAO and SPECT which reflects relative CBF during the brief period of cocaine intoxication, but CBF was not quantitated. We studied the effects of cocaine hydrochloride on absolute CBF using a modified microsphere model for CBF quantitation with Tc-99m-HMPAO SPECT.

METHODS: Four cocaine dependent individuals have received IV cocaine hydrochloride 40 mg vs. placebo in a double-blind, placebo-controlled. crossover design protocol. SPECT images were co-registered to MRI using a modified Pelizzari and Chen method and the following regions were delineated: whole brain, caudate, putamcn, globus pallidus, thalamus, ant. cingulate, pre-frontal, pre-central and occipital gyri, and cerebellum. Absolute and relative blood flow measures were then calculated.

RESULTS: Cocaine produced significant subjective “high” and was associated with a mean decrease of 29.7% in absolute whole brain blood flow among 4 subjects. Decreases in absolute CBF in other brain regions sampled ranged from 21.1-36.6%.

DISCUSSION: In general, the relative CBF findings in this study are similar to those reported elsewhere. However, comparisons are limited by methodological differences and the small number of subjects in this study. The percent decrease in whole brain blood flow in this study is approximately twice the percent decrease in whole brain cerebral glucose utilization measured in a previous study. This finding has implications for kinetic modeling calculations in studies employing radiotracers in which tracer delivery to the brain is a function of cerebral blood flow.

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EFFECTS OF INTRAVENOUS SELF-ADMINISTERED COCAINE ON SINGLE CELL ACTIVITY IN THE NUCLEUS ACCUMBENS OF THE RAT

L. L. Peoples, R. Bibi, and M. O. West

In order to study the as yet unknown neuronal mechanism(s) involved in cocaine reinforcement, electrophysiological techniques were used to characterize the activity of single nucleus accumbens septi (NAS) neurons in rats self-administering cocaine. Male Long-Evans rats (300g) were chronically implanted with a jugular catheter and microwire arrays positioned for recording in the NAS (level skull; 0.7 -2.2 mm AP and 0.8 - 2.2 mm ML, from Bregma; and -6.8 mm DV from skull). That recorded cells were NAS neurons was verified histologically. During the self-administration session, each lever press was followed by a 0.2 ml intravenous infusion of cocaine solution (either 0.33 mg or 0.16 mg cocaine/infusion), a 7.5 sec tone, and a 20 sec time-out period. The motor correlates of 32 neurons were assessed during a pre-drug period using PEH analysis of specific locomotion and rest nodes and/or comparisons of tonic firing rate (Hz) during periods of rest and periods of experimenter-induced locomotion. Any neuron exhibiting greater than a 10% difference in firing rate across rest and movement was categorized as exhibiting firing rates related to movement. Relative to rest, 65% of the neurons increased firing during movement and 35% decreased firing. For most of the neurons excited by movement, tonic firing rates in the cocaine self-administration period were intermediate to pre-drug rest and locomotion rates; for all the neurons inhibited by movement, tonic firing rates during self-administration were lower than both rest and locomotion pre-drug rates. During cocaine self-administration, 70% of 48 neurons exhibited firing rates which were correlated with the cocaine-reinforced lever press. The majority of these neurons (67.6%) were inhibited in the 1 min which immediately followed the lever press. Many of the neurons exhibiting post-lever press inhibition also exhibited an anticipatory excitation in the 1-3 min immediately preceding the press. The remaining, smaller number of responsive neurons exhibited mirror image patterns: excitation post-lever press, which in some cases, was coupled with anticipatory inhibition. The correlation of NAS cells with movement suggests that the lever press correlates could merely reflect differences in motor behavior pre- and post-lever press. Assessment of this hypothesis can be accomplished by the use of behavioral clamps in which firing rate is assessed during the same motor behavior pre- and post-lever press. Preliminary results of such analyses revealed that measuring neural activity during either similar locomotion or stereotypy epochs pre- and post-lever press did not alter the lever press correlate. This finding, if consistent over a larger number of neurons, would leave open the possibility that the lever press correlate reflects the reinforcing and/or pharmacological effects of cocaine.

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IN VIVO PROTON MAGNETIC RESONANCE SPECTROSCOPY OF ETHANOL IN RHESUS MONKEY BRAIN

M. J. Kaufman, T. Chiu, J. H. Mendelson, B. T. Woods, N. K. Mello, S. E. Lukas, P. A. Fivel, and L. G. Wighton

Magnetic Resonance Spectroscopy (MRS) of brain ethanol has been reported in humans and animals. Although brain ethanol levels approximate venous blood ethanol concentrations (BAL), MRS brain ethanol levels generally reflect only 20 - 30% of temporally concordant BAL. Recent clinical studies from our laboratory in subjects consuming moderate amounts of ethanol (10-20 drinks per week) revealed nearly 40% detection of brain ethanol by MRS compared with 20% detection in subjects consuming 2-4 drinks per week. These data suggest that MRS ethanol detection may be altered by history of ethanol exposure. Parametric studies required to resolve this issue are difficult to conduct in humans due to pervasive and uncontrolled ethanol/polydrug use as well as ethical considerations, but animal models of chronic ethanol exposure are well established. Consequently, we examined the feasibility of using a nonhuman primate model to detect brain ethanol with MRS.

Three adult male rhesus monkeys *(Macaca mulatta)* were anesthetized with ketamine (7.5 mg/kg, i.v.) and xylazine (0.75 mg/kg, i.v.). MRS was conducted on a 1.5 T whole-body imager (General Electric, Milwaukee, WI) with a 3 inch surface coil, using the STEAM pulse sequence. Paired spectra (TE 30 ms, TE 270 ms) were acquired from a 7.5 cc voxel positioned over the caudate nucleus and putamen prior to and for two hours following ethanol administration. *N*-acetylaspartate (*N*-AA), present in brain at approximately 7 mM, was used as an internal standard to calculate concentrations of cerebral metabolites and ethanol. Ethanol was administered via nasogastric tubes (0.8 g/kg). Venous blood samples were collected for analysis of BAL by gas chromatography.

Baseline spectra had resonances at 3.2 ppm (choline), 3.0 ppm (total creatine) and 2.02 ppm (*N*-AA). After ethanol administration, the methyl protons of ethanol were detected at 1.2 ppm. *N*-AA resonance intensity was not altered by acute ethanol administration. Brain ethanol levels were only a fraction of temporally concordant BALs (29 and 18 % in TE 30 ms and TE 270 ms spectra, respectively). Regression analyses revealed highly significant correlations between brain ethanol levels and BAL.

These findings are the first *in vivo* ethanol measurements in monkey brain by MRS. The fractional detection of brain ethanol and the concentrations of choline and total creatine found are consistent with values reported in human studies. These results demonstrate the feasibility of using rhesus monkeys to study changes in MRS brain ethanol detection resulting from repeated ethanol exposure

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RESPIRATORY-STIMULANT EFFECTS OF CAFFEINE DURING ACUTE AND CHRONIC NICOTINE ADMINISTRATION IN RHESUS MONKEYS

L. L. Howell

Clinical studies have shown that cigarette smokers metabolize caffeine more rapidly than non-smokers. However, the consequence of chronic exposure to nicotine on sensitivity to the physiological effects of caffeine has received little attention experimentally. The present study investigated the respiratory effects of caffeine during acute and chronic nicotine administration in unanesthetized, seated rhesus monkeys (n=6). Ventilation was measured continuously by enclosing each monkey's head in a fitted Lexan helmet while a pressure transducer measured differences in pressure produced by inspirations and expirations against a constant flow of air (pressure-displacement plethysmograph). Procedures were used to manipulate central, CO_2-sensitive mechanisms and peripheral, O_2-sensitive mechanisms involved in the chemical regulation of ventilation. Drugs were administered i.m. using a cumulative-dosing procedure while subjects breathed air alone (normocapnia), 3%, 4% and 5% CO_2 balanced in air (hypercapnia) and 10% O_2 balanced N_2 (hypoxia). Plasma levels of caffeine and its primary metabolite, paraxanthine, were determined after i.m. administration of caffeine (10.0 and 30.0 mg/kg) using HPLC analysis and UV detection. Prior to and during chronic nicotine administration, blood was withdrawn from the saphenous vein at 0.5, 1.0, 2.0, 6.0 and 24.0 hr post-injection of caffeine. Acute caffeine (3.0-30.0 mg/kg) administration had pronounced respiratory-stimulant effects during conditions normocapnia, hypercapnia and hypoxia: Acute nicotine (0.3-3.0 mg/kg) administration had only modest respiratory-stimulant effects during normocapnia and hypercapnia, and the combined effects of nicotine and caffeine were additive during normocapnia. In contrast, chronic nicotine (1.0 mg/kg/day) administration for 28 days via osmotic pumps attenuated the effects of caffeine during hypoxia. Additionally, caffeine plasma half-life was reduced significantly in all subjects. The results indicate that altered sensitivity to the respiratory-stimulant effects of caffeine during acute and chronic nicotine administration likely involves different pharmacological mechanisms.

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CHANGES IN STAGES OF QUITTING CIGARETTE SMOKING AMONG CHRONIC PSYCHOTIC PATIENTS LIVING IN BOARD AND CARE HOMES

R. G. Hall, M. DuHamel, R. McClanahan, C. Nason, P. Schiller, and L. Tao

To understand more about the smoking status of chronic psychiatric patients in Board and Care homes, we interviewed 58 patients using the Stages of Change Questionnaire at baseline and six months. Patients were seen twice monthly so we were aware of changes in their smoking status. We hypothesized there would be few changes in the patients' Stage of Change/Smoking Status at a six month follow-up and that few patients would attempt to quit smoking. We compared the percent of subjects in each smoking status at Baseline and Six Month Follow-up. If there was little change most of the subjects could be found in the same stage/status at both periods. See Table One.

Table One
Percent Patients at each Stage of Change/Smoking Status-Baseline and Six Months

		Stage of Change/Smoking Status at 6 Month Follow up				
		Pre-contem-plation	Contem-plation	Prep/ Action	Quit Six + Months	Never Smoked
Baseline	Precontem-plation	**53.5**	3.4	0	0	0
	Contem-plation	6.9	**3.4**	5.1	0	0
	Preparation/ Action	0	0	**0**	0	0
	Quit Six + Months	0	0	0	**12.2**	0
	Never Smoked	0	0	0	0	**15.5**

Most smokers, 84.6%, did not change their status. Of the three (5.1%) patients who went from contemplation to action, only one quit for more than two days. Few psychiatric patients changed their smoking status over a six month period. We had only 3 attempts among 58 patients. All those who attempted to quit were announced contemplators. All three subjects seemed helped by staff assistance in a stop smoking program that included nicotine replacement. While staff were helpful, it was not sufficient to lead to a protracted period of not smoking, nor to induce other contemplators to actually make a quit attempt. Other interventions are needed to help these patients quit.

AFFILIATIONS:

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DO METHADONE MAINTENANCE PATIENTS WANT TO STOP SMOKING CIGARETTES?

J. A. Kennedy, M. I. Walter, S. K. Mikulich, and T. J. Crowley

Cigarette smoking prevalence is high (80-98%) among substance abusers, but nicotine dependence has not been a priority in substance abuse treatment. Stages of change identified in smoking cessation research include: Precontemplation (not thinking of quitting smoking in the next 6 months), Preparation (planning to quit in the next 30 days and having at least a 24-hour quit attempt in the past year), and Action (remaining abstinent from smoking after quitting 0-6 months ago); these have not been examined in methadone maintenance populations.

METHODS:

We interviewed 144 methadone maintenance patients to determine smoking prevalence, carbon monoxide (CO) levels, interest in smoking cessation treatment, and stages of change. We then offered a free 10-week smoking cessation program using nicotine patch, CO monitoring, and weekly group meetings; we examined recruitment and retention, stages of change, smoking cessation outcome, and cost.

RESULTS:

Smoking prevalence was 85%, and among these smokers 55% were in precontemplation, 36% in contemplation, and 9% in preparation. Over half (52%) wanted treatment, but only 21 (17%) entered treatment; 95% were nicotine dependent by DSM III-R criteria. Only 4/21 (19%) had quit at the end of 10 weeks, and relapse is probable for some with continued follow-up; others decreased smoking and nicotine tolerance Fagerstrom scores, and many progressed in their stages of change. An unexpected problem was self-report of no cigarettes but elevated CO levels due to use of marijuana.

CONCLUSIONS:

1) As expected, smoking prevalence was high at 85% in methadone maintenance patients.
2) Intervention was difficult; though half wanted treatment, only 17% entered the group.
3) Quit rates were low; at the end of 10 weeks only 19% quit; however, patients did decrease smoking and nicotine tolerance Fagerstrom scores, and many progressed in their stages of change.
4) Statistical analyses were limited by the small number, but success did not appear to be related to methadone dose, Fagerstrom score, or use of illicit drugs.
5) Cost of the intervention was considerable in light of quit rates.

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THE TREATMENT OF SOBRIETY: A DEVELOPMENTAL MODEL OF RECOVERY

P. Banys

Recovery from alcoholism may be theoretically conceptualized as a continuing process which recapitulates other, earlier tasks in human development. This paper describes a psychodynamic phase model of recovery from alcoholism which has organized a clinical treatment program at the San Francisco VA Medical Center.

This model is constituted by the following four phases: ***Crisis, Abstinence, Sobriety, and Recovery.*** For the patient, each phase of recovery calls for the solution of phase-specific tasks. For the therapist, each phase requires shifts in technique appropriate to the tasks of that phase. Phase progression depends on task-completion, not on time-in-program. Early phases emphasize behavioral management and the completion of intensive program requirements. More advanced phases progressively introduce additional psychotherapeutic elements, although insight-oriented psychotherapy is always conceptualized as a risk factor for relapse. Groups are conceptualized as transitional objects intermediate between pathological self-reliance and true object relations. Group therapy is utilized, not as a venue for confrontation, but as a holding environment for the largely non-verbal processes of identification with other recovering individuals.

In this model, relapse is conceptualized as a failure of treatment structure rather than as a failure of the patient. Relapse leads to an intensification of treatment through reassignment to an earlier, more highly structured, phase of treatment. In addition to the behavioral maintenance of abstinence, recovery tasks eventually include the need to repair and reconstruct damaged or caricatured personal relationships. In longstanding alcoholism such interpersonal damage has often been too great to repair, and advanced therapeutic tasks center on the working-through of loss, grief, guilt, and remorse.

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A CLINICAL TRIAL OF CUE EXPOSURE COMBINED WITH COGNITIVE-BEHAVIOURAL TREATMENT FOR ALCOHOL DEPENDENCE

J. Pead, J. Greeley, A. Ritter, T. Murray, B. Felstead, R. Mattick, and N. Heather

In this study in progress we seek to improve the potency of relapse prevention procedures as they are routinely conducted in a clinical setting by having coping skills acquisition occur in the presence of alcohol. Patients are randomly assigned to one of two treatment conditions: 1) cognitive-behavioural treatment integrated with 40 hours of cue exposure (n = 66) or 2) cognitive-behavioural treatment alone (CBT) (n=66). These group based treatments occur in two phases. The first is three weeks of intensive outpatient day-treatment (9am-4pm, 4 days a week). The second is 9 weeks of aftercare (weekly 2 hour evening sessions) including in vivo behavioural rehearsal. Structured homework exercises are given during both phases of treatment. All patients are followed up 3, 6 and 12 months after treatment.

PATIENT CHARACTERISTICS:

(N=20) All males	
Mean age (years)	37
Marital status	%
Single, never married	25
Married, living with spouse	8
Married, separated	42
Divorced	25
Employment	
Employed full-time	17
Self-employed	8
Unemployed	75

Education	%
Year 8	8
Year 9	33
Year 10	18
Year 11	33
Year 12	8

Daily alcohol consumed in last 30 days: 289 gms
Goal of long term abstinence: 75%
Severity of Alcohol Dependence Questionnaire: 31
Beck Depression Inventory: 13

PRELIMINARY FINDINGS:

Patients and staff find CBT + cue exposure highly acceptable and credible. Although there is considerable variance desire for alcohol is higher in the CBT + cue exposure group than the CBT alone group during treatment. Patients rate both negative and positive affects as being equally elicited in cue exposure. Sustained group based cue exposure provides a more realistic simulation of real life alcohol exposure than previous brief individual exposure treatments.

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Drug Services Victoria, University of Melbourne, National Drug and Alcohol Research Centre, AUSTRALIA

ALCOHOL USE AND FAMILY DRINKING IN A STUDENT POPULATION: GENERIC AND ALCOHOL-SPECIFIC PROBLEM-SOLVING

D. A. Mathis and J. J. Platt

Alcohol abuse is an increasing concern among young Americans, particularly college students. Delineating factors contributing to young-adult alcohol abuse is imperative for the development of effective prevention and intervention programs. A number of studies have indicated that family factors are important correlates of alcohol abuse in offspring, and that children of alcohol-abusing parents may have personal and interpersonal skill deficits contributing to their own alcohol abuse. A growing body of literature suggests that generic problem-solving abilities may, in part, mediate alcohol and other substance abuse. Alcohol abusers have also been shown to have social skill deficits in specific alcohol-related problem situations. Marlatt identified a deficiency in the ability to recognize alternative courses of action to alcohol-related problems. The present study examined the relationship between generic and alcohol-specific interpersonal skills and personal/parental drinking patterns in a young-adult non-treatment sample. The skills examined included the ability to generate: 1) step-by-step means for attaining desired ends (means-end thinking); and 2) alternative solutions to a problem. Platt's measures of generic problem-solving were adapted for alcohol-specific assessment. Subjects were 39 female undergraduates, averaging 23.5 (±.83) years of age. The average age of first drink was 14.1(±.63) years. Eighty-one percent of the sample reported drinking at least one alcoholic beverage during the past month; 52.4% reported drinking more than four drinks per drinking occasion. Personal and parental drinking were significantly related ($p \leq .01$). Univariate analyses indicated that significantly fewer step-wise solutions to alcohol-related interpersonal problems were generated by offspring of parents who consumed more than four drinks on a typical drinking occasion ($p \leq .02$). In addition, the overall ability to generate alternative solutions was somewhat lower among those consuming four or more drinks ($p \leq .12$); alcohol-specific alternative thinking was somewhat elevated among those subjects who limited intake to 1-3 drinks per episode ($p \leq .15$) than for those who drank in excess of four drinks. These data help delineate the underlying relationship between social-skill deficits and personal/parental alcohol consumption in a non-treatment population, and have important implications for the development of effective prevention programs.

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MARIJUANA USE IN PATIENTS SEEKING TREATMENT FOR COCAINE DEPENDENCE

A. J. Budney, S. T. Higgins, W. K. Bickel, and M. L. Van Etten

Objective and Method: The majority of cocaine-dependent persons seeking treatment also abuse marijuana, with prevalence estimates of marijuana abuse ranging from 25-70%. This study assessed marijuana use and associated factors in 124 persons seeking outpatient treatment for cocaine dependence, and examined the relationship between marijuana use and initial response to a behavioral treatment for cocaine dependence. Marijuana users vs. non-users and marijuana dependent vs. non-dependent persons were compared on sociodemographic and drug-use variables. The relationship between marijuana and cocaine use during treatment was examined using 52 patients who received a behavioral treatment.

Results: Marijuana users were more likely to be male and less likely to have ever been married than non-users. They initiated cocaine use at a younger age, used cocaine and alcohol more frequently, spent more money on cocaine, scored higher on the medical, drug, alcohol, and psychiatric subscales of the ASI, and were more likely to report headaches, nausea and dealing drugs as consequences of their cocaine use. In addition, marijuana-dependent patients were younger, were more likely to have legal problems, and reported mote sleep problems and cough/sore throats associated with their cocaine use than those who were not dependent Marijuana dependence was not predictive of cocaine use during treatment, but frequency of use prior to treatment did predict outcome. Heavy marijuana users were less likely to meet criterion levels of success (> 90% cocaine-negative urine tests) than light users ($p = .05$). Marijuana use during treatment was also predictive of cocaine outcome ($p = .02$), and frequency of use appeared to moderate this relationship.

Conclusions: These findings indicate concurrent marijuana use among cocaine abusers is associated with increased drug-use severity, psychosocial impairment, and poor outcome during treatment, however, exceptions are evident. Controlled, prospective research examining the influence of marijuana use on cocaine treatment outcome is needed so that empirically-based guidelines for addressing marijuana use during treatment can be developed.

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THE MULTIDIMENSIONAL ASPECTS OF COCAINE CRAVING

E. G. Singleton, S. T. Tiffany, J. E. Henningfield, and C. A. Haertzen

New questionnaires have been developed to provide valid and reliable self-report formats to assess drug craving. In the initial validation study, craving consisted of an amalgam of four prominent factors: 1) irresistible urges and desires, 2) intent to use cocaine, 3) lack of control over use, and 4) anticipation of positive outcomes, and were positively associated with neeative mood. lack of confidence in ability to quit, and cocaine use. Examination of item content and behavior of the factors within the amalgam suggested naming the factors emotionality, purposefulness, compulsivity, and expectancy. The initial validation sample was randomly split into two subgroups and factor-based questionnaire responses were assessed by exploratory and confirmatory cluster analyses. Results were double cross-validated and compared to three traditional ways of assessing craving: a single item, a composite score, and an index. Five distinct multivariate clusters or patterns of factors were found. The patterns would not have been identified by traditional one-dimensional craving measures. Findings suggest craving for cocaine is a multidimensional construct. Synergistic applications of craving reduction techniques and pharmacological interventions may be necessary.

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MOTIVATION, AFFECT, AND RESPONSE TO DRUG CUES IN METHADONE-MAINTAINED COCAINE-DEPENDENT PATIENTS

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

To investigate motivation for abstinence in patients entering treatment for cocaine addiction, and to explore relations among motivation and other psychological states, we developed a two-part questionnaire (the MFAQ) assessing: (1) obstacles to abstinence, and (2) incentives for abstinence. We were particularly interested in examining relations among motivation, depression, self-efficacy, and response to drug-related cues. We administered the MFAQ, the Beck depression inventory, and a self-efficacy scale, together with a cue-reactivity protocol, to 75 cocaine-abusing methadone-maintained patients as they entered treatment for cocaine addiction. The sample consisted of 31 males and 44 females (39 white, 31 African-American, and 5 Hispanic). They used cocaine an average of 4.27 times per week.

Principal components analyses (PCA) were performed on the MFAQ and the self-efficacy questionnaire and factor scores calculated for each subject. Three independent variables were then created: (1) high/low depression; (2) high/low craving in response to cues; (3) high/low aversion to cocaine in the presence of cues. A series of 2 x 2 (depression x craving and depression x aversion) Analyses of Variance were then conducted with the following measures as the dependent variables: motivation factor scores, self-efficacy factor scores, mean confidence in treatment score, and frequency of cocaine use. Main effects were found for aversion to cocaine in the presence of cues and for depressed affect. “Disinhibitors” (subjects whose aversion to cocaine decreased in the presence of cues) and subjects with depressed affect both had high scores on the motivation factor labeled “self-medication.” Patients with depressed affect also reported feeling less self-efficacious (more vulnerable to cocaine use) in response to stress, use cocaine more frequently than non-depressed patients, and have more confidence that treatment will help their cocaine dependence. No main effects were found on any measure for the category “craver/non-craver.” Significant interactions were found between depressed affect and aversion to cocaine that suggested an “approach/avoidance conflict” in the non-depressed “disinhibitors.”

Our findings, while preliminary, suggest that disinhibition of the desire for cocaine in the presence of cues, rather than craving per se, together with depressed affect, may be interesting measures to include in future treatment outcome research, both as potential predictors of treatment outcome and targets for intervention.

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UNTREATED RECOVERY FROM COCAINE DEPENDENCE

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A growing body of evidence shows many substance dependent individuals can recover from psychoactive substance *(i.e.,* opiate, alcohol, cocaine, nicotine) abuse without obtaining formal treatment. Very little is known about the psychological processes mediating such change. Such data may eventually enhance treatments for substance dependence and provide an empirical basis for psychological interventions. The present study is an investigation of 50 former cocaine abusers, recruited through advertisements in the mass media, all of whom met criteria for DSM-3R cocaine dependence and who had been abstinent for a minimum of one year (mean=4.1 years since cocaine resolution with minor post-resolution use) at the time of interview. A semi-structured interview assessed history of substance use, especially alcohol and cocaine use, biopsychosocial consequences of cocaine abuse, the trigger for resolution from cocaine, maintenance of abstinence, coping with urges to use cocaine, family history of substance abuse and psychiatric history. A comparison sample of 21 untreated, active cocaine abusers (all of whom met criteria for DSM-3R cocaine dependence) were administered the same assessment interview excluding the questions addressing cocaine resolution. Results showed the two samples to be comparable demographically *(i.e.,* approximately 30 years old. unemoloved, single, high school education), Males comprised 55% of the entire sample. The resolved group had used cocaine for 10 years prior to resolving; the active abusers had a 8.9 year history of use. Both groups had a history of polysubstance abuse (5 to 6 drugs lifetime); the resolved and non-resolved groups consumed 8.2 standard drinks vs 7.5, respectively, when drinking; the amounts of cocaine used per episode were also similar (2.5 grams vs 1.6 gms, respectively). The major triggers for cocaine resolution were cognitive re-appraisal of the impact of cocaine, interpersonal stress, deteriorating health and lack of money. Maintenance of recovery was associated with support from significant others and modification of overall life functioning *(e.g.,* change of friends, leisure activities, work, address).

AFFILIATION:

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SHAPING BY SUCCESSIVE APPROXIMATIONS: AN INNOVATIVE TREATMENT OF COCAINE ABUSE

R. Elk, J. Grabowski, H. Rhoades, J. Schmitz, and R. Spiga

Development of effective treatments for cocaine dependence is essential. Shaping by successive approximations involves reinforcing successive approximations of a desired behavior until the goal is reached. This intervention has been demonstrated to be effective in the treatment of other behavioral problems, but has been implemented only infrequently in drug abuse treatment. The purpose of this investigation was to test the efficacy of an innovative shaping procedure in reducing cocaine use in two cocaine-dependent populations.

METHODS:

Subjects: Ten cocaine-dependent patients who participated in two separate studies with the same treatment intervention. Five of the patients were pregnant women, and the other five required prophylactic treatment for Tuberculosis. Eight were primarily opiate dependent and two primarily cocaine dependent. The majority had been using cocaine for ten or more years. Urine Screens: Urine samples were collected at each visit. Qualitative urine testing and semi-quantitative testing for cocaine metabolite (benzoylecgonine) were conducted. Design: Within-subject A-B design. No interventions on cocaine use in baseline. During the contingent phase, subjects were reinforced for: (i) A decrease in benzoylecgonine, (ii) Cocaine-free sample, (iii) Additional reinforcer if all samples per week met criteria for decrease in benzoylecgonine or were cocaine-free. Time in study varied. Analysis: Within-subject differences were compared using the z-test, and grouped data analyzed using the t-test. Differences over time were analyzed using a multiple comparison procedure.

RESULTS:

Eight patients remained in treatment until completion (10 of 18 weeks). In comparing the contingent phase with baseline: There was an increase in cocaine-free samples in eight patients (statistically significant in four patients and for the group [$p<0.05$-<0.0001]); There was a decrease in the quantity of benzoylecgonine in eight patients (statistically significant in five patients [$p<0.0005$]); Seven patients had proportionally more consecutive cocaine-free weeks (statistically significant in two patients [$p<0.0002$]). There was a significant increase for the group as a whole in the proportion of cocaine-free samples during months one through five in the contingent phase compared to baseline [$p<0.0001$].

CONCLUSIONS:

Shaping by successive approximations is a promising intervention in the treatment of cocaine abuse. Retention was high. During the shaping procedure there was an increase in cocaine-free urine samples throughout study participation, a decrease in the quantity of cocaine metabolite and an increase in consecutive cocaine-free weeks. Systematic replications in larger N studies are being conducted at our clinic.

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PREDICTORS OF INITIAL TREATMENT RETENTION IN COCAINE ABUSERS

R. J. Lamb, D. Marlowe, D. Festinger, and L. Kirby

This study examined client return from an initial orientation session to an initial counseling session 1-3 days later. Subjects were 92 consecutive patients attending an orientation session at a treatment program for cocaine addiction in Camden. Subjects had a median age of 30, and were predominantly black (83%). single (75%). males (72%). abusing crack (77%). Slightly more than half (53%) graduated high school and 46% had current criminal justice system involvement. Few were employed (11%) and 15% were homeless.

Low anxiety (84% v. 59% return rate; X^2=6.299, df=1, P<O.05; defined as BAI scores < 10) and significant depression (73% v. 55% return rate; X^2=2.764, df=l, P<0.10; defined as BDI scores >18) predicted return. A history of NA involvement (72% v. 53% return rate; X^2=3.721, df=1, P<0.10). no current criminal justice involvement (72% v. 55% return rate; X^2=2.949, df=1, P<0.10), and Camden residence (69% v. 50% return rate; X^2=2.818, df=1, P<0. 10) predicted return. These last three factors interacted positively; the presence of all three factors was associated with a 93% return rate, while the absence of one or more of these factors was associated with a 48% return rate (X^2=14.439, df=1, P<0.001).

Factors not predictive of return were graduating high school (X^2=1.115, df=1, NS), income (no reported income, income ≤ $10,000, and income > $10,000; X^2=0.473, df=2, NS), marital status (single, married, separated/divorced; X^2=0.029, df=2, NS), current living arrangements (alone, with children, living with spouse, living with parents or relatives, living with friends, or living in a shelter or homeless; X^2=1.706, df=5, NS). patient gender (x^2=0.410, df=1, NS), patient age (median split; X^2=1.181, df=1, NS). frequency of cocaine (X^2=0.882, df=4, NS; treatment entry required cocaine use in the past month) or alcohol use (X^2=5.663, df=5, NS; not in last month, less than weekly, 1-2 times per week, 3 to 6 times per week, daily, or 2 or more times per day), history of AA involvement (X^2=0.139, df=1, NS) or number of past treatment episodes (none, 1, 2, >3 ; X^2=2.802, df=2, NS). In summary, making treatment convenient and reducing patient anxiety at treatment entry may enhance treatment retention.

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ASSESSMENT OF POST-HOSPITALIZATION TREATMENT NEEDS AND PREFERENCES IN COCAINE ABUSERS

J. M. Schmitz, L. Oswald, L. Baldwin, and J. Grabowski

In recent years there has been a trend toward reducing the length of a hospital stay for drug and alcohol treatment. Little is known about the optimal combination of inpatient and outpatient treatment, or how these environments interact with specific patient characteristics in predicting outcome. This study reports the results of an initial investigation of the outpatient treatment needs and preferences perceived by hospitalized cocaine patients. Forty cocaine deoendent patients (26M, 14F, 30.3±4.8 yrs.) of a 28-day inpatient treatment program completed a 4-page survey measuring preference for various outpatient treatment opportunities. Eighty percent of patients rated 12-step meetings as being extremely important, while 68% rated relapse prevention as extremely important. Following these two services, in order of importance, were employment counseling (50%), treatment for family/marital (40%), psychological (28%); medical (25%), and legal (21%) problems. When asked to choose, 55% of patients preferred 12-step meetings over relapse prevention. This preference is consistent with the predominate view of cocaine addiction as a disease (93%), rather than a "bad habit" (7%). Finally, 66% of patients chose a group format over an individual mode of treatment delivery. For each ASI problem area *(e.g.,* employment), patient-rated ASI severity scores were positively related to survey ratings of importance of outpatient treatment for that problem *(e.g.,* employment counseling). We have demonstrated a method of identifying relative preferences for outpatient treatment following hospitalization. In an ongoing study we are examining the role of patient-rated treatment needs in relation to aftercare treatment attendance and outcome.

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AFFILIATION:

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CHARACTERISTICS OF STIMULANT ADDICTS WHO RESPONDED POSITIVELY TO OUTPATIENT TREATMENT

R. A. Rawson, S. Shoptaw, M. McCann, and S. Minsky

Researchers and clinicians are interested in identifying the most appropriate match between patient characteristics and drug treatment modality. The present study examined post hoc associations between pretreatment characteristics and treatment outcomes for subjects who received outpatient treatmcnt for stimulant dependence.

METHOD: This study used data gathered from two NIDA funded studies that provided outpatient treatments to 246 stimulant dependent subjects at the Matrix Center between 1988-1991. Data analyses involved univariate and multivariate analyses of the following: biological measures (in-treatment UA (weekly UA, 3-consecutive and 8-consecutive weeks negative UA) and 12-month follow-up UA); and behavioral measures (weeks in treatment and number of weekly treatment activities).

RESULTS AND DISCUSSION: Results based on 12-month follow-up UA results showed that abstinent subjects reported they used cocaine on fewer days (baseline days = 5.4) than subjects not abstinent in the 30 days before admission (baseline days = 13.4, $t=2.15$, $df=98$, $p<.05$). Follow-up abstinence status also associated with the following baseline compliants: nervousness ($X^2=4.52$, $df=1$, $p<.05$), headache ($X^2=5.26$, $df=1$, $p<.05$), panic ($X^2=7.07$, $df=1$, $p<.01$), suicidal thoughts ($X^2=4.18$, $df=1$, $p<.05$), confusion ($X^2=4.73$, $df=1$, $p<.05$), loss of consciousness ($X^2=9.33$, $df=1$, $p<.01$), and depression ($X^2=4.34$, $df=1$, $p<.05$).

Ethnicity status varied by ethnicity for average weekly negative UA results (AfrAm- 58.8%, Cauc- 69.4%, LatinAm- 75.4%; $F=3.11$, $df=2,143$, $p<.05$), for 3 consecutive weeks negative UA (AfrAm- 61.5%, Cauc- 83.3%. LatinAm-64.7%; $X^2=8,13$, $df=1$, $p<.01$), and for 8 consecutive weeks negative UA (AfrAm- 17.9%, Cauc- 50.0%, LatinAm- 29.4%; $X^2=12.50$, $df=1$, $p<.01$). Ethnicity also varied significantly with average weeks in treatment (AfrAm- 15.2, Cauc- 20.5, LatinAm- 16.2; $F=7.41$, $df=2,142$, $p<.001$) and treatment activities per week (AfrAm- 3.0, Cauc- 3.3, LatinAm- 3.9; $F=4.04$, $df=2,140$, $p<.05$).

Our findings indicated that the best candidates for using outpatient treatment for stimulant dependence were those with the following characteristics at treatment entry: (1) elevated pretreatment levels of physical symptoms, (2) dysphoric mood states, (3) psychiatric distress, and (4) lower levels of pre-treatment stimulant use. The clinical profile for those most likely to be abstinent at 12-month follow-up based on these retrospective data was someone using decreasing amounts of stimulants while experiencing substantially increasing physical and psychological distress from their drug use. Findings presented here provide an initial empirically based description of patient characteristics of those most likely to successfully use an outpatient stimulant drug treatment modality.

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PREDICTING CLIENT RETENTION AND TREATMENT EXPOSURE IN COCAINE ABUSE TREATMENT

J. A. Hoffman, B. D. Caudill, J. J. Koman, III, J. W. Luckey, and P. M. Flynn

The current investigation examined the utility of fixed and dynamic client variables in predicting client retention and treatment exposure rates. Analyses of a group of 329 cocaine abusers, the majority of whom were crack smokers revealed no statistically significant effects for gender, age frequency of cocaine use, frequency of any drug use, or other behavioral and psychological variables. Program characteristics; however, or the frequency, intensity, and/or type of treatment services offered, were highly predictive of client retention and treatment exposure patterns. Client treatment exposure and retention rates were significantly enhanced by providing clients with more frequent and intensive group therapy (2-hour sessions live days a week), or by adding individual psychotherapy, or individual psychotherapy plus family therapy, to the "standard group therapy" treatment (90-minute sessions two days a week). Adding individual treatment services to the "intensive group therapy" condition had no impact on client retention or treatment exposure rates. Overall, these findings for a population of crack users suggest that cocaine abuse client retention and treatment exposure rates are more highly related to the type of, and intensity of, treatment services offered than they are to client characteristics.

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RETENTION, ENGAGEMENT, AND PSYCHOSOCIAL OUTCOMES FOR SUBJECTS IN NEUROBEHAVIORAL TREATMENT FOR STIMULANT DEPENDENCE

J. Obert, S . Shoptaw, R. Rawson, and M. McCann

A recent report found that subjects who stayed longer in Matrix treatment exhibited significantly better abstinence outcomes than those who engaged for shorter treatments at 12-month follow-up. This study asked: (1) Is there a replicable treatment dose/abstinence response association for Matrix treatment; and (2) Is there an association between in-treatment abstinence variables and abstinence status at follow-up?

METHOD: Subjects were 146 stimulant addicts, a NIDA funded treatment demonstration project. Drug use data included weekly and follow-up urinalyses at 6-months. In treatment abstinence definitions used were 3 consecutive weeks and 8 consecutive weeks negative UA results. Behavioral data included length of time in treatment and number of weekly treatment activities. Treatment length was dichotomized into shorter and longer groups using the mean treatment for all subjects (20 weeks). Dose-response associations were tested using 2 methods: (1) assigning subjects into longer (>20 weeks) and shorter (< = 20 weeks) treatment groups and comparing along dependent measures; and (2) examination of treatment outcomes stratified on abstinence criteria. The typical subject was a 31 year-old male (19% females), cocaine addict (8.9% methamphetamine) with 12.8 years of education.

RESULTS AND DISCUSSION: **Question 1: Is there a replicable dose-response association for Matrix treatment?** Subjects averaged 67.3% negative weekly in-treatment urinalyses. Comparable to other outpatient drug treatments, 75.3% of subjects were able to achieve 3 consecutive weeks while 39.0% achieved 8 consecutive weeks abstinence during treatment. Subjects with longer treatments showed significantly better abstinence outcomes than subjects with shorter episodes using 3 consecutive (X^2 = 37.80, df = 1, p<.001) and 8 consecutive weeks criteria (X^2 = 37.16, df = 1, p<.001). Subjects also reported significant reductions in days and grams used in the previous 30 days at baseline and at follow-up. **Question 2: Do in-treatment abstinence variables associate with follow-up abstinence status?** Results showed 52.7% of subjects who achieved 3 consecutive weeks abstinence during treatment were abstinent at 6-month follow-up compared to 5.6% who achieved 3 weeks and were not abstinent at 6-months (X^2 = 24.93, df = 1, p<.001). Similarly, 63.2% who achieved 8 consecutive weeks were abstinent at 6-months compared to 27.0% who achieved 8 weeks and were not abstinent at 6-months (X^2 = 18.80, df = 1, p<.001). Subjects with longer treatments were more likely abstinent at 6-months (61.04%) than those with shorter treatments (18.84%; X^2 = 26.77, df = 1, p<.001). This study replicated previous findings and provided strong support for a treatment dose/abstinence response for stimulant abusing subjects receiving Matrix treatment. Results also provided empirical support for using in-treatment abstinence data as an indicator of subject abstinence status for up to 6 months after initiation of treatment. Results indicated how events that occur during Matrix treatment might relate to abstinence status at follow-up.

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SOCIAL SUPPORT, SUBSTANCE USE, ILLEGAL ACTIVITIES, AND PSYCHOPATHOLOGY IN CRACK SMOKERS ENTERING COCAINE ABUSE TREATMENT

B. D. Caudill, J. W. Luckey, J. A. Hoffman, P. M. Flynn, R. L. Hubbard, and S. G. Craddock

The current investigation examined social support characteristics of 199 crack smokers who entered an outpatient cocaine abuse treatment program in Washington, District of Columbia. Clients' levels of social support were related to historical and recent drug use, arrests and illegal activities, psychological distress, and psychopathology. Factor analyses of 56 questions relating to social support was used to identify three factors, namely "social support satisfaction" (SSS), "support for positive lifestyle" (SPL), and "drug and heavy alcohol use in clients' social network" (DAU). Responses to the questions for each factor were then standardized and summed to obtain a factor score. Statistically significant relationships were found between each of the three factor scores and many of the measures, particularly current functioning. In general, drug and heavy alcohol use in clients' social network (DAU) was most strongly related to current drug use behavior, behavioral problems, and feelings of interpersonal sensitivity and paranoia. Support for a positive lifestyle (SPL) was related negatively to behavioral problems and the greater the support, the later the onset of drug and heavy alcohol use. Those with more social support satisfaction (SSS) reported less behavioral problems and psychological distress on all dimensions and less daily use of alcohol (but not other drugs) in the past year.

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DETERMINANTS OF RETENTION IN COCAINE TREATMENT

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

The relative lack of demonstrated success of treatment for cocaine addiction may be attributed to at least two problems: treatments themselves may not contain the necessary components to motivate, counteract cravings, and assist users in initiating and maintaining behavior change; and cocaine users may not remain in treatment long enough to obtain desired benefits. Although demographic variables and substance use history have been identified as factors related to retention in cocaine treatment, studies have not investigated factors that are proximal to non-attendance and amenable to behavior change. We examined factors related to early drop-out among 56 cocaine abusers entering treatment at the Seattle VA Hospital. At admission, subjects completed the University of Rhode Island Change Assessment Scale, Curry's Cocaine Motivation Questionnaire, and Hall's Thoughts About Abstinence. Immediately following attendance or non-attendance at outpatient sessions they completed brief questionnaires comprised of open-ended questions about intrapersonal. interpersonal, behavioral, and environmental factors associated with attendance and non-attendance. Subjects were followed for eight weeks. Drop-outs were interviewed one week and one month following their last treatment session. The results of two separate logistic regression analyses, one of demographic and drug use history variables, the other of cognitive variables, indicated that early drop-outs (fewer than 3 sessions) had higher Precontemplation scores than those attending 3+ sessions. They were younger and had more lifetime years of regular cocaine use. To avoid wasting or disrupting addiction treatment, screening and intake procedures are often designed to "weed out" Precontemplation-stage people who do not perceive a need for treatment. Brief motivational interventions might, instead, assist them to move to the next stage of change (Contemplation). Qualitative data on intrapersonal, situational and interpersonal factors associated with attendance and non-attendance have been analyzed for 20 subjects. Some of the same factors lead to dropping out *and* attending treatment. Participants' cognitive appraisals of these experiences may determinine whether or not the experiences result in a return to treatment. This suggests reframing, i.e., providing alternate ways of looking at situations associated with dropping out. In addition, the qualitative data suggest that an attrition prevention program should include the following components: information about common reasons for dropping out, so that clients can anticipate potential difficulties; specific coping skills for dealing with high risk drop-out situations; and concrete outreach or intensive case management to reduce barriers to participation.

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AFFILIATION:

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PREDICTORS OF RETENTION AMONG DRUG USERS IN DAY TREATMENT

J. Guydish, M. Chan, D. Werdegar, and A. Acampora

INTRODUCTION:

Walden House, Inc., is a residential therapeutic community (TC) in San Francisco. In 1989, Walden House developed an intensive drug abuse day treatment program using TC principles. This program is best defined as a non-residential TC, or as a "modified" TC. This study was designed to assess retention, and factors related to retention, among clients entering the non-residential TC.

METHODS:

Clients enrolled in the intensive day treatment program were recruited to participate in a longitudinal study of treatment outcomes. Current and newly admitted clients were included (N=91). Six-month retention (including treatment for clients transferred to another Walden House program) was calculated as number of days continuously enrolled in treatment. The relationship of retention to demographic data, ASI composite scores, and measures of psychiatric status and social support was assessed.

RESULTS:

Demographic data are given in Table 1. Gender, ethnicity, drug of choice, age, and years of education were not associated with retention. Level of severity for drug problems ($r=-.24$, $p<.05$) and psychiatric problems ($r=-.22$, $p<.05$) were inversely related to retention, as were Beck Depression scores ($r=-.24$, $p<.05$) and number of prior drug treatment episodes ($r=-.21$, $p<.05$). Last, increased social support was positively correlated with retention ($r=.28$, $p<.01$). In multiple linear regression analyses predicting retention, three variables (social support, Beck Depression score, number of prior treatments) accounted for 11.5% of the variance.

DISCUSSION:

Severity of drug use and psychiatric symptoms were inversely related to retention, and level of social support was positively correlated with retention. Although the variance accounted for by these factors was modest, it is similar to that reported in other studies of retention in drug treatment. Identification of clients with this symptom profile, and enhanced interventions targeting these clients early in treatment, may influence retention rates and treatment outcomes.

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Institute for Health Policy Studies, University of California, San Francisco, Walden House, Inc., San Francisco

CORRELATES OF COCAINE USE REDUCTION

A. Paredes, E. Khalsa, R. Lunn, and D. Anglin

In this study we attempted to identify the association between pre-treatment variables (sociodemographic, developmental, and patterns of drug use) and reduction in cocaine use after a therapeutic intervention. All 294 patients participated in the same initial treatment, after which they could self-select further treatment or not. Patients were grouped on the basis of the change between pre- to post-treatment cocaine use level: group 0, no change in their level of use; group 1 decreased their use by one level; group 2 decreased their use by two levels; and group 3 reduced their cocaine use by 3 levels. Specially designed schedules were used at the beginning of the index treatment. The Natural History Interview was used to collect detailed data concerning the addiction career and was updated at the first and second year follow-ups after treatment entry. ANOVAs showed that there were pre-treatment differences between the cocaine reduction groups. We found that patients who used more cocaine (in grams) prior to the index treatment were more likely to make substantial reductions in their cocaine use after treatment. No relationships were found between cocaine reduction group and any of the developmental variables studied. Although history of heavy use of alcohol among these patients was rather common, no clear relationship was observed between history of heavier alcohol use and level of cocaine use reduction. A discriminant analysis was conducted. A first root revealed that the groups with more substantial cocaine reduction (groups 2 and 3) tended to have used significantly higher amounts of cocaine during the pre-treatment phase than patients who either failed to change their cocaine use or reduced use by one level. A second root revealed that those patients involved in more serious deviant behavior such as selling/fencing stolen goods, and stealing from the family were members of groups with the least cocaine use reduction. Inversely, those patients exhibiting the most substantial reduction were less likely to be significantly involved in such criminal activities. In the last analysis it was determined that the reduction level groups were also different in terms of first return to cocaine use and rate of return at 24 months. Utilizing measures derived from the patterns of cocaine use and other pre-treatment characteristics, it could be possible to define a function that describes the likelihood of belonging to specific reduction groups. We are conducting additional analyses to assess whether characteristics measured by the variables in the function could be overridden by therapeutic interventions.

AFFILIATION:

UCLA Drug Abuse Research Center and West Los Angeles Veterans Administration Medical Center.

FACTORS ASSOCIATED WITH RETENTION IN TWO INTENSIVE OUTPATIENT SUBSTANCE ABUSE PROGRAMS

J. S. Knisely, D. L. Haller, K. S. Dawson, R. K. Elswick, and S. H. Schnoll

The Center for Perinatal Addiction offers intensive outpatient treatment for pregnant women and women with young children. The purpose of the present study was to evaluate the effect of various factors on length of time in treatment. Fifty-two subjects were randomly assigned to either the Time-Limited Program (TL) or Self-Paced Program (SP). Research assistants administered a battery of psychological tests. In addition to treatment program (TL vs SP), the effect of IQ, age, referral status, residence status, legal status, number of Axis I and Axis II disorders, number of previous substance abuse treatment attempts, education, and neighborhood quality (crime and drugs) on dropout rates were assessed using a Proportional Hazards Regression. Most subjects were single (96%), African American (83%), poly-drug users (85%) with a mean age of 27. The primary drug of choice was cocaine (77%), opiates (11%), alcohol (8%), or marijuana (4%). Program ($p<.04$). age ($p<.004$), residence status ($p<.05$). legal status ($p<.05$) and number of previous treatments (1, $p<.04$; 2, $p<.02$; three or more, $p<.001$) were significantly associated with dropout rate. Those subjects in the SP program were twice as likely to drop out than those in the TL program. Also, the risk of drop out was twice as likely for those in the SP program and not in our residence and four times greater for subjects in the SP program with no legal problems. Subjects were three to seven times more likely to stay in treatment if they had been in treatment before. These results indicate that a number of factors contribute to dropout for pregnant and recently post-partum addicts participating in intensive outpatient treatment. Situational factors appear to influence treatment retention, whereas psychological factors do not. The women most likely to be retained in treatment were older, assigned to the TL program, had prior substance abuse treatment, and were experiencing current legal problems. In addition, those in a supervised living situation remained in treatment longer than those living in the community.

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RETENTION AS A FUNCTION OF PSYCHOPATHOLOGY

D. L. Haller, J. S. Knisely, K. S. Dawson, R. K. Elswick, and S. H. Schnoll

Substance abusers are known to be at high risk for treatment dropout and psychological variables have been shown to impact retention in some sub-populations (Jacobsen & Kosten 1989; Kosten *et al.,* 1986; Woody *et al.,* 1991). The purpose of the present study was to examine the effect of type and extent of Axis II pathology and depression on dropout.

One hundred and six pregnant or recently post-partum substance abusers were randomly assigned to one of two intensive outpatient treatment programs were administered a battery of psychological tests. Factors of interest were ASP, depression, and number of Axis II disorders. Depression was assessed via the SCID and Axis II disorders were determined by the SIDP-R, MMPI-2 (Morey Personality Disorder Scales), and MCMI-II. Subjects were assigned Axis II diagnoses only when criterion were met on two of three tests.

Most of the women were single (95%). African American (82%), polydrug users (85%) with a mean age of 27. The primary drug of choice was cocaine (81%), opiates (8%), ETOH (8%), or marijuana (3%). A Proportional Hazards Regression revealed that depression and number of Axis II diagnoses were not associated with retention (number of days in treatment. However, ASP was significant ($p <= .009$) and the estimated relative risk was 1.9. Women assigned to the SP program with ASP were twice as likely to be retained as those without ASP. Chi-square analyses ruled out the possibility that this finding was an artifact of increased legal involvement for those with ASP.

Perhaps due to program characteristics, ASP was related to retention in the opposite direction from what was predicted. Overall, findings suggest that psychopathology may be relatively unimportant to retention of perinatal substance abusers. These findings are not inconsistent with those of an earlier study (Haller *et al.,* 1993) where psychological factors were of less significance than environmental factors such as housing. Such findings suggest the need to focus on fufillment of concrete needs and to, perhaps, adopt a primary case management approach.

References available upon request.

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PSYCHOPATHOLOGY IN SUBSTANCE ABUSERS ENROLLED IN DAY TREATMENT

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

OBJECTIVE: To assess the prevalence of psychopathology in a population of substance abusers seeking treatment in an intensive day treatment program.

METHODOLOGY: Clients (N=91) enrolled in an intensive day treatment program were interviewed with regard to demographics, substance abuse, education and employment, social support, and psychiatric characteristics. Instruments used to measure levels of psychopathology included the Addiction Severity Index (ASI), Beck Depression Inventory (BDI), the Structured Clinical Interview for DSM-IIIR Diagnosis (SCID), and a Social Support Evaluation measure. This is a presentation of baseline psychological status data.

RESULTS: Descriptive and correlation analyses were performed with the following results: Population demographic characteristics were mean age 33 years; 75% male; and ethnicity African American 54%. white 33%. Hispanic 9%. and Asian American 4%. Fourty-five percent of the cohort had a history of psychiatric treatment, either inpatient or outpatient; 30% had BDI scores in the moderate to extremely severe ranges; and 12% had at least one DSM-IIIR diagnosis. BDI scores were significantly correlated to ASI composite scores in the areas of alcohol abuse ($r=.21$, $p<.05$). drug abuse ($r=.37$, $p<.001$), and legal status ($r=.28$, $p<.01$); and to the Social Support Evaluation score ($r=-.53$, $p<.001$).

DISCUSSION: Studies were conducted at a community based drug treatment center that carefully screens and limits admissions of dually diagnosed clients. Even so, a high proportion of clients enrolled in this program were shown to have experienced past psychological treatment, and several upon testing were diagnosed with at least one DSM-IIIR disorder. In addition, many exhibited high levels of current depression. Moreover, the degree of depression correlated positively with the levels of drug and alcohol abuse, and legal involvement. Conversely, a negative correlation was shown between depression and social support, indicating that those with higher levels of depression also tended to have lower levels of social support.

These findings suggest that testing clients for psychopathology upon admission to treatment programs may reveal conditions that would benefit from special interventions, thereby improving treatment.

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AFFILIATION:

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SPECIAL NEEDS OF WOMEN IN DRUG ABUSE TREATMENT

M. Price, M. Chan, J. Guydish, and D. Werdegar

OBJECTIVE: To determine whether the treatment needs of women who abuse substances are different from the needs of men substance abusers.

METHODS: Participants in a therapeutic community (TC) substance abuse day treatment program (n=162) were interviewed using the Addiction Severity Index (ASI) and the Beck Depression Inventory (BDI), and a comparison was made of women and men.

RESULTS: Women constitute 37% of the sample. There were no significant differences in education, number of years of prior drug use or depression scores. Significant findings are as follows: Women entering treatment tended to be younger, were more likely to live with children, with or without a partner (chi sq.=5.6, $p<0.001$). and were much more likely to live alone with their children (chi sq.=12.7, $p<0.001$). Men were more likely to have lived in a controlled environment (prison, hospital, residential treatment, or other institution) (chi sq.=3.92, $p<0.05$), more often had a history of incarceration (chi sq.=20.5, $p<0.001$) and had been incarcerated for longer periods of time than women ($t=4.7$, $p<0.01$).

DISCUSSION: The appearance of the crack cocaine epidemic during the past decade has seen an extensive increase in the numbers of women seeking treatment for substance abuse. This increase could be partially attributed to maternal prenatal drug use, where women are often compelled by child welfare services to seek treatment as a condition to retaining custody of their children. The relatively young age of women entering drug treatment may also be related to the demand for services focusing primarily on pregnant and postpartum women. The percentage of women living with their children suggests that drug treatment programs may need to consider the inclusion of child care among the services they offer.

The numbers of men with history of incarceration and with usual living arrangements in a controlled environment may indicate that the therapeutic community inadvertently caters to males with criminal histories. Traditional drug treatment programs designed for a predominately male population with extensive criminal history may not adequately address the needs of women who abuse substances. There appear to be differences between women and men who abuse substances that warrant further study and which may be used to develop more effective treatment programs.

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PRIMARY CARE-BASED INTERVENTIONS FOR PREGNANT COCAINE-ABUSING WOMEN: COMPARISON OF TREATMENT ENROLLEES AND REFUSERS

J. A. Largo, R. S. Schottenfeld, J. Pakes, and B. Forsyth

Routine drug abuse screening in a hospital-based prenatal clinic utilizing a structured interview and urine toxicology testing identified cocaine use during pregnancy in 16.5% of 1709 women screened between January of 1991 and November 1992. Women with current cocaine use are offered randomized treatment in either an enhanced primary care program or comprehensive day treatment with on-site day care and home-based services.

We compared women who enrolled in treatment (62.2%) with treatment Refusers to identify factors associated with successful intervention. A significant proportion of Enrollees identified cocaine as their major drug problem (70.4% vs 43%) and were more likely to seek prenatal care during their last trimester (63.2% vs 25.6%). Compared with the Refusers, Enrollees were less likely to have a confidant (79.3% vs 92.4%) and to have wanted the pregnancv (36.8% vs 55%). There were no significant differences on demographic characteristics, history of alcohol, cigarettes and other drug use. Factors that differentiated between the two groups can be used to plan more effective interventions.

AFFILIATION:

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COUNTERING COUNTERTRANSFERENCE ISSUES IN CHEMICAL DEPENDENCY TREATMENT OF MULTIPROBLEM PREGNANT WOMEN -- DRAMATIC IMPROVEMENTS IN OUTCOME

A. M. Seiden, J. M. Chandler, and G. Davis

Developing effective therapist expectations and realistic treatment goals is notoriously difficult in chemical dependency treatment. Reality predicts high probability of lapse/relapse; efficacy requires maintaining a goal of overall progress. In treatment of pregnant, medically indigent, chemically dependent women, we have observed countertransference (CT) issues as a major barrier to efficacy. The most frequently observed CT included: (1) patients' difficult, painful lives: poverty (often extreme); homelessness; deprivation of education and job skills; trauma including physical, emotional, and sexual violence; exploitative and/or neglectful significant others; dependence on social networks which support addiction, risk-taking, and/or criminal behavior rather than recovery; untreated difficult psychiatric illness (especially personality disorders): untreated difficult medical illness (including HIV): (2) patients' lack of hope for the future (including inability to protect their children from similarly painful lives, or indeed to retain custody of children); (3) patients' impaired self esteem. Frequently observed CT manifestations included (1) "who wouldn't use under these circumstances?" (2) attempts to "rescue" patient in intended helpfulness which is ultimately patronizing and disempowering; (3) therapeutic overambition, underambition, or fuzzy goals.

Initial outcomes were not good: of the first 38 patients admitted to the program, over the first two years, only five (13%) had completed the entry phase (i.e. had attained a drug free state and regular program attendance). None had completed middle or advanced recovery phases. The most typical pattern was: sporadic attendance at CD treatment; all or most urines drug-positive; moderate use of medical, social, and entitlement services.

After a program intervention, outcomes were much better. In the past 6 months, of 15 active patients, nine (60%) had graduated from the entry phase (drug free and attending regularly) and of these eight (89%) have maintained gains through short-term and intermediate-term continued care *(i.e.* the length of follow-up to date).

Addressing staff countertransference issues and expectancies led to increased counselor expectations of patients; patient attendance and interest in program increased while the program itself became more demanding of both counselors and patients. In this outpatient program, initial outcomes approaching those typically found for more advantaged groups of patients have been achieved, and these gains have been greatest for patients newly admitted since the program intervention occurred.

REFERENCES: Available upon request from senior author.

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AFFILIATION: Cook County Hospital, Department of Psychiatry, New Start Program: Comprehensive Care for Pregnant Drug Abusers, Chicago, IL

EVOLVING TREATMENT MODELS FOR SUBSTANCE-ABUSING FAMILIES

T. Washington

This paper will describe the evolution of a new form of outpatient drug treatment, specifically designed for pregnant and post-partum cocaine-abusing women and their children. The Mothers Project, a comprehensive service demonstration and research program integrates prenatal and pediatric care, home-based family support, therapeutic daycare and traditional drug treatment to positively affect the addictive behaviors of parents and prevent poor development and placement outcomes for children. Initial attempts to coordinate the varied service modalities were complicated by conflicts in philosophies, focus of care, and limit-setting among different disciplines. What emerged over time was the development of a model of treatment which requires flexible staff roles, racial and ethnic composition of staff that reflects the client population, loosening of rigid professional hierarchies that denigrate clients and a strong commitment to children, while encouraging individual responsibility and client empowerment. Case examples will be used to illustrate clinical administrative situations which the program has confronted.

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PARTICIPATION OF MOTHERS IN A COMPREHENSIVE OUTPATIENT DRUG TREATMENT PROGRAM

J. Howard, L. Beckwith, and M. Espinosa

An outpatient program of treatment and support (including transportation and child care services) was offered to pregnant and post-partum women who abused cocaine and who at some time in the past had been reported to child protective services for suspected child abuse or neglect. Each woman was assigned a primary home intervener who made a minimum of two home visits per month over an eighteen-month period. To date, 62 women have been enrolled in this clinical services program. Although the majority of women did keep their appointment for home visits, clients during the first year attended an average of 17% of center-based activities during a three-month sample period. During the second year's three-month sample, this rose to 20%. And during the third year, with the implementaion of additional components, clients attended approximately 24% of center-based program activities during a three-month period. Although this increase is not clinically significant, the actual number of clients attending at least one center-based session during the three-month sample periods did rise dramatically, from 35% during the first year to 95% during the third year.

Clients who participated were more likely to describe themselves as having more years of cocaine use and more severe alcohol use, and were less likely to report symptoms of paranoia and/or delusional thinking. Participation was not observed to correlate with maternal age, number of children, or years of education. As previous studies also have observed, the findings suggest that participation in a drug treatment program is associated with heavier drug and/or alcohol use.

In conclusion, implementing effective clinical services for substance-abusing women is an evolving process that must be based upon a recognition of the clients' ability to utilize services. With the incorporation of additional program components to address such issues as community life skills, personal development, and enrichment activities (field trips), the number of clients who attended the program during the sample period increased. However, the number of sessions attended bv each individual client did not significantly change. Thus, further investigation of methods (in addition to child care and transportation services) to increase the participation of substance-abusing women in outpatient treatment is warranted.

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SOCIAL, BEHAVIORAL, AND EDUCATIONAL PERFORMANCE IN PRESCHOOL AND PRIMARY GRADE CHILDREN WHO WERE PRENATALLY EXPOSED TO ALCOHOL AND OTHER DRUGS

N. K. Young

This study explored social competence, behavior, and academic performance in 53 prenatally alcohol- and other drug-exposed preschool and primary-grade children (mean age 77 months) who participated in a Los Angeles school-based early intervention program, Prenatal Exposure to Drugs (PED). The children were exposed to a variety of drugs including alcohol (46%), cocaine (86%), marijuana (36%), PCP (39%), nicotine (3%), and heroin (8%).

The study analyzed data from: educational psychologists' assessment of developmental delavs: the Achenbach Child Behavior Checklist (CBCL); the Achenbach Teacher's Report Form (TRF); academic performance; and the child's placement history including the number and length of time in care-giving settings.

Findings include evidence of a 25% developmental delay at discharge from the program in more than fifty percent of children in memory abilities, visual-perceptual-motor skills, attending behaviors, visual-perceptual skills, and social abilities. Over one-third of the sample had delays in tine motor and conceptualization domains and exhibited outbursts.

In comparison to established norms, there were no significant differences between PED girls and a clinic-referred sample on the CBCL on the attention problems, delinquent, aggressive, and externalizing behavior scales and no differences on the TRF on social, thought, and attention problems and aggressive and externalizing behavior. There were no significant differences between the PED boys and the clinic-referred group on the CBCL in social, thought, and attention problems and delinquent behavior and on the TRF on the aggressive and externalizing behavior scales.

The age of the child was significantly related to every area rated by teachers except somatic complains. As the age of the child increased, the teachers observed the behavior more frequently. The child's age explained between 14 and 35% of the variance in the dependent variable. There were no significant relationships between the caregivers' rating of the child and the child's age.

There were no significant differences between PED children and their classmates on any of the academic performance domains graded. PED children scored higher on average than their classmates in every academic subject except handwriting and written composition and lower in every social and behavior domain except "is dependable." Half of the children who were in the primary grades were in regular education classrooms.

The number of out-of-home foster placements was significantly related on the CBCL to the withdrawn, attention, and delinquent behavior scales. The length of time in the current care-giving setting was inversely related to all domains on the CBCL except somatic complaints and explained between 17 and 34% of the variance.

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COUPLES IN SUBSTANCE ABUSE TREATMENT

R. I. Kim, K. L. Sees, and K. L. Delucchi

Limited research has been done on couples in substance abuse treatment. Previous research have indicated that couples are highly correlated in treatment retention and drug use, and among patients who enter substance abuse treatment, couples tend to remain abstinent longer and have higher treatment retention than others (Anglin *et al.,* 1987ab). The objectives of this study were to explore outcome variables of treatment attrition (days in treatment), drug use (confirmed opioid use by urine toxicology with self-report), and self-reported measures (number of symptoms present, craving, and withdrawal). Subjects were 17 opioid addicts who participated with their partners in a large clinical trial (N=108) of psychosocial interventions (*i.e.,* high and low intensities) in a long-term methadone detoxification treatment protocol[1]. These 17 subjects were compared with their partners, and with the remaining 91 subjects who did not have partners in treatment. Couples (subjects with their partners) included 15 females and 19 males (15 heterosexual and 2 gay couples) with the age range of 24 to 54 years (m= 38.2); 58% white, 21% black; 97% unemployed; and 76.5% with no legal problems. The remaining 91 subjects in treatment consisted of 31 females and 60 males with the age range of 20 to 63 (m=40.4); 47% White, 28% Black; 89% unemployed; and 69% with no legal problems.

Within the 17 couples, there was a strong correlation in treatment attrition ($r=.61$, $p<.01$). Furthermore, at specific assessment points, significant positive correlations ($p < .05$) for opioid use and self-reported measures of symptoms were found, suggesting similarities within couples. When comparing subjects in treatment with their partners and those in treatment without a partner, significant differences were noted. Those in treatment with their partners used less opioids, had less number of symptoms, and reported less craving and withdrawal ($p<.05$). There was no difference in treatment attrition between these two groups. However, there was a recognizable (statistically not significant) difference between coupled and non-coupled females. Female subjects in treatment with their partners stayed longer than female subjects who were in treatment without a partner. Therefore, advocating for couples to enroll in a substance abuse treatment together may be helpful for the treatment process and a better treatment outcome. A critical research direction would be to develop an operationally-defined comparative design between couples and non-couples that is relatively matched in sample size. SF-TRU Study: High-intensity versus low-intensity substance abuse treatment in a 180-day methadone detoxification program. PI:K.Sees. For details, see CPDD Abstract #121 (Sees *et al.).*

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AFFILIATION:

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METHODS FOR THE ANALYSIS OF COCAINE USE IN A STUDY OF OPIOID DEPENDENCE

K. L. Delucchi and K. L. Sees

The characterization and analysis of cocaine use in a study designed to treat primary opioid dependence may prove problematic due to small effect sizes, noisy data, and subject attrition. This study compared statistical analysis options for such a situation. Data used were three outcome variables from a study (n=88) comparing high- versus low-intensity psychosocial treatment in a long-term (180-day) methadone detoxification clinic; percent of urinalyses positive for cocaine 30-days prior to assessment; self-reported frequency of cocaine use; and craving. Methods compared were 1) single summary mean, 2) pre-post change over time, 3) treatment-group by time ANOVAs, 4) least-square estimates of change, and 5) weighted least-squares estimates of change. Analyses were replicated using simple imputed data for missing outcomes.

Results demonstrated a wide range of p-values and estimated effect sizes across methods. As predicted by theory, least-squares estimation of change proved most powerful. Weighting by the inverse of estimation quality improved sensitivity. No good second choice emerged among the remaining methods. The use of "last-observation carried forward" imputation produced similar results with one major exception. The estimated variances for each group's mean slope coefficients shrunk dramatically, indicating potentially biased estimation. Although not often seen in the substance abuse literature, the use of least-square estimates to detect differences in change over time in this common design is recommended.

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COCAINE USE DURING LONG TERM METHADONE DETOXIFICATION

H. W. Clark, K. L. Sees, K. L. Delucchi, P. M. Reilly, D. Tusel, and P. Banys

We are reporting on cocaine use during a study which investigated whether high-intensity psychosocial substance abuse treatment improved treatment outcome compared to low-intensity treatment during long-term methadone detoxification. The psychosocial intervention targeted drug and alcohol abuse in opioid dependent individuals. Outcome measures for both opioids and cocaine in this sub-study were: (1) percent of urine toxicology screens positive during the 30 days prior to each assessment; (2) self-reported frequency of use, and (3) craving. These results were separated by ethnicity for African American, white, and "other" subjects.

Of the 108 subjects, 29.6% were African American, 48.2% were white, and 22.2% "other." The only significant demographic difference between ethnic groups was mean age, with African Americans 42 years, whites 38 and "other" 40.7 years ($p<0.02$). More African Americans entered the study with cocaine-positive urine toxicology screens (74%) than whites (56%) who had more positives than "others" (33%) ($p=0.026$). During the stabilization phase, the percent cocaine positive urine toxicology screens remained significantly higher for African Americans compared to whites ($p=0.0054$). In the weekly urine toxicology screens, 37.5% of African-Americans, 23.1% of whites, and 14.4% of "others" always tested positive for cocaine ($p=0.11$). No similar differences were found for the proportion of subjects who never tested positive for cocaine. Frequency of cocaine use was significantly higher for African Americans compared to whites during the stabilization phase ($p=0.0138$), as was cocaine craving ($p=0.0185$). The intensity of psychosocial treatment did not have an effect on cocaine use during methadone induction or stabilization phases.

Provision of increased psychosocial services does not affect cocaine use during long-term methadone detoxification. Because African Americans appear to abuse cocaine more, treatment interventions specific to the needs of this population should be developed.

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SITUATIONS THAT OCCASION COCAINE USE AND STRATEGIES USED TO AVOID COCAINE USE IN METHADONE MAINTENANCE PATIENTS

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

The importance of antecedent events in relapse and maintenance of drug use has been recognized. Most research on antecedent control of drug abuse has examined Pavlovian conditioning mechanisms in substance abuse. Another antecedent function is suggested by the operant conditioning model: a discriminative stimulus function. Thinking about discriminative stimuli, may lead to identification of different antecedents than would be identified by concentrating on the Pavlovian model. This preliminary investigation provides information regarding discriminative stimuli that might occasion cocaine use and the strategies that drug abusers use in trying to abstain when faced with these stimuli.

A semi-structured interview assessing cocaine use situations and strategies to avoid cocaine use was completed by 264 patients in four methadone clinics. To be eligible subjects had to have used cocaine during the past twelve months. Subjects were given a list of environmental stimuli, activities, and emotions and asked which set the occasion for their cocaine use. Subjects identified a mean of 15 situations as setting the occasion for cocaine use, with some subjects indicating as many as 30. The five situations most often identified by subjects were: having cocaine present (86% of the subjects), being offered cocaine (85%), having money available (83%), being bored (74%), and having nothing to do (72%). After identifying all the situations that were likely to lead to cocaine use, subjects were asked to choose the situation that was most likely to lead to cocaine use when it occurred, even if it did not occur very often. The five situations identified as most likely were: having money available (23%), having the drug present (21%), feeling depressed (8%), being bored (7%), and using alcohol (5%). All but four of the situations (music, smells, coming to the clinic, and attending 12-step meetings) were identified as the most problematic by at least one subject. Environmental stimuli were more likely to be identified than either activities or emotions. This was especially true for white subjects. Black and Hispanic subjects identified emotions more frequently than whites ($\chi^2(6, N=264) = 15.8, p<.015$). Subjects identified 7 - 8 strategies they had employed in trying to stop cocaine use. Some identified as many as 17 strategies, while others could not identify any. Avoiding people and places was the strategy most frequently cited.

These results have implications for applying stimulus control procedures in the treatment of cocaine abuse. First, the wide variety of situations identified as problematic emphasizes the importance of individualizing treatment. Second, the large number of strategies subjects report already using suggests that treatment providers could assess and build on clients' baseline coping skills. Finally, the results suggest many subjects need to be taught additional strategies for supporting cocaine abstinence, as avoidance, the strategy most frequently identified, is often impractical.

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CONTINGENT ACCESS TO METHADONE MAINTENANCE TREATMENT: EFFECTS ON COCAINE USE OF MIXED OPIATE/COCAINE ABUSERS

M. Kidorf and M. L. Stitzer

Methods are needed to motivate improved outcome during methadone treatment, particularly with regard to continuing supplemental drug use (*e.g.,* cocaine). The present study tested contingent access to methadone treatment as an incentive. Forty-four mixed opiate/cocaine abusers participated in a 90-day pre-maintenance probationary program. They were stablized on 50 mg of methadone and assigned to one of two treatment groups. Contingent treatment patients were required to submit two consecutive weeks of cocaine-free urines sometime during their first seven weeks of treatment to gain entry into two years of methadone maintenance. For noncontingent patients, access to methadone maintenance was based on a yoked-control procedure. Patients not accepted to methadone maintenance were given a six week detoxification. Patients in the contingent treatment group were more likely to submit two consecutive weeks of cocaine-free urines than patients in the comparison group (50% vs. 14%; $p<.01$). This study extends previous research by focusing exclusively on mixed opiate/cocaine abusers and by introducing early in treatment a highly structured, clearly specified contingency in which a specific duration of treatment availability was used to promote improved outcome. The results demonstrate that contingent access to a longer duration of methadone maintenance provides a practical and effective incentive to obtain short-term cocaine abstinence. The 50% success rate observed is encouraging for a drug abuse intervention aimed at eliminating cocaine use.

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PSYCHOPATHOLOGY AND RETENTION IN COGNITIVE-BEHAVIORAL TREATMENT FOR COCAINE-USING METHADONE PATIENTS

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

The relationship between psychopathology and retention was examined in a cognitive-behavioral treatment program for cocaine-using methadone patients. Subjects were assigned randomly either to (1) high-intensity individual and group therapy or (2) a low-intensity, once-weekly cocaine group. Psychopathology at baseline was measured by DSM-III-R Axis I and Anti-Social Personality diagnoses (using the SCID), mood disturbance (Profile of Mood States [POMS] and Negative Affect Scale), and psychological symptoms (Brief Symptom Inventory [BSI]). The initial 80 patients who enrolled in the study treatments were followed-up for six months, which was the planned duration of treatment. Two-way analyses of variance indicated that the psychopathology measures and treatment condition had no significant main effects on treatment retention, but that there were significant interaction effects ($p<.05$), *i.e.,* subjects in the low intensity treatment who scored high on one of several psychopathology measures (DSM-III-R depression, number of DSM-III-R diagnoses, Total POMS, Total BSI, Negative Affect) had lower treatment retention than other subjects. Severity of psychological impairment was more predictive than type of psychiatric disorder (except for depression). The results suggest that the high intensity treatment condition succeeded in retaining high psychopathology patients who might otherwise have dropped out.

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SERUM METHADONE LEVELS IN 180-DAY METHADONE DETOXIFICATION: ARE THEY CLINICALLY USEFUL?

D. Tusel, K. Sees, P. Reilly, and P. Banys

This paper reports findings of the clinical utility of serum methadone levels during a study whose primary objective was to compare the effectiveness of a high versus low intensitv level of psychosocial treatment in a long-term (180-Day) methadone detoxification treatment program. During the first several weeks of treatment signs or symptoms of opioid withdrawal led to methadone dose increases up to 80 mg per day. Two weeks, after initial dose stabilization, a trough serum methadone level was drawn. If the level was 150 ng/ml or higher, no further dose change occurred. If the level was below 150 ng/ml, a methadone dose increase was prescribed and a second trough serum methadone level was drawn two weeks later. Subjects (N=125) tended to be living without a partner, unemployed, and male. Most were Caucasian, abused at least one other drug in addition to heroin, have 12 or less years of education, and average age was 39.8 years (range 20-63). Ninety-four patients remained in treatment long enough to assess and reassess, if necessary, their serum methadone levels. (17 subjects dropped out early, 11 were involuntarily discharged for failure to comply with the study conditions, and three failed to follow through with going to the laboratory.) Sixty-one (65%) met the cutoff for adequate serum methadone level (150 ng/ml) and no dose change occurred (mean methadone dose=54 mg). Twenty-two subjects (23%) had their methadone dose raised. Ten of these subjects attained adequate trough serum methadone levels (mean methadone dose=59). Twelve subjects did not attain the targeted level (mean methadone dose=67 mg). Another 11 subjects (12%) whose trough serum methadone level was below 150 ng/ml refused to increase their methadone dose (mean methadone dose=47 mg). The percentage of urine toxicology screens positive for opioids at baseline and at each monthly assessment point for each group was determined. No difference in illicit opioid use among the groups was found when looking at this variable alone. In addition, there were no differences in mean withdrawal rating (0-100 analog scale) or in mean number of withdrawal symptoms and signs (Modified Opiate Withdrawal Scale.)

As expected from our previous study and those of others, there was no correlation between methadone dose and serum methadone level. A significant difference in the percentage of opioid positive toxicology screens was related to the intensity of psychosocial treatment, however. (Those subjects in the highly intensive psychosocial treatment condition had significantly fewer opioid positive urine toxicology screens.) Considering the lack of correlation between serum methadone level and outcome, and the cost of quantifiably analyzing serum for methadone ($25 to $75 each), this brings into question the clinical utility of trough serum methadone levels in the treatment of heroin addiction.

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AFFILIATION:

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SELF-EFFICACY AMONG OPIOID ADDICTS IN 180-DAY METHADONE DETOXIFICATION TREATMENT

P. M. Reilly, K. L. Sees, M. S. Shopshire, K. L. Delucchi, D. J. Tusel, P. Banys, and H. W. Clark

Self-efficacy has been applied successfully to the treatment of alcoholism and smoking cessation. Few studies, however, have examined the relationship between self-efficacy and other drugs of abuse. This study examined the self-efficacy model within the context of 180-day methadone detoxification treatment.

Subjects were 74 opioid addicts who were enrolled in a treatment study that compared high- versus low-intensity psychosocial treatment. Treatment included three phases: induction, stabilization, and taper. Self-efficacy was measured by a confidence questionnaire which asked subjects to estimate on a 0-100% rating scale their confidence in their ability to avoid using illicit opioids in high-risk situations. As expected, self-efficacy increased from induction to stabilization, was sustained across the stabilization phase, and gradually decreased during the taper phase. In addition, self-efficacy measured at the start of stabilization predicted illicit opioid use across the stabilization phase. Similarly, self-efficacy measurements at the end of stabilization predicted illicit opioid use during the taper phase. Futhermore, self-efficacy predicted illicit opioid use better than demographic variables or intensity of psychosocial treatment.

Results of this study suggest that success in detoxification can be improved if patients' mastery over high-risk situations can be increased. They further suggest that interventions to increase self-efficacy within the context of methadone detoxification should be developed and explored.

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AFFILIATION:

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HIGH- VERSUS LOW-INTENSITY SUBSTANCE ABUSE TREATMENT

K. L. Sees, D. J. Tusel, P. Banys, P. M. Reilly, H. W. Clark, and K. L. Delucchi

The objective of this study was to investigate whether high-intensity psychosocial substance abuse treatment improved treatment outcome when compared to low-intensity treatment during long-term (180-day) methadone detoxification. Outcome measures were: 1) attrition; 2) drug use; and 3) symptoms, craving, and withdrawal. Forty-three percent of subjects completed the final-assessment: 96 completed the induction phase (assessments 1 & 2), but did not complete the stabilization phase (assessment 2-5); 74 completed the stabilization phase, but not the taper phase (assessment 5-7); and 46 completed all three phases. Between the high and low groups, no differences were found in the median number of days in treatment (high median = 165 days, low median = 170 days) and early drop-out (leaving before day 173). An interaction between Antisocial Personality Disorder (ASP) and treatment group regarding the length of treatment was found, however (log-rank X^2=13.6, $p<0.01$). ASP-positive subjects in high treatment and ASP-negative subjects in low treatment tended to stay longer in treatment than their comparison groups. Statistically significant differences were found between treatment groups, with the high-intensity subjects using opioids less often. The mean percentage of positive urine toxicology screens during the 30 days prior to each assessment was significantly lower for the high-intensity group across the induction ($p<.01$) and stabilization phases ($p<.01$). Subjects in the high-intensity condition also showed a lower mean percentage of positive urine toxicology screens in the taper phase, but this was not statistically significant. Although no treatment group differences were found, self-reported symptoms, craving, and withdrawal changed over time. The mean number of symptoms decreased over the stabilization phase ($p<.01$) and increased over the taper phase ($p<.01$). Craving and withdrawal significantly decreased once subjects were given their first dose of methadone ($p<.01$), did not change across the stabilization phase, and gradually increased during the taper phase ($p<.01$).

We concluded that provision of psychosocial services increases opioid abstinence rates among detoxification patients.

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THERAPEUTIC COMMUNITY METHODS IN METHADONE MAINTENANCE (PASSAGES): A PRELIMINARY EVALUATION

G. L. Staines and S. Sacks

This study evaluates Passages, a day-treatment program based on therapeutic community methods suitably modified for heroin addicts in methadone clinics. The main goals of Passages are to-reduce the incidence of substance use, reduce high-risk AIDS-related behavior, increase prosocial behavior, and improve psychological functioning. Data were collected from face-to-face structured interviews and urine toxicological records at a free-standing methadone program located in New York City. The present design of the study is an open clinical trial evaluating Passages and non-Passages clients. Compared to the non-Passages group, the Passages group showed significantly greater reductions in drug use at six-month follow-up for both cocaine ($p < .01$) and heroin ($p < .01$). These findings on changes in drug use were sustained by both the self-report and the urine toxicological data. High-risk behavior (*i.e.,* needle use) is reduced, though non-significantly, in both the Passages and non-Passages groups. Passages is associated with increased prosocial behavior: the Passages group showed significantly greater reductions in criminal activity at follow-up ($p < .05$) as compared to the non-Passages group. Passages clients were more disturbed on initial measures of psychological functioning, and improvement is noted for many clients on clinical ratings. However, the psychological measures do not substantiate these impressions at present. Planned analyses include assessing change for a larger sample of clients and, on the larger sample, for the sub-group of clients who have had maximum exposure to Passages. The present study demonstrates the efficacy of providing enhanced treatment for methadone clients.

AFFILIATION:

National Development and Research Institutes, Inc., New York, NY

DO SOCIAL PROBLEM-SOLVING SKILLS RELATE TO AIDS-RISK BEHAVIORS AMONG INTRAVENOUS DRUG USERS (IDUs)?

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

Intravenous drug users (IDUs) are at high-risk for HIV infection because they engage in a wide range of drug-use and sexual AIDS-risk behaviors, almost all of which have interpersonal aspects. For example, IDUs must interact with other high-risk individuals in order to maintain their injection drug use, providing the opportunity for sharing contaminated needles or having unprotected sex with an infected partner. At the&me time, IDUs are deficient in those social problem-solving skills that are required for effectively addressing problems of everyday living, including effective step-wise planning to reach a goal, generating alternative problem solutions, recognizing the consequences of actions, and thinking in terms of cause-and-effect relationships. Because AIDS-risk behaviors typically entail interaction with others, a lack of planfulness, consideration of potential risks, and evaluating alternative courses of action are factors hypothesized to underlie AIDS-risk behaviors.

The present study examined the association between selected risk behavior items on the AIDS initial assessment interview (AIA), and scores on a social problem-solving test battery. Subjects were 401 IDUs not enrolled in drug treatment, who completed the measures prior to entering a problem-solving skills training AIDS-intervention study. Results indicated that social problem-solving deficits were related to higher levels of injecting drugs with others ($p \leq .05$), borrowing or renting used needles ($p \leq .01$), and injecting cocaine ($p \leq .05$) or a heroin-cocaine mixture (speedball; $p \leq .05$). Identification of a number of HIV-risk behaviors associated with deficits in interpersonal cognitive problem-solving skills suggests that these abilities may mediate specific risk-behaviors. In addition. these data suggest that some IDUs with relatively high problem-solving abilities may attempt to reduce risk by limiting needle-sharing to an intimate partner, whom they may perceive as less risky. Thus, this study provides a key step towards understanding the cognitive processes that may underlie AIDS-risk behaviors and the utility of a cognitive problem-solving AIDS intervention. This understanding has important implications for developing effective AIDS intervention strategies.

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THE AVAILABILITY OF SIGNIFICANT OTHERS TO AID IN THE TREATMENT OF OPIOID DEPENDENCE

K. Silverman, K. L. Preston, A. T. McLellan, M. L. Stitzer, J. V. Brady, and C. R. Schuster

Research suggests that the involvement of drug-free significant others in the treatment of alcohol and cocaine abuse can improve treatment outcome by increasing the initiation and maintenance of abstinence (Higgins *et al.,* in press; McCrady *et al.,* 1986; O'Farrell and Cowles 1989). It is not clear, however, how many persons heavily involved with drugs and alcohol have drug-free significant others who would be willing to assist them in treatment. To determine the likelihood that patients receiving methadone treatment could recruit a close friend or relative (*i.e.,* a significant other) who does not use drugs to aid them in their drug treatment, we conducted a survey in four different methadone treatment clinics. Three of the clinics were located in Baltimore; one was located in Philadelphia. Of the clients interviewed from each of the four programs (Programs A [n=49], B [n=48], C [n=54], and D [n=98]), 6, 17, 30, and 31 percent, respectively, reported that they could not identify a drug-free significant other who would be willing to participate in their treatment. Only 45, 48, 30 and 18 percent of clients, respectively, reported that could identify a drug-free significant who would definitely be willing to participate in their treatment. The remaining clients in each program were uncertain as to whether or not their drug-free significant others would be willing to participate in their treatment. These results suggest that for a substantial proportion of patients receiving methadone treatment, significant others may not be readily available to participate in treatment. If we are to take advantage of the role which significant others can play in assisting clients to achieve and maintain abstinence, we may have to develop procedures to identify and recruit suitable significant others to participate in treatment.

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IS MORE TREATMENT ASSOCIATED WITH BETTER OUTCOME?

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

Do patients who receive more treatment services show more positive changes at follow-up in the substance-related, psychosocial and medical areas of the Addiction Severity Index (ASI)? Do males or females and African Americans or Latinos differ in the amount of treatment services received? To answer these questions, 407 methadone maintenance patients were administered the Addiction Severity Index (ASI) shortly after intake. The Treatment Services Review (TSR), an instrument which measures treatments received in each of the seven ASI areas - medical, financial, drug, alcohol, legal, family/social, psychiatric - was administered for four weeks. The measure of outcome was the follow-up ASI which was readministered three months after treatment entry to ascertain whether subjects' problem levels had improved over baseline levels.

Thus far, the analyses have revealed that there is limited indication of more treatment services received by women than men. Some differences in treatment services were found between African Americans and Latino patients. Lastly, there was a positive association between total services received and improvement from baseline to the three months in the medical, alcohol, and psychiatric problem areas.

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THE EFFICACY OF METHADONE: A LITERATURE REVIEW OF EVIDENCE FROM CLINICAL TRIALS AND EPIDEMIOLOGICAL STUDIES

F. Vocci and C. Wright

Despite almost 30 years of use as a medication for the treatment of opiate (narcotic) dependence, the efficacy of methadone is often questioned due to an apparent dearth of adequate and well controlled clinical trials substantiating its effectiveness. Four randomized trials have been performed in which fixed (Strain *et al.,* 1992) or flexible doses (Newman and Whitehall 1978) of methadone were compared to either a placebo, a "no medication" group (Gunne and Grondbladh 1984), and an untreated control group (Dole *et al.,* 1969). In the placebo controlled trials the results were overwhelmingly positive in favor of methadone in terms of retention and a decrease or cessation of illicit opiate use. Supportive evidence was also provided from the other randomized trials favoring a salutary effect of methadone on retention and drug use. A recent trial which used two doses of methadone in comparison to buprenorphine also supports the efficacy of methadone insofar as a dose effect was noted (Johnson *et al.,* 1992). Epidemiological studies of methadone maintenance treatment have: 1) reported impressive reductions of 5 (Grondbladh *et al.,* 1990) to 10 fold (Gearing 1977) in the death rate in the narcotic dependent population; 2) corroborated a dose effect relationship for methadone to reduce intravenous drug use (Ball *et al.,* 1988) and improve treatment retention (Capelhorn and Bell 1991); and 3) established a superior effect of methadone maintenance versus other (drug-free) modalities in terms of treatment retention as reported for the DARP study (Joe and Simpson 1975) and the TOPS (Hubbard *et al.,* 1989). Results from controlled trials and epidemiological studies support the conclusion that methadone maintenance treatment is a highly effective intervention for the management of narcotic dependence.

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DE-NICOTINIZED CIGARETTE REDUCES WITHDRAWAL SCORES AND INCREASES SATISFACTION IN 12-HOUR ABSTINENT SMOKERS

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Although it has been established that contextual and sensory factors are important modulators of symptoms of heroin withdrawal, there has been little study of the role of such factors on tobacco withdrawal symptoms. The availability of a "de-nicotinized" cigarette, "Next", facilitated our conduct of such a study. The perception by smokers that "Next" may be "safe" (*i.e.,* non-addicting) because it has been de-nicotinized is questioned here. The purposes of this study were to determine whether "Next" could increase blood nicotine levels in deprived smokers and reduce signs of withdrawal or satisfy smokers' craving for cigarettes.

The effects of "Next" (FTC nicotine delivery = .09 mg; tar = 10 mg) were compared to those of Marlboro (nicotine = 1.1 mg; tar = 16 mg) on physiological and subjective measures in seven male smokers that were tobacco deprived for 12 hours. On one day they smoked varying "doses" of "Next" cigarettes and on another day they smoked Marlboro. Doses were administered via a five port cigarette holder, such that subjects smoked 0, 1, 2, or 4 active cigarettes at a time. The remaining ports were filled with a non-tobacco (lettuce leaf) cigarette, Bravo. Subjects were instructed to puff every 30 seconds for a total of eight puffs according to the following procedure: puff for one second, inhale and hold smoke for five seconds, then exhale.

"Next" and Malhoro caused equal increases in exhaled carbon monoxide. indicating that each cigarette delivered similar levels of CO under actual smoking conditions. In contrast, Malboro increased plasma nicotine levels by 10.1 ng/ml after the four cigarette condition, whereas "Next" produced no increase in plasma nicotine or cotinine levels. Both Marlboro and "Next" significantly reduced the Hatsukami withdrawal scale total score; scores on the craving item were also reduced. There were significant and orderly increases in subjects' ratings of "liking", "good effect" and "satisfaction" across doses, with no difference between cigarettes, *i.e.,* scores increased as a direct function of the number of active cigarettes in the holder. These results emphasize that factors in addition to nicotine influence cigarette satisfaction and may temporarily decrease withdrawal from short term abstinence.

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ACUTE PSYCHOACTIVE EFFECTS OF TESTOSTERONE

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Anabolic-androgenic steroids (AAS) are used by athletes to enhance performance and physique. Case reports and observations propose that AAS have mood elevating properties and that chronic use leads to addiction. The aim of this study was to test the hypothesis that testosterone (T), a commonly abused AAS, is acutely psychoactive, producing characteristic subjective effects similar to other substances of abuse. In a double blind fashion, according to balanced latin-square design, ten paid adult male post-addict volunteers received a dose of intramuscular T (50, 100 or 200 mg), morphine (10 mg) or placebo for five consecutive days, Physiologic effects and self-reported and observed effects measured by the specific Drug Effect (SDE) questionnaire and the Drug Rating Questionnaire (DRQ) were recorded. T produced no significant changes in self-reported or observed measures, while morphine did induce statistically significant changes in several measures-"feel the drug", "like the drug", and "feel high." In conclusion, T, unlike other substances of abuse, produced no acute psychoactive effects.

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A CLINICAL EVALUATION OF THE STIMULANT KHAT AND OF THE KHAT ALKALOID CATHINONE

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The leaves of the khat bush have a stimulating effect, and the habit of chewing this material is prevalent in East Africa and southern Arabia. In this region, the khat plant is cultivated widely, and it is consumed at a rate of some five million portions per day (Kalix 1990). Recently, this drug has been encountered by US troops in Somalia, and in the United States it has been scheduled under the Controlled Substances Act.

The effects of khat are thought to be due to cathinone, a phenylalkylamine alkaloid that has been isolated from the leaves some 15 years ago; this substance has been shown in animal experiments and in vitro studies to have amphetamine-like effects (WHO Advisory Group 1980).

Since it is known that khat can induce moderate but persistent psychic dependence (Eddy *et al.,* 1965), and since its consumption may cause psychotic behavior (Pantelis *et al.,* 1989), we decided to evaluate the effect of khat in humans by a double-blind experiment under clinical conditions. We prepared batches of chopped khat leaves of which the alkaloid content had been determined (Mathys and Brenneisen 1993), as well as khat from which the alkaloid had been removed by extraction. Both types of material were masticated for 60 min by six healthy volunteers in individual tests using a balanced experimental design. In an analogous experiment, we administered pure cathinone and placebo in gelatine capsules.

As expected, the absorption of cathinone from the plant material was significantly slower than from capsules. Cathinone-containing khat, administered at a dose of 0.8 mg cathinone /kg bodyweight, as well as pure cathinone (0.5 mg /kg bodyweight) enhanced systolic and diastolic blood pressure, and increased the ratings for stimulation/euphoria and amphetamine effects as determined through standardized questions from the Addiction Research Center Inventory. In both experiments, these changes were concomitant with the presence of cathinone in blood plasma.

Our observations provide strong support for the contention that the psychostimulant and sympathomimetic effects observed after the chewing of khat leaves are due to their constituent cathinone.

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COMPARATIVE EFFECTS OF FLUNITRAZEPAM AND TRIAZOLAM IN HEALTHY VOLUNTEERS

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Flunitrazepam is an hypnotic benzodiazepine which is misused by opioid addicts and methadone maintenance patients in Spain and other countries. The purpose of the present work was to compare the effects of flunitrazepam (F) with the hypnotic benzodiazepine triazolam (T).

METHODS: Ten healthy male volunteers without history of drug abuse or dependence participated in the study. They received in an outpatient setting single oral doses of flunitrazepam (0.5, 2 mg), triazolam (0.25, 0.5 mg) and placebo. Triazolam doses were selected in a previous pilot trial. The study followed a randomized, double-blind, and latin-square dosing. Drug effects were evaluated over a six hour period, using psychomotor performance tasks (simple reaction time, DSST, body balance, Maddox-wing), subjective effects questionnaires (visual analog scales, 49-item ARCI, 72-item POMS, pharmacological identification), and physiological measures (blood pressure, heart rate and temperature).

RESULTS: Both drugs at the highest doses impaired the performance on reaction time, DSST and Maddox-wing. Only flunitrazepam produced a decrease in the balance time. F2 increased measures related to sedation and ratings of "high", "good effects", "liking", "bad effects" and "drunken". Triazolam only increased ratings of "drowsiness". F0.5 and T0.25 produced exophoria, increased PCAG scores and decreased BG. T0.25 augmented simple reaction time. Highest doses of F and T were identified mainly as a sedative, whereas the low doses were identified as placebo.

CONCLUSIONS: The results of this study suggest that flunitrazepam and triazolam have a different profile of pharmacological effects. Flunitrazepam 2 mg produced some effects noticed as pleasant by the subjects, which could indicate greater abuse liability than triazolam.

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POSITIVE URINE ABUSCREEN ONTRAK FOR BENZOYLECGONINE AND EFFECTS AFTER INGESTING COCA TEA INFUSION OR COCA LEAVES

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Oral ingestion of coca tea infusion or coca leaves has been traditionally used in the Andean region. Effects of oral ingestion have not been systematically studied with subjects ingesting more than one coca tea bag or eating crushed coca leaves. In this study, 13 healthy volunteers (7 females, mean age 27.8 years, mean weight 62.9 Kg) with histories negative for cocaine use participated in a double-blind, inpatient setting in Lima, Peru. Eight subjects were tested with coca leaf, one each at 1, 2, 4, or 6 bags in 500 ml hot water (coca tea) or mixed with 200 Gm corn pudding (mazamorra). Each bag contained 1 Gm of crushed coca leaves (with approximately 5 mg of cocaine). Five subjects were tested with placebo (decaffeinated non-coca herbal tea or corn pudding). All urine samples collected at two and five hours after subjects received coca leaves in either tea infusion or mazamorra tested positive for benzoylcegonine with the Abuscreen Ontrak assay (sensitivity cut off = 300 ng/ml). All subjects who received placebo showed negative urine tests. No significant changes occurred in blood pressure, pulse rate, respiration rate, or skin temperature at two or five hours after coca ingestion. All subjects had normal Hamilton Anxiety Scale scores before and five hours after coca ingestion. These findings show that oral ingestion of as little as one bag of coca tea can result in a positive urine assay for cocaine metabolites for at least five hours, even though subjects showed no measurable physiological effects.

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PUPILLARY EFFECTS OF INTRAVENOUS AND SMOKED COCAINE IN HUMANS

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Tonic measures of pupillary diameter and phasic measures of the pupillary response to a light flash (light reflex) reveal drug actions on the central and peripheral neural systems that modulate the ocular response. Commonly abused drugs of several diverse pharmacological classes modify the pupillary light reflex but the effects of cocaine on these measures has not been studied. The purpose of the present study was to characterize dynamic pupillary responses after cocaine administration by the intravenous (IV) and smoked routes of administration.

Seven male subjects with histories of smoked and IV cocaine use were given smoked cocaine base (0, 10, 20 and 40 mg) and IV cocaine hydrochloride (0, 11.2, 22.4, 44.8 mg) cocaine in ascending order and a single oral dose of cocaine hydrochloride (22.4 mg). Polaroid photos of the pupil were taken before and 2.5, 10, 15, 30, 60, 120 and 240 min after drug administration, whereas the dynamic pupillary measures were obtained before and 15, 30, 60, 120 and 240 min after drug. Dynamic measures included constriction amplitude and constriction and dilation velocities from a Pulse Medical Instrument monocular pupillometer.

Mydriasis occurred immediately after placebo and cocaine administration. Placebo-induced mydriasis returned to baseline by 15 min, whereas the cocaine response persisted for up to 120 min. The amplitude of constriction and constriction and dilation velocities decreased as a function of cocaine dose. Although the maximal effects were similar, recovery occurred sooner after smoked than IV doses. Oral cocaine caused qualitatively similar effects but the onset was delayed and peak effects were obtunded. Differences between routes of administration reflect changes in bioavailability. The increase in pupil size and the concomitant decrease in constriction amplitude is a pattern unlike that reported in two studies with other abused drugs including amphetamine. Increases in pupil size and decreases in constriction amplitude imply enhanced adrenergic pupillary input, whereas the decrease in dilation velocity indicate diminished adrenergic tone. Thii disparity suggests that the pupillary effects of cocaine are mediated through redundant and opposing neural systems.

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PSYCHOACTIVITY OF RITANSERIN AND ITS INTERACTION WITH INTRAVENOUS COCAINE

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Ritanserin is a serotonin two receptor antagonist of potential therapeutic use in the treatment of cocaine abuse. To study the interaction and safety of oral Ritanserin and intravenous cocaine, a single-blind study was conducted in eight males with histories of intravenous cocaine abuse. Subjects received on days one to three a single dose of intravenous cocaine (0, 25, and 50 mg). Following this on days three to twelve they received oral ritanserin 5 mg (n-4) or 10 mg (n=4). On days nine to twelve they received a single dose of intravenous cocaine (0, 12.5, 25, 50 mg). Effects were assessed on measures of subjective, behavioral and physiologic responses including signs, symptoms, and Addiction Research Center Inventory Scales. Ritanserin alone produced minimal subjective responses and was most frequently identified as a placebo. Subjects also reported that they were "full of energy" (8/8), and observers that they were "sleepy" or "relaxed" on days five and six. Them were no physiologic changes noted with ritanserin alone. Intravenous cocaine produced expected subjective, behavioral and physiologic responses. Following ritanserin these cocaine effects (AUC scores and maximum change from baseline) were reduced for the items "feel the drug", "rush", "liking", "jittery", "down", and "how much like cocaine?". Observers reported a decrease in "restlessness" and an increase in "talkativeness". Systolic and diastolic blood pressures were decreased but heart rates were unaltered. Plasma levels of ritanserin confirmed that the drug was taken as instructed and that repeated doses of descriptive and not inferential statistics were calculated since the study was single blind and neither drugs nor dosages were given in random order. In summary ritanserin alone had little measurable acute subjective response except a reported increase in energy and questionable sedation. Ritanserin appeared to interact with cocaine in the direction of attenuation of cocaine responses. There was no evidence of any toxic or adverse interaction that would preclude the study of ritanserin as a treatment drug for cocaine dependence.

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CNS EFFECTS OF CARBAMAZEPINE IN COCAINE ABUSERS

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Since carbamazepine (CBZ) has been reported to be useful in the treatment of cocaine-dependent patients (Halikas *et al.,* 1992), a laboratory study was designed to elucidate. its potential mode of action by evaluating its ability to reduce cocaine self-administration. In screening for this study, an excessive EEG beta activity was observed in cocaine-dependent individuals. They had EEG beta levels which were more than 3 standard deviations above age-matched norms. Thus, we hypothesized CBZ would reduce the EEG beta activity and this change would correspond with a reduction in cocaine self-administration. Eighteen cocaine-dependent (DSM-IIIR) subjects (no other current drug dependence except nicotine) participated in this inpatient study, using a double-blind, double-dummy, active placebo (diphenhydramine 25 mg Bid) controlled design. Three groups of 6 subjects each achieved target CBZ plasma levels of 0, 1-3 ug/ml; or 4-7 ug/ml. Each week, three-minute continuous EEG eyes open, eyes closed, and photic driving conditions were conducted to monitor the CNS effect of CBZ. In the eyes closed condition, CBZ significantly decreased EEG beta activity in the F3 area ($P<.05$), and increased EEG theta activity in the P3, C4, and 02 areas ($p<.05$). These findings suggest CBZ only had cocaine-dependent individuals.

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INTERACTION OF BUPRENORPHINE WITH COCAINE AND MORPHINE CHALLENGE ON CRAVING SELF-REPORTS

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INTRODUCTION: Advances in medication development for substance abuse disorders require study of possible adverse physiologic and behavioral interactions of new medication with substances which may be concomitantly abused. Such assessments can be carried out in controlled, carefully monitored conditions which insure minimal risks for subjects who participate in the study. Buprenorphine does not accentuate cardiovascular, respiratory and temperature changes induced by cocaine and morphine (Teoh *et al.,* 1993). The purpose of this study was to assess craving for opioids and cocaine following intravenous administration of morphine and cocaine in men with concurrent heroin and cocaine dependence prior to and following initiation of buprenorphine pharmacotherapy.

METHOD: Thirty-six men (mean age=33) were admitted to the clinical research ward for methadone detoxification and remained on the unit for 30 days. The first seven days were drug-free followed by administration of three randomized single-blind challenge doses with cocaine, 30mg, morphine 10mg or saline placebo on three consecutive days. Following the three challenge days, subjects were given ascending doses of sublingual buprenorphine (total dose of 4 or 8mg/day) during five consecutive days. Subjects were then maintained on buprenorphine for six consecutive days and the challenges were repeated. Subjects were then given the choice to detoxify from buprenorphine over a five day period or to be discharged to an outpatient buprenorphine treatment program. Subjects were asked to complete daily a craving intensity scale and reports of their craving for cocaine, heroin, "speedball" and no drug every 30 minutes following challenge until 11:30 p.m.

RESULTS: Buprenorphine treatment was associated with a significant decrease in self-reported craving for cocaine, heroin and speedball. Heroin craving decreased the most ($p=0.0001$) and cocaine the least ($p=0.02$) during buprenorphine treatment. A dose dependent anti-craving effect of buprenorphine was not observed. Challenges with cocaine and morphine did not increase craving with respect to a preceding non-challenge day.

CONCLUSIONS: These findings supports the safety of cocaine and opioid challenges during buprenorphine maintenance.

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AN ASSESSMENT OF THE CROSS-REACTIVITY OF LEVO-ALPHA-ACETYLMETHADOL (LAAM) WITH URINARY ASSAYS FOR METHADONE

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

Levo-alpha-acetylmethadol (LAAM) is under consideration by the Food and Drug Administration for opiate dependence treatment. On June 8, 1993 the FDA Drug Abuse Advisory Committee unanimously agreed that the data provided to it regarding the safety and effectiveness of LAAM support its approval. It is a synthetic opioid structurally related to methadone with multiple actions qualitatively similar to other mu-opioid agonists. It differs from classical morphine-like agonists primarily with respect to its duration of activity. Its unique kinetic profile allows LAAM to be given effectively on three-times-weekly or alternate-day schedules.

The purpose of the present evaluation was to assess the cross-reactivity of LAAM with enzyme immunoassay (EIA) and fluorescence polarization immunoassay (FPIA) for urinary methadone using gas chromatography/mass spectroscopy (GC/MS) for confirmation of the results.

The study was conducted at the Philadelphia VA Medical Center and was part of a larger evaluation of LAAM pharmocokinetics. Participants (n=11) were stabilized on methadone prior to study enrollment. LAAM was administered three-times-weekly on Mondav, Wednesday, and Friday at 8AM. The first dose was given on Friday morning following a subject's admission to the hospital. This initial LAAM dose. as well as the Monday and Wednesday doses were 1.3 times the prior methadone dosage and ranged from 52 to 104mg. Subsequent Friday doses were 20% higher. Urine samples were collected prior to the first LAAM dose (day 0) and on study days 1, 2, 3, 15, 16, and 17. Samples were stored at -20 degrees C until analyzed. All assays were performed blindly on freshly thawed samples.

Thirty samples analyzed by GC/MS were below the 300 ng/ml cutoff level; 12 of these tested positive by FPIA, and 2 also tested positive by EIA. The means + SD for urinary methadone levels for samples that tested positive and negative by FPIA were 127 ± 98 and 51 ± 54 ng/ml, respectively, ($t=2.47$, $df=15.5$, $p=0.03$). Values for combined urinary LAAM, nor-LAAM, and dinor-LAAM levels for samples that tested positive and negative by FPIA were 6424 ± 3316 and 2920 ± 1006 ng/ml, respectively, ($t=3.55$, $df=-12.4$, $p=0.004$). These results suggest that LAAM and/or one or more of its metabolites cross-react with the FPIA, but probably not the EIA for methadone.

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AN EVALUATION OF THE EFFECTS OF LEVO-ALPHA-ACETYLMETHADOL (LAAM) ON THE HUMAN ELECTROCARDIOGRAM

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Levo-alpha-acetylmethadol (LAAM) is a synthetic opioid structurally related to methadone that is under consideration for approval as a treatment for opiate dependence. On June 8, 1993 the FDA Drug Abuse Advisory Committee unanimously agreed that the data provided to it regarding the safety and effectiveness of LAAM support its approval. The purpose of the present study was to further evaluate the effects of LAAM administration on the human ECG. It was part of a larger study assessing the pharmacokinetic profile of LAAM and its metabolites in individuals previously maintained on methadone. Initially, ECGs were used by site physicians as one component of the safety battery used to exclude or remove patients and to determine whether follow-up cardiac evaluation was indicated. Later these ECGs were scrutinized beyond their original intent (patient safety) to assess whether LAAM affected various indices of the cardiac cycle.

The study was conducted at three sites and consisted of an 18-day inpatient phase and 21-day outpatient follow-up phase. LAAM was administered three-times-weekly at 1.3 to 1.56 times the methadone dose. Doses ranged from 52 to 125 mg. ECGs were obtained prior to LAAM administration, and at the end of the inpatient phase, or day eighteen. Thirty-one subjects were enrolled in the protocol. Evaluable ECGs were obtained from 20 subjects. Seven subjects who returned to methadone following the inpatient phase received their first dose on day eighteen, before the ECG was performed. ECGs were coded and then reviewed by two cardiologists in a blinded fashion.

A statistically significant prolongation of the QTc interval was observed when the 20 subjects were considered together; but not when those who received LAAM or methadone just prior to the second ECG were considered separately. Regression analysis, performed to determine whether there was a dose-response relationtship between changes in the OTc interval and plasma levels of LAAM and its metabolites, did not reveal any statistically significant associations. There was no evidence that the change in QTc interval was clinically significant. Even though temporally related to LAAM administration, there were too many confounding variables to conclude that the prolongation was a direct pharmacological action of the drug. In conclusion, this evaluation of ECGs from twenty subjects transferred from methadone treatment to LAAM demonstrated only a small prolongation of the QTc interval which was not clinically significant.

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OPIOID DISCRIMINATION IN HUMANS: SUBJECTIVE AND DISCRIMINATIVE EFFECTS OF PROGRESSIVELY LOWER TRAINING DOSE

K. L. Preston and G. E. Bigelow

Drug discrimination performance is often thought to reflect the subjective effects of drugs. One way of assessing the relationship between subjective and discriminative effects is to examine the extent to which the two covary as experimental parameters are manipulated. Therefore, the purpose of this study was to examine the extent of covariation of subjective and discriminative drug effects as the dose of the discriminated training drug was progressively lowered. Participants were six adult male volunteers with histories of opioid abuse who were currently nondependent. 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. The hydromorphone 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. Measures of subjective and physiological effects were concurrently collected during each discrimination session. Both traditional and non-traditional measures of subjective effects were used. Traditional measures were adjective rating scales, the Addiction Research Center Inventory and global ratings of drug effects. The non-traditional subjective measures were discriminatively trained visual analog scales on which subjects rated the similarity of the study drugs to the training drugs; the training drugs themselves served as the reference points for the scales.

As dose decreased, discriminative performance was generally well-maintained, although the percent of drug-appropriate responses to hydromorphone did decline from 98% to 75%. The magnitude of hydromorphone's subjective and physiological effects also decreased as dose decreased. At the lowest dose there were no statistically significant effects of hydromorphone on any traditional subjective effect or physiological measure, although discrimination behavior and the non-traditional discriminiatively trained subjective effect measures remained statistically significant. These data indicate substantial covariation of subjective effects and discrimination performance but suggest that discrimination behavior may be more statistically sensitive than traditional subjective effects measures for differentiating among drug conditions.

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EFFECTS OF BUPRENORPHINE IN MORPHINE-DEPENDENT SUBJECTS

K. J. Schuh, S. L. Walsh, M. L. Stitzer, K. L. Preston, and G. E. Bigelow

Buprenorphine, a partial agonist at *mu* opioid receptors, is proposed for use in the treatment of opioid dependence. Buprenorphine can produce agonist effects in non-dependent individuals, and antagonist effects in highly opioid-dependent individuals. These antagonist effects may be determined, in part, by the level of opioid dependence. For example, acute doses of buprenorphine precipitated severe withdrawal in subjects maintained on 60 mg methadone/day (June *et al.,* 1993) and limited withdrawal in subjects maintained on 30 mg (June *et al.,* in prep). The present ongoing study assesses the relationship between the level of baseline opioid dependence produced by a shorter-acting opioid (i.e., morphine) and the pharmacodynamic effects of buprenorphine.

Six opioid-dependent males lived in a Residential Unit for nine weeks. Subjects were given a partial detoxification during the first week to achieve a common, low level of dependence. During the next eight weeks, they received four intramuscular (i.m.) morphine injections each day at 7:00 am, 12:00 pm, 5:00 pm, and 10:00 pm. The dose started at 15 mg/day and doubled every 2 weeks to a maximum of 120 mg/day. During the 2nd week of each dose level, subjects participated in 4 experimental challenge sessions on separate days and received placebo, 0.3 mg naloxone, 30 mg morphine, or buprenorphine in random order. The first three subjects received 3.0 mg buprenorphine and the others received 6.0 mg. These test injections replaced the 12:00 pm morphine injections on session days. Because of its long duration of action, test sessions were not scheduled the day after buprenorphine challenges. Physiological, subjective, and observer-rated measures were recorded via an on-line computer system.

Buprenorphine produced primarily agonist effects in morphine-maintained subjects. Cross tolerance was observed as morphine maintenance dose increased. Thus, few agonist effects were observed at the highest maintenance level (120 mg/day). Mild withdrawal symptoms were observed following buprenorphine in two of six subjects maintained on 120 mg morphine daily. Therefore, because limited antagonist effects occurred, the transition from short-acting opioids to buprenorphine should be accomplished without significant adverse effects.

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ACUTE PHYSICAL DEPENDENCE IN HUMANS FOLLOWING EXPOSURE TO SHORT-ACTING OPIOID DRUGS

M. K. Greenwald and M. L. Stitzer

Naloxone can precipitate withdrawal signs and symptoms after a single dose of opioid agonist. This suggests that physical dependence begins with the first exposure. The "acute physical dependence" model is an efficient way (relative to chronic dosing) to characterize the dependence potential of opioids. Previous studies in our laboratory have precipitated withdrawal after longer-acting opioid *mu* agonists (morphine, methadone).

The purpose of this study was to determine whether withdrawal can be precipitated after single dose exposure to short-acting opioid drugs. We examined dose effects and duration of acute physical dependence (via naloxone challenge) following pretreatment with single doses of short-acting fentanyl and very short-acting alfentanil. It was predicted that *intensity* of precipitated withdrawal effects would be related to agonist pretreatment dose, whereas *duration* of physical dependence would be related to the drug's duration of action; specifically, physical dependence should be detectable longer for fentanyl than alfentanil.

Eight male regular heroin users (not physically dependent) lived on a residential unit for 5.5 weeks and participated in experimental sessions twice weekly. Each subject was exposed to ten conditions in a placebo-controlled, randomized crossover, double-blind design: fentanyl (.125 and .25 mg/70 kg), alfentanil(1.0 and 2.0 mg/70 kg) and saline i.v. injection, followed by naloxone (10 mg/70 kg) i.m. at one and six hours. Fentanyl and alfentanil doses were selected for equianalgesic potency.

For both opioid agonists, dose-related changes in subjective reports (*e.g.,* "high" and "good effect") and physiological responses (pupil constriction, respiratory rate depression) peaked within ten minutes and dissipated more quickly for alfentanil than fentanyl. Subjective and physiological effects were consistent with an 8:1 (alfentanil:fentanyl) relative potency ratio.

When naloxone challenge followed fentanyl and alfentanil pretreatment at one hour, similar increases in withdrawal symptom reports (e.g.. composite withdrawal symptom index, ratings of "bad drug effect" and "withdrawal sickness"). In contrast, naloxone at six hours precipitated withdrawal responses only for the higher dose (.25 mg/70 kg) of fentanyl in the absence of residual agonist effects.

In summary, results confirm that there is dependence potential associated with short-acting opioid drugs. Precipitated withdrawal was observed after a single exposure to fentanyl and alfentanil, suggesting that even brief periods of receptor occupancy can produce physical dependence. Precipitated effects could be observed longer (up to 6 hours) for fentanyl than alfentanil, implying that the duration of acute physical dependence is related to the drug's duration of action.

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EFFECTS OF TRAMADOL IN OPIOID-DEPENDENT VOLUNTEERS

J. Camí, X. Lamas and M. Farré?

Preclinical and clinical studies, together with epidemiological data, suggest that tramadol has a low abuse liability. In non-dependent humans (Preston *et al.,* 1991), the highest dose of tramadol (300 mg, i.m.) produced some subjective effects that were not clearly morphine-like. The present study was carried out to assess the opioid agonist and antagonist properties of tramadol in opioid-dependent subjects.

METHODS. Six adult male methadone-maintained volunteers (30 mg/24 h, p.o.) participated as inpatients. Subjects were tested in three sessions separated by 24 or 48 h. Tramadol hydrochloride (100, 300 mg) and placebo were administered i.m., using a double-blind, latin-square design. Effects of drugs were assessed at baseline, and for 240 min postadministration. Subject- and staff-rated measures of effect included six visual analog scales, an adjective rating list, a 49-item short form of the ARCI, and a drug class questionnaire. Physiological measures were collected along the sessions.

RESULTS. The doses of tramadol produced no effects, as compared with placebo, in any variable. Although some subjects classified the effects of tramadol as different to placebo, the classifications were not consistent across subjects and doses. In contrast, the effects of morphine (20 to 60 mg, i.m.) and naloxone (0.1 and 0.2 mg, i.m.) in a previous study carried-out in the same subjects were, as expected, typical of an opioid agonist and antagonist, respectively (Lamas *et al.,* 1993).

CONCLUSIONS. The lack of agonist or antagonist effects after the administration of tramadol allows two interpretations: 1) since the antinociceptive effects of tramadol are not exclusively mediated by opioid mechanisms, a dissociation between the analgesic potency of tramadol and its potency in producing subjective effects could exist; 2) the doses administered in this study were not large enough to produce measurable subjective effects in tolerant subjects. These results suggest that, at the doses administered, tramadol has no effect in opioid-dependent humans, supporting that the abuse liability of tramadol is probably low. Higher doses and direct comparisons with standard drugs would be needed to fully assess the abuse liability of tramadol.

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SUBJECTIVE-EFFECTS PROFILE AFTER DAILY METHADONE MAINTENANCE DOSE

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Forty-eight (24 male, 24 female) methadone maintenance clients were administered a subjective effects battery consisting of the Addiction Research Center Inventory (ARCI), Opiate Symptoms Checklist (OSC), the Profile of Mood States (POMS), and several visual analog scales (VAS). They completed the computer-based battery (courtesy R. Foltin) 30 minutes before and 90 minutes after receiving their regular methadone maintenance dose. There were no gender differences on age, years of education, or verbal age. Neither the average dose nor number of months in the program differed for males and females. However, women evidenced higher baseline depression levels (p <.004). Men and women had similar drug use histories with regard to years of opiate use and number of previous drug abuse treatments. In addition there were no gender differences in the percentage of clients testing positive for drug use or number of positive tests in those clients, either in the week before the study or in the previous six months. However, men had used illicit opiates more recently than women (p <.005). Individual scale scores of the ARCI changed dramatically after methadone administration (p <.0001). Sedative (PCAG) and dysphoric (LSD) effects decreased, while euphoric (MBG) and stimulant (BG, A) effects increased. There were no changes in opiate withdrawal/intoxication symptoms (OSC). Robust shifts in mood (POMS) also were apparent (p <.0001). Anxiety, Depression, Anger, Fatigue, and Confusion scores fell after methadone administration, while Vigor, Friendliness, Arousal and Positive Mood scores all increased. Effects of methadone on VAS scores were less substantial. All subjects reported feeling more "high" (p <.0001) and sedated (p <.02), less "down" (p <.02), and tended toward less endorsement of wanting Heroin (p <.1) after methadone. Females tended to have higher scores than males before dosing and exhibit less drastic changes after methadone. For example, men endorsed feeling more anxious than women (p <.002), and wanting significantly more Cocaine (p <.05) and Heroin (p <.02). Males reported feeling less Elation than females before methadone and more after (G*T: p <.04), indicating a stronger response to methadone. In summary, administration of a client's daily methadone maintenance dose did not affect opiate intoxication/withdrawal symptoms but did lessen feelings of dysphoria and sedation and increase euphoric and arousal effects. In addition, female mood scores seem less affected by methadone administration than are males', although doses were equivalent.

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STUDIES IN HUMAN ORAL DRUG SELF-ADMINISTRATION: METHADONE

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Relative reinforcing effects of different concentrations of methadone were investigated by examining the effects of response requirement on self-administration of methadone across a range of concentrations. Methadone maintenance patients stabilized at a dose of 80 mg were recruited as subjects. Completing a response requirement of 32, 64, or 128 responses on one button dispensed 10 ml of drug solution. An equivalent response requirement on a second button dispensed 10 ml of vehicle. Concentrations of methadone solutions were 0.108, 0.054 or 0.027 mg/ml. Unconsumed methadone was administrated 30 minutes post-session. Amount of methadone consumed decreased as i) concentration was decreased and ii) work requirement increased. Thus, the 0.108 mg/ml dose concentration maintained more responding than the 0.054 mg/ml and 0.027 mg/ml dose concentrations. The resistance of responding maintained by 0.108 mg/ml dose concentration. This procedure provides an important model examining behavioral mechanisms of methadone dose ingestion and deprivation in patients.

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SUBJECTIVE AND PERFORMANCE EFFECTS OF BUSPIRONE, DIPHENHYDRAMINE, LORAZEPAM, AND PENTOBARBITAL

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The present study was designed to assess the subjective and performance effects of buspirone, diphenhydramine, lorazepam, and pentobarbital. Seventeen healthy adult males with histories of recreational sedative abuse participated in a double-blind crossover study in which subjects received placebo, buspirone (30, 60, and 120 mg), diphenhydramine (100, 200, and 400 mg), lorazepam (1, 2, and 4 mg) and pentobarbital (50, 100, and 200 mg) once each, in random sequence, on a total of 13 separate days. Compounds were administered in identically appearing capsules. Subject-rated subjective effects and psychomotor and cognitive performance were assessed each day 30 minutes before and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, and 24 hours following drug administration. The study is ongoing: the present results are a preliminary analysis with data from 17 subjects. All four drugs produced dose related increases in ratings of drug strength. Performance effects were dose related, peaked at one or two hours and gradually returned to baseline within 6 hours. Buspirone, diphenhydramine, lorazepam. and pentobarbital were differentiated on a variety of these performance measures. High doses of all four drugs significantly decreased scores on the circular lights test (a measure of psychomotor performance speed). Diphenhydramine, lorazepam, and pentobarbital, but not buspirone, significantly decreased digit-symbol-substitution test scores. Only lorazepam produced significant decreases in picture recognition consistent with the amnestic effects of other benzodiazepines.

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RELATIVE AMNESTIC EFFECTS OF LORAZEPAM (LZ), DIPHENHYDRAMINE (DPH), AND SECOBARBITAL (SECO)

J. D. Roache and D. L. Creson

The effects of LZ (2 and 3 mg/70kg) and DPH (100 and 150 mg/70kg) were compared to placebo and 200 mg/70kg SECO in ten normal male subjects. SECO was administered before and was repeated again after the other doses (placebo, LZ, and DPH) were administered in balanced Latin Square sequences. The first SECO dose produced larger effects than the other drugs on most measures and the repeat SECO dose showed that tolerance had developed during the within-subject dosing. Both LZ and DPH produced dose-related effects. Similar degrees of subjective sedation were observed for both drugs on several different subject rating scales. Whereas LZ produced more psychomotor impairment than DPH, both drugs produced similar performance generally decreased as the delay interval increased (0-16 sec). Memory impairments for most drug conditions were greater at the longer delay intervals indicating a "drug-induced forgetting".

These results demonstrate that LZ and DPH produce similar degrees of short-term memory impairment at similarly sedative doses. In contrast to previous comparisons in which LZ was reported to be more amnestic than other sedative drugs, this result indicates that the benzodiazepine, LZ, has a similar amnestic potential compared to sedative antihistamines.

LZ and DPH were compared using a conventional within-subject Latin Square Design. However, the administration of SECO before and after the Latin Square sequence provides additional information. For one thing, LZ and DPH doses can he compared not only to the negative control observation (placebo) but also to a positive control (SECO). The lesser effect of SECO upon repetition of the dose after the Latin Square sequence represents some kind of tolerance to sedative effects. Whether this reflects an acquired tolerance in the traditional pharmacological sense or whether it represents an exacerbated effect of the initial dose exposure cannot he determined at this time.

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SECOBARBITAL OCCASIONS NOVEL-APPROPRIATE RESPONDING BY HUMAN TRIAZOLAM DISCRIMINATORS

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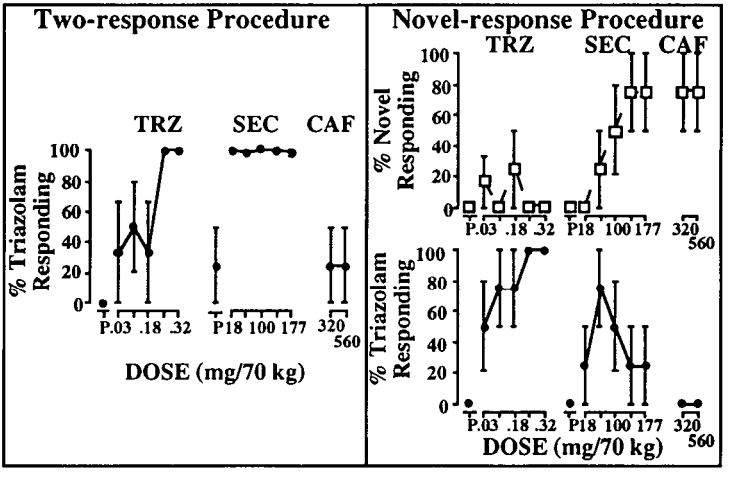
The discriminative stimulus (DS) effects of benzodiazepines and barbiturates are often indistinguishable, although these drugs are pharmacologically distinct and their DS effects can be differentiated using specific antagonists or judicious selection of training stimuli. The present experiment used a "novel-response" procedure that provides a response alternative appropriate in the presence of novel-drug effects (i.e., effects unlike either training stimulus) to assess whether this procedure would differentiate secobarbital from triazolam in human triazolam discriminators. Humans (N=6) were trained to discriminate triazolam (0.32 mg/70 kg, p.o.) from placebo under a two-response drug discrimination training procedure. After acquisition of the discrimination (4 to 5 sessions), dose-effect curves were determined for triazolam (0.1-0.32 mg/70 kg), secobarbital (56-177 mg/70 kg) and two doses of caffeine (320 and 560 mg/70 kg) under a standard two-response procedure (drug vs. placebo) and/or the novel-response procedure. Under the two-response procedure, triazolam and secobarbital substituted for triazolam while caffeine produced predominantly placebo-appropriate responding (left). Under the novel-response procedure, triazolam still produced almost exclusively triazolam-appropriate responding, while secobarbital and caffeine produced a mean of at least 75% novel-appropriate responding (right). These results suggest that qualitative comparisons of novel drug stimuli can be made by considering response distributions across all three response alternatives. In terms of similarity to triazolam in the current experiment, triazolam > secobarbital > caffeine.



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THE SUBJECTIVE, BEHAVIORAL AND COGNITIVE EFFECTS OF SUBANESTHETIC CONCENTRATIONS OF ISOFLURANE AND NITROUS OXIDE IN HEALTHY VOLUNTEERS

J. P. Zacny, J. L. Lichtor, R. Martin, P. Hoffmann, and G. Sparacino

INTRODUCTION: Isoflurane is frequently used as a general anesthetic, but is sometimes employed in conscious sedation surgical procedures. No studies to date have systematically characterized the psychoactive effects of isoflurane. Accordingly, we assessed isoflurane effects across two subanesthetic concentrations. In the same study, subjects were also exposed to nitrous oxide so comparisons and contrasts could be made between these two inhaled anesthetic agents.

METHODS: A prospective, crossover, double-blind trial was conducted in nine healthy volunteers in which we examined the effects of isoflurane (0.0.0.3 and 0.6%) and nitrous oxide (0, 20 and 40%). Dependent measures included subjective effects (*e.g.,* visual analog scales, MBG and LSD scales of the ARCI), psychomotor performance (*i.e.,* Digit Symbol Substitution Test [DSST], reaction time, coordination), and memory (immediate and delayed free recall). Concentrations of anesthetics were chosen so that they would be equivalent in anesthetic efficacy at the time the main battery of testing was conducted (15 minutes into the 30-minute inhalation period).

RESULTS AND CONCLUSIONS: Self reported "strength of drug effect" ratings were similar between the two agents, and were concentration-related. Both agents increased VAS ratings of "high," "coasting (spaced out)," "tingling," "dizzy," and "confused", and decreased ratings of "hungry". LSD scores were significantly increased by nitrous oxide ($p<0.01$), and marginally increased by isoflurane ($p=0.07$). The two agents differed most on the VAS ratings of "stimulated" and "sedated": nitrous oxide significantly increased "stimulated" ratings, but did not affect "sedated" ratings. Isoflurane significantly increased "sedated" ratings, but did not affect "stimulated" ratings. DSST performance, reaction time, and coordination were grossly impaired by isoflurane. Nitrous oxide impaired coordination and DSST performance, but to a much lesser extent than did isoflurane. Although both agents impaired memory, delayed free recall was impaired to a greater extent by isoflurane. The subjective and behavioral differences noted between the two general anesthetics suggest that the physicochemical mechanisms of action which underlie these effects differ between the two agents.

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EFFECTS OF THE 5-HT_3 RECEPTOR ANTAGONIST, ONDANSETRON, ON BEHAVIORAL AND SUBJECTIVE RESPONSES TO ETHANOL IN NORMAL, HEALTHY VOLUNTEERS

P. Doty, J. P. Zacny, and H. de Wit

Several lines of evidence from laboratory animal and clinical studies suggest that the 5-HT_3 receptor subtype may mediate some of the CNS effects of ethanol. For example, the discriminative stimulus effects of ethanol in laboratory animals were blocked by specific 5-HT_3 receptor antagonists (Grant and Barrett 1991). In addition, the 5-HT_3 receptor antagonist, ondansetron, decreased consumption of ethanol in laboratory animals and in ethanol-dependent patients (Sellers et al., 1992). The present study evaluated the effects of ondansetron pretreatment on the acute physiological, behavioral and subjective responses to a moderate dose of ethanol in normal, healthy volunteers. Thirteen male and female moderate drinkers (average 11.2 drinks/week) participated in a double-blind, placebo-controlled, crossover design study. During the six sessions, subjects were given an intravenous infusion of ondansetron (0, 0.15 or 0.30 mg) and five minutes later consumed a beverage containing either placebo or ethanol (0.5 g/kg) For three hours after the beverage was consumed, physiological, behavioral and subjective measures were taken at regular intervals.

Ethanol alone produced prototypic subjective effects, including increases in ratings of liking and euphoria. Ondansetron alone produced subjective effects that did not differ from placebo. On most of the dependent measures, pretreatment with these doses of ondansetron did not significantly alter the effects of ethanol. However, ondansetron pretreatment did significantly attenuate ratings of drug liking and elation relative to those observed when ethanol was administered alone. Further examination of the data revealed that this attenuation only occurred in a few individuals. Results from this type of study will be useful in determining mechanisms underlying the behavioral and subjective response to ethanol and other abuse drugs in healthy volunteers and in developing pharmacotherapies for drug abuse treatment.

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Available upon request.

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ALCOHOL AS A CONDITIONED ELICITOR OF ALCOHOL-RELATED RESPONSES

J. M. White and V. W. Rees

Responses to drugs can be conditioned by associating the drug effect with drug-predictive cues. Exposure to such cues, without drug administration, may evoke conditioned responses that are opposite to the usual drug effect (Siegel 1983). Such responses are observed in drug users when exposed to drug-related stimuli. Amongst alcohol abusers a common phenomenon is "loss of control" following consumption of a relatively small amount of alcohol. A conditioning model proposes that alcohol itself has become a conditioned stimulus because it predicts further alcohol consumption (Ludwig *et al.,* 1974). Acquisition of CRs to a low dose cue has been demonstrated in animal subjects (Greeley *et al.,* 1984), but not previously in humans. This study attempted to demonstrate the acquisition of conditioned heart rate and skin resistance responses to a low dose of alcohol. In six conditioning sessions, ten social drinkers received a low dose of alcohol (the CS; 0.10 g/kg) 15 minutes prior to a high dose (US; 0.55 g/kg). The conditioned response to the low alcohol dose cue was then tested in the absence of the usual environmental and drink-flavour cues. A control session tested for the possible influence of cues provided by the general experimental procedure. The heart rate response to the low dose was 9.8% below baseline, and was distinguishable from the preconditioning response by a Session xTime interaction [$F(2,18) = 4.45$, $P < .05$]. The skin resistance response to the low dose cue differed from baseline by 15%, although this did not differ significantly from pre-conditioning levels [$F(2,18) < 1.0$]. The present data extend the body of human research on cue-elicited conditioned responding to include drugs as conditioned as well as unconditioned stimuli, and suggest a mechanism for the loss of control phenomenon.

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THE EFFECT OF FOOD DEPRIVATION ON ALCOHOL CONSUMPTION IN BULIMIC AND CONTROL WOMEN

C. M. Bulik and E. C. Brinded

Food deprivation in the form of dieting and fasting is a central feature of bulimia nervosa during inter-binge intervals producing biological changes characteristic of the starvation state (Laessle *et al.,* 1988). Food deprivation studies on humans are few and have provided only marginal evidence for the food deprivation effect in humans (Zacny and deWit 1989; Zacny and deWit 1992). No studies have examined whether food deprivation may also contribute to the high rates of substance abuse seen in bulimic women (Bulik 1987; Bulik *et al.,* 1992; Pyle *et al.,* 1981). We hypothesized that short-term food deprivation would lead to increased alcohol consumption in controls and that the magnitude of the effect may be increased in women with bulimia nervosa as dieting often precedes episodes of binge-eating and this rebound disinhibition may also generalize to other reinforcers.

METHODS:

Five bulimic women (B) and five controls (C) spent four consecutive evenings in the laboratory and underwent two food deprivation (D) (19 hours) and two non-deprivation (ND) sessions. Subjects were randomly assigned to order of presentation. Baseline and half hourly breath alcohol level (BAL) readings and Visual analog scales (VAS) for mood and hunger were taken. Subjects watched a 2-hour segment of an epic movie each evening and drank *ad lib* from a refrigerator/bar in the experimental room. A range of alcoholic and nonalcoholic beverages and 50 grams of plain popcorn were available.

RESULTS:

No significant differences on age, body mass index, or number of grams of alcohol consumed in D vs. ND conditions were found. BALs were significantly higher in the ND than in the D conditions. Calories consumed due to alcohol did not differ by diagnosis or deprivation condition. Calories consumed due to noncaloric beverages were significantly greater in C than B women.

DISCUSSION:

Food deprivation did not lead to increased self-administration of alcohol in B or C women. The duration and intensity of food deprivation as well as maintenance at below ideal body weight may be important factors in eliciting the effect. B women consumed significantly fewer calories due to nonalcoholic beverages suggesting they consumed alcohol more efficiently without excess calories.

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PARKINSONIAN PATIENTS REPORT BLUNTED SUBJECTIVE EFFECTS OF METHYLPHENIDATE

A. M. Persico, S. Reich, J. E. Henningfield, M. J. Kuhar, and G. R. Uhl

Dopaminergic brain circuits important for psychostimulant reward and reinforcement have been identified in animal studies. Lesions of VTA dopaminergic neurons blunt psychostimulant self-administration in rats.

Human VTA systems are substantially different from those in rats. Brains of patients with idiopathic Parkinson's disease show depletion of VTA neurons, with reductions of 40-60% of these neurons identified in quantitative pathological studies of these brains post-mortem.

To test the requirements for intact dopaminergic systems for subjective stimulant effects in man, we have examined responses to methylphenidate in Parkinsonian patients and neurologically-intact sex, race and age-matched controls. Patients and controls were free of substantial depression of dementia. Patients were assessed for physiological and psychological responses to placebo and four doses of methylphenidate, administered orally, in separate sessions. Parkinsonian patients maintained their anti-Parkinsonian drug regimens unchanged. Responses were corrected for placebo response, and values for each Parkinsonian patient were compared to those of an age-and sex-matched neurologically-normal control subject.

Drug-induced changes in subjective ratings of "good" feelings and overall drug responses, as well as alterations in seated heart rate, were blunted in the Parkinsonian patients in comparison to the age-matched control subjects. These differences did not correlate with duration of disease or L-dopa dosage.

These results provide support for "dopaminergic hypothesis" of psychostimulant reward in man. They also may suggest a possible basis for the depressive mood disturbances found in many Parkinsonian patients.

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DISCRIMINATIVE STIMULUS EFFECTS OF TRIPELENNAMINE IN HUMANS

S. Evans, J. Henningfield, and C. E. Johanson

Drug discrimination methods have been applied to the study of the stimulus properties of a variety of drugs in humans. One group of drugs that has received little attention is the antihistamines despite their wide-spread over-the-counter use and side effects that indicate CNS activity. In the present study, 20 normal volunteers were trained to discriminate 75 mg tripelennamine from placebo. The experiment consisted of 33 experimental sessions during which subjects reported to the laboratory in the morning for a 3 to 4 hour period. Subjects sometimes participated concurrently. At the beginning of the session, they filled out several mood questionnaires, performed several performance tasks, their behavior was rated by observers, and they ingested a capsule. The assessment was repeated at regular intervals. Correct identifications were reinforced with bonus money. Thirteen of the subjects learned the discrimination and nine of these were tested with additional drugs. Drugs that were identified as tripelennamine by over 75% of the subjects included diazepam and diphenhydramine and there was some evidence of dose-related effects with higher doses producing a greater percentage of tripelennamine-appropriate responses. Averaging across all subjects, there were significant drug-by-time interactions indicating that tripelennamine produced time-related increases in diastolic blood pressure and heart rate as well as increases on the Fatigue scale on the POMS and the PCAG scale of the ARCI. There were no differences in subjective effects between discriminators and non-discriminators. Similar effects were seen with the drugs that substituted although diazepam had different physiological effects. Although amphetamine was tested as a negative control, over half of the subjects discriminated both doses as tripelennamine. Its physiological effects were similar to tripelennamine but its subjective effects were placebo-like.

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COCAINE AS A DISCRIMINATIVE STIMULUS IN HUMANS

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This study evaluated whether an oral dose of the CNS stimulant cocaine can serve as a discriminative stimulus in humans. Four male and one female cocaine-abusing volunteers (ages 27-41) were trained to discriminate between cocaine (80 mg/70 kg, P.O.) and placebo. Monetary reinforcers were earned for identifying correctly the letter code associated with each substance. After two training sessions, the ability to discriminate between the two training conditions was tested. In subjects who met the criterion for discrimination (*i.e.,* >80% correct responding on four consecutive sessions), dose-effect curves were determined for orally-administered cocaine (0, 20, 40, 80, 120 mg/70 kg). intranasally-administered cocaine (0, 20, 40, 80, 120 mg/70 kg) and the benzodiazepine triazolam (0, 0.25, 0.50 mg/70 kg, P.O.). All five subjects met the criterion for the cocaine-placebo discrimination within 4-7 sessions. Novel cocaine doses via either the oral or intranasal route of administration generally produced dose-related increases in cocaine-appropriate responding; whereas triazolam produced predominantly placebo-appropriate responding. Cocaine via both routes produced qualitatively similar increases in stimulant-like self-reports; whereas triazolam produced increases in sedative-like ratings. Throughout dose-effect curve determinations, the training dose of cocaine and placebo continued to be identified correctly in four of five subjects (range: 67-100% correct responding). These results suggest that orally-administered cocaine (80 mg/70 kg) is discriminable from placebo, has behavioral effects that are qualitatively similar to intranasal cocaine, and has pharmacological specificity as a discriminative stimulus.

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COCAINE-INDUCED CONTEXT-SPECIFIC SENSITIZATION IN HUMANS: PRELIMINARY RESULTS

R. B. Rothman, D. A. Gorelick, X. Guo, R. I. Herning, W. B. Pickworth, T. M. Gendron, and J. E. Henningfield

Stimuli paired with cocaine injections acquire incentive motivational properties. Classical conditioning using cocaine as the unconditioned stimulus is readily found in humans. Some studies suggest that conditioned drug effects play a critical role in the relapse of opiate as well as cocaine addicts. Understanding the neurochemical mechanisms which mediate the acquisition of the unconditioned stimulus properties of cocaine, as well as their expression, may be a crucial first step in the process of developing medications to facilitate abstinence in a clinical setting.

Pert, Weiss and Post introduced a simple and powerful one-session conditioning paradigm with cocaine to characterize the unconditioned stimulus properties of cocaine in rodents. Their results indicate that conditioning plays a major role in the development of behavioral sensitization. We used a design-similar to that of the rodent studies to determine if context-dependent cocaine-conditioning could be demonstrated in humans. End-point measures included subjective-effect scales, vital signs, EEG, motor activity as measured by wrist activity meters, pupil-responses and plasma prolactin. The physiological data and limited subjective effects data are presented here.

Twenty-five physically healthy male and female subjects, age 21 to 45 years, with a history of using intravenous (IV) cocaine at least three times in the month prior to admission were enrolled in the study. To mimic the "home" and "test" cages, two rooms were used: a small "test chamber" and a large "home" room with a window and furnishings. On the first day, each subject received a drug infusion (either SAL or 40 mg IV COC) double-blind in both locations. On the second day all subjects received a drug infusion (SAL or 25 mg COC IV). A PAIRED Group (#1) received COC on both days in the test chamber. An UNPAIRED group (#3) received COC in the home room on day 1, and COC in the test chamber on day 2. A CONTROL-1 group (# 2) received COC only on day 2 in the test chamber. A CONTROL-2 group (# 4) received COC in the test chamber on day 1, and SAL in the test chamber on day 2. The cocaine-induced responses of groups 1 and 3 on day #2 (PAIRED vs UNPAIRED) were analyzed by ANOVA to determine if conditioned-sensitization developed. There were no significant differences across all end-points. The cocaine-induced responses of groups 1 and 2 (UNPAIRED vs CONTROL-1) on day 2 were analyzed by ANOVA to determine if sensitization developed. The only significant difference occurred in the diastolic BP measurement, where the effect of cocaine in group 1 was decreased relative to group 2. These results suggest that unlike the data observed in rats, a single conditioning session is not sufficient to produce either conditioned or unconditioned sensitization to the physiological effects of cocaine in humans. Likely explanations for these negative findings are that the stimulus-properties of the two environments were not different enough and/or that more than one conditioning session may be required. In future studies, we plan to use four conditioning sessions.

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COCAINE CRAVING DURING A RESIDENTIAL TRIAL WITH COCAINE-DEPENDENT HUMANS

L. L. Weinhold, D. A. Gorelick, and J. E. Henningfield

Cocaine has been reported to acutely increase, rather than satiate, its own craving (Jaffe *et al.,* 1989), but individual differences have never been systematically explored. This study addressed this issue in the context of a human experimental model of cocaine self-administration. Eighteen Cocaine-dependent (DSM-IIIR criteria) subjects (14 men; 15 blacks, 3 whites; mean [±S.D.] age 32.9 ± 4.5 years; cocaine use in prior 30 days 20.5 ± 7.8 days & 10.4 ± 12.4 gms), with no other current substance dependence except nicotine (n = 8). were housed for 7-10 weeks on a closed research ward. Subjects could pay $1 (in tokens) to initiate a self-administration session three times (at 2-hr intervals) every Monday, Wednesday, and Friday, alternating with three daily money ($2) delivery sessions. The double-blind IV injections were either cocaine-25 mg on two days or saline-1 ml on one day each week. Cocaine craving was measured by computer-presented 100-mm visual-analogue scales (VAS) labeled "craving," "want," and "need" given before and for nine minutes after each session's injection. A 5-point Likert scale item labeled "craving for cocaine" was given 10-15 minutes after each session's injection or money delivery, abridged ARCI given about 20 minutes afterwards, and the POMS given about 25 minutes afterwards.

After a week (1) of ward acclimation and a baseline week (2) of self-administration sessions, 6 subjects each were randomly assigned double-blind to one of three targeted CBZ plasma levels: 0, 1-3 ug/ml, or 4-7 ug/ml. All subjects also received active placebo of diphenhydramine-25 mg bid. All subjects maintained their targeted plasma levels during weeks four and five, so data were analyzed only from weeks two, four, and five. Statistical analyses were done by 1-way ANOVA, except that comparisons between the different craving measures were done by Pearson correlation coefficient. Subjects fell into two groups in terms of pattern of cocaine craving: nine subjects ("cocaine-induced cravers") (3 from each medication group) had low baseline levels of craving and significantly increased craving at all time points after cocaine injection; nine other subjects ("constant cravers") had low to high baseline craving and no significant change in craving after cocaine. The cocaine-induced cravers also showed higher ARCI LSD subscale scores and higher POMS anxiety subscale and total scores after cocaine injection than after saline injection. Neither group showed increased craving after saline injection or money delivery. The two groups differed in only two subject characteristics: mean ± SD) age (30.7 ± 1.4 vs 35 ± 1.7 years) and MJ use in 30 days prior to the study (0.1 ± 0.1 vs 1.9 ± 0.8 days). All 3 VAS craving scales were significantly correlated, but cocaine-induced cravers had lower and more variable correlations (r's = 0.66 to 0.82) than did constant cravers (r's = 0.96-0.97).

These findings show that there are substantial individual differences among cocaine addicts in baseline cocaine craving and cocaine-induced craving, but do not suggest what subject characteristics might be associated with this.

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CIGARETTE SMOKING NOT AFFECTED BY COCAINE SELF-ADMINISTRATION

A. Radzius, N. J. Carriero, L. L. Weinhold, D. A. Gorelick, and J. E. Henningfield

Acute administration of psychomotor stimulants increases cigarette smoking for 1-3 hours. As part of a larger study on effects of carbamazepine (CBZ) on cocaine self-administration, data on ad lib smoking were collected using computerized cigarette dispensers. Subjects were 8 (5 male) cocaine-dependent (DSM-III-R criteria from Diagnostic Interview Schedule) cigarette smokers with mean (±S.D.) age of 33 (±3.3) years and smoking duration of 19.6 (±4.27) years. Their prestudy self-reported daily cigarette intake was 12.25 (±4.84) cigarettes and Fagerstrom Tolerance Questionnaire score of 5.75 (±1.28). While on the closed research unit, number of cigarettes smoked per day prior to start of the study was 16.0 (±6.05). Subjects were HIV negative, not pregnant or lactating, not currently drug-dependent except for nicotine (N=4) and had no clinically significant medical or psychiatric problems. During test sessions on Monday, Wednesday and Friday of each week, subjects could obtain either cocaine (25 mg IV) on two days or saline (1 ml IV) on the third day, three times per study day at two-hour intervals (drug condition was double-blind). Paired t-tests were performed on the number of cigarettes dispensed on days that subjects received either cocaine and saline. After baseline week, subjects were placed on CBZ to achieve plasma levels of 1-3µg/ml or 4-7µg/ml, plus diphenhydramine (DPH) (25 mg BID). Analyses were performed on days subjects were taking CBZ plus DPH by a 3-way (cocaine self-administration opportunity, CBZ dose, before or during CBZ) ANOVA. We found no significant cocaine effect on the number of cigarettes dispensed by condition whether analyzed by 24-hour, 8-hour (0000-0759, 0800-1559, 1600-1159), or 4-hour time blocks immediately following the day's last test session (1600-1959). 3-way ANOVA did show a significant CBZ effect (1 cigarette increase) during the 0800-1559 hour time period. These findings do not support the generality of the hypothesis that chronic cocaine self-administration produces increased smoking over time intervals longer than 1-3 hours. However, they do not rule out the possibility that cocaine use in a non-laboratory environment is accompanied by acutely increased smoking.

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A METHOD FOR DELIVERING SMOKED DRUGS OF ABUSE IN HUMANS: PRELIMINARY FINDINGS

A. J. Jenkins, R. M. Keenan, J. B. Kivett, K. Demuth, A. V. Neu, S. J. Heishman, J. E. Henningfield, and E. J. Cone

In the past, it has been difficult to study the dose-related effects of drugs of abuse by the smoking route. The primary reason was the technological difficulties associated with administering precise doses while minimizing the pyrolysis of parent drug. We modified a previously described method for smoked cocaine delivery (Hatsukami *et al.,* 1990) and adapted the computerized drug delivery system which utilized a nichrome wire coil heating element for drug volatilization. The coil was inserted into brass tubing at both ends and mounted in a machined plastic plug (Smoking Insert). The insert was placed in a smoking chamber connected to a differential pressure transducer that allowed detection of air flow changes. A Pyrex mouthpiece was positioned over the wire coil and held in alignment by the smoking chamber. An AC-DC transformer was turned on and off whenever the computer sensed a change in air flow through the smoking chamber. Drug in solution of known concentration was loaded onto a pre-weighed wire coil with a 1cc disposable syringe. The coil was dried at room temperature for 24 hours, then reweighed. After baseline measures were collected, the subject was instructed to exhale and the mouthpiece was inserted into the mouth. The subject was instructed to inhale, thereby changing the air flow through the smoking chamber. The differential pressure transducer via a pneumotachograph signaled this change to the computer which activated the power supply. The coil was heated and the drug volatilized under continuous air flow conditions. The dose was inhaled as a single puff.

This system was utilized for a series of clinical studies to compare the dose-related pharmacokinetic and pharmacodynamic effects of intravenous, oral, and smoked drugs of abuse. Human volunteers, 21-40 years old, in good health and with a recent history of drug use, were administered four intravenous, one oral (except nicotine) and four smoked doses. One of the smoked doses was randomly repeated. Physiological, subjective, behavioral and pharmacokinetic parameters were measured. Clinical studies with cocaine and nicotine were completed and a study of heroin is in progress.

The volatilized components of the smoking device were determined. Drugs in solution were applied to the coil in the same manner as for drug administration. Upon volatilization, the smoke was collected in a cold trap and analyzed by GC/MS in scan mode. The percentage recovery of patent drug and the identity of other major components were determined. Methamphetamine was recovered quantitatively when the hydrochloride salt was volatilized. The percentage recoveries of other drugs were as follows: cocaine base, 94%; heroin base, 89%; phencyclidine base, 93%; and nicotine, 96%.

In summary, an existing computerized drug delivery system for smoked cocaine delivery was adapted to administer other drugs, such as nicotine and heroin, by the smoked route. The system was efficient in delivering parent drug in a single puff. The smoking device is currently utilized in a series of clinical studies to compare the pharmacokinetic and pharmacodynamic effects of different routes of drug administration.

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PERFORMANCE EFFECTS OF SMOKED NICOTINE AND COCAINE IN HUMANS

R. C. Taylor, R. M. Keenan, S. J. Heishman, A. V. Neu, and J. E. Henningfield

Nicotine and cocaine are widely abused drugs with stimulant properties. In general, studies investigating the effects of nicotine and cocaine on human performance have have shown small increases in response rate and/or reaction time in tests of psychomotor abilities. However, the results of studies that have involved administration of nicotine by cigarette smoking are often difficult to interpret because of an unknown nicotine dose due to variations in smoking behavior. A new methodology for delivering precise doses of smoked drugs in a single inhaled bolus to humans has been developed. Two within-subjects studies were conducted in which the behavioral effects of nicotine and cocaine were systematically measured using this method of precise dosing of smoked drugs. The dose and time course effects on psychomotor performance were measured repeatedly after doses of nicotine and cocaine were administered

In one study, male volunteers (N=5) who smoked at least one pack of cigarettes daily, were administered 0, 0.75, 1.5, and 3.0 mg of nicotine on separate days after overnight tobacco abstinence. Subjects were also tested after smoking cigarettes and after 9 hr of tobacco deprivation. In the second study, male volunteers (N=7) reporting weekly crack cocaine use received 0, 10, 20 and 40 mg of smoked cocaine base on separate days. Performance measures in both studies included choice reaction time (CRT), and the digit-symbol substitution task (DSST).

Performance measure scores were analyzed as change from baseline scores in a within-subject, repeated measures 2-factor ANOVA, with dose and time as factors. Analysis indicated that smoked nicotine produced a significant condition by time interaction on the percent of correct responses on the DSST. There was a non-significant increase in the number of attempted trials on the DSST which was inversely related to dose and produced an inverted-U dose-response function for the first 30 minutes postdrug. The low dose produced an increase comparable to that observed after ad lib cigarette smoking, and higher nicotine doses produced less of an increase. Neither smoked nicotine nor cigarette smoking produced significant changes in CRT performance. Smoked cocaine produced a non-significant trend toward increased number of percent correct responses on the DSST, and had no effect on the CRT response rate or accuracy.

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CHRONIC AND ACUTE TOLERANCE TO SUBJECTIVE AND CARDIOVASCULAR EFFECTS OF NICOTINE IN HUMANS

K. A. Perkins, J. E. Grobe, W. A. Reynolds, R. L. Stiller, C. Fonte, and J. Goettler

Tolerance to nicotine may be associated with tobacco dependence and reflect physiological adaptation to nicotine. This study examined differences in subjective and cardiovascular responses to nicotine as a function of differential past history of nicotine exposure (i.e. smokers vs. non-smokers, chronic tolerance) and of differential immediately preceding nicotine exposure (acute tolerance). Subjects were smokers (9 male, 9 female) and non-smokers (9 M, 9 F) similar in age (21.2 vs. 23.2 years, resp.) and body weight (66.2 vs. 67.5 kg). Mean smoking history for smokers was 21.2 cigs/day for 3.2 years, and mean Fagerstrom Tolerance Questionnaire score was 5.9. Subjective measures were Profile of Mood States (POMS) scales of Tension, Confusion, Vigor, Fatigue, and Arousal; and visual analog scales (VAS) of Head Rush, Jittery, and Relaxed. Cardiovascular measures were heart rate (HR) and systolic (SBP) and diastolic (DBP) blood pressure from Dinamap automated recorder. Subjects each participated in 4 sessions after overnight abstinence from smoking, food, and caffeine. Sessions involved intake of 0, 5, 10, or 20 ug/kg nicotine by measured-dose nasal spray at 30 minutes for 2 hours (trials 1-4) in a within-subjects design. Smaller responding in smokers vs. non-smokers was viewed as evidence of chronic tolerance. A challenge dose of 20 ug/kg on trial five followed trial four on each day. Smaller responses on this trial as a function of larger dosing during trials 1-4 would suggest acute tolerance. Subjective and cardiovascular measures were obtained over the first seven minutes after each dosing. Blood samples to determine plasma nicotine were obtained from half of each group.

Non-smokers unexpectedly showed reduced plasma nicotine concentrations at each dose (by 25-30%), compared with smokers [consistent with study of i.v. nicotine by Benowitz and Jacob (Clin Pharmacol Ther 53:316-323, 1993)]. Thus, responses were analyzed after adjusting for the apparent difference in nicotine pharmacokinetics due to smoking status. Significant dose-dependent changes were seen in most subjective and all cardiovascular responses in both groups. Significant dose x group interactions were also observed for all subjective measures except VAS-Relaxed. Responses of smokers were clearly shifted to the right and/or dampened for most subjective measures, suggesting chronic tolerance. However, smokers showed greater responses on POMS scales of Vigor and Arousal. Differences in cardiovascular responses were small and non-significant. Acute tolerance was observed for VAS scales of Head Rush, Jittery, and Relaxed (decrease), and for POMS scales of Tension and Confusion, as well as for SBP, less so for DBP, and not for HR, after adjusting for plasma nicotine concentrations. There were no differences between smokers and non-smokers in acute tolerance to any responses. In conclusion, smokers showed reduced responding (chronic tolerance) to most subjective effects of nicotine, especially those which might be considered "aversive" (*e.g.,* POMS-Tension, VAS-Jittery), but enhanced responding to other, possibly "stimulating" effects (*e.g.,* POMS-Vigor, POMS-Arousal) of nicotine. Acute tolerance was also observed primarily for "aversive" effects and not for "stimulating" effects. Chronic tolerance was not observed for cardiovascular responses, although there was weak evidence of acute tolerance. Uneven pattern of tolerance between subjective and cardiovascular responses suggests different mechanisms may be responsible for these effects.

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COTININE: AN ACTIVE METABOLITE OF NICOTINE

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Cotinine, the major metabolite of nicotine, has generally been considered to have minimal pharmacologic activity. Data collected in human volunteers has shown little pharmacologic effects as a result of cotinine administration. However, investigation of the behavioral effects of cotinine in animals has shown that cotinine produces some nicotine-like responding in several behavioral paradigms and across animal species. In this study, intravenous cotinine base (and placebo) was administered to abstinent cigarette smokers to determine its pharmacodynamic effects in this setting.

Fourteen healthy male cigarette smokers, who reported no history of alcohol or drug dependence, participated in a placebo-controlled double-blind outpatient trial performed over nine days. Using a randomized counterbalanced-order design, cotinine base (30 mg) and placebo were administered intravenously after 48 hours of cigarette abstinence during two experimental sessions. Physiologic, biochemical and subjective measurements were made at baseline, 5, 15, 30, and 60 minutes post-drug. A two within-subject factor (Dose x Time) repeated measures analysis of variance was performed.

The results showed that 48 hours of cigarette abstinence induced significant increases in the tobacco withdrawal syndrome symptomatology. Cotinine administration compared to placebo produced subjective differences in self-reported ratings of restlessness ($p<0.02$), anxiety/tension ($p<0.005$), insomnia ($p<0.02$). sedation ($p<0.02$) and pleasantness ($p<0.05$). In addition, cotinine concentrations were found to be similar to those commonly achieved during daily cigarette smoking, with no change in serum nicotine concentration.

In abstinent cigarette smokers, these data suggest that cotinine is behaviorally-active at blood concentrations similar to those commonly achieved through daily cigarette. smoking. Also, intravenous cotinine administration in abstinent cigarette smokers appears to be safe.

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COGNITIVE AND BEHAVIORAL EFFECTS OF NICOTINE IN SMOKERS AND NONSMOKERS

J. E. Grobe, K. A. Perkins, R. L. Stiller, and R. G. Jacob

Understanding cognitive and behavioral effects of nicotine may provide insight into the reinforcing aspects of the drug which may relate to tobacco initiation and maintenance. Furthermore, examining effects of nicotine in both smokers and non-smokers allows one to distinguish between those effects which may be due to withdrawal relief vs. those due to "true" or direct actions of the drug. Subjects were smokers and non-smokers (n=18 each), with equal numbers of males and females in each group. For smokers, mean smoking history was 21.2 cigs/day for 3.2 years. Each subject was administered 0, 5, 10, and 20 ug/kg nicotine via a measured dose nasal spray, with each dose given on a separate day. For each session, subjects completed three baseline trials followed by four dosing trials, each 30 minutes. During each trial subjects completed a computerized battery containing five cognitive and behavioral tasks: physiological hand tremor, finger-tapping rate, hand-steadiness, numerical version of the Stroop task, and delayed recognition memory task. In addition, blood samples were drawn during each trial from half the subjects to assess plasma nicotine concentrations.

Blood analysis revealed that non-smokers showed lower plasma levels for each dose, as recently reported by Benowitz and Jacob (Clin Pharmacol Ther 53:316-323, 1993). Due to this difference, data were adjusted for corresponding plasma level. Smokers and non-smokers differed at baseline on some measures (less hand tremor, slower Stroop responding, poorer memory), perhaps due to withdrawal. Nicotine dose increased tremor in a linear fashion for both groups ($p<.001$). but the curve for smokers was dampened and shifted to the right, consistent with tolerance. Nicotine impaired hand-steadiness in linear fashion equally for both groups ($p<.001$). Nicotine also increased finger-tapping for both groups ($p<.03$), but the relationship was curvilinear with respect to dose and shifted to the right for smokers. Nicotine decreased reaction times on the Stroop for both groups ($p<.02$) and the curve for smokers was shifted to the right. However, nicotine had no significant effect on Stroop interference effect. Nicotine improved memory performance for both groups ($p<.05$), although non-smokers appeared to be impaired at the highest dose. Furthermore, improvement in performance for both groups was primarily due to decreased false alarm rates ($p<.02$). To our knowledge, this last finding is one of the first demonstrations of an absolute enhancement in cognitive performance due to nicotine in non-smokers. Nicotine's effects on a number of measures suggest that the drug induced a generalized behavioral activation which may be important in understanding the reinforcing value of tobacco use, although the mechanisms of action may vary across measures. A number of nicotine's effects appear to be non-linear with dose. Nevertheless, our results indicate that smokers may become tolerant to some of nicotine's effects, as many of the dose-response relationships were dampened and/or shifted to the right for smokers. Collectively, it appears that the behavioral and cognitive effects of nicotine in smokers may represent both the direct actions of the drug *(i.e.,* observed in non-smokers) as well as effects that are due to relief of withdrawal *(i.e.,* improved poor baseline performance of smokers).

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EFFECTS OF NICOTINE ON HUMAN COOPERATIVE RESPONDING

R. Spiga, J. Schmitz, D. R. Cherek, and R. H. Bennett

Subjects participated in 3 daily 30 minute sessions. Between the sessions subjects were permitted to smoke ad lib their usual cigarette brand, were abstinent, or received placebo, 2 or 4 mg nicotine gum. During the session cooperative behavior was established and maintained by experimental contingencies that scheduled two periods. During the first period subjects working alone earned points exchangeable for money by pressing a button. During the second period subjects could either work with the other person or work independently. Working with the other person, the cooperative response, was maintained by points exchangeable for money added simultaneously to the subject's and fictitious partner's counter. Both counters were visible to the subject. Working independently, the non-cooperative option, was maintained by points exchangeable for money being added only to the subject's counter. Cooperative responding was greater following ad lib smoking and acute administration of 4 mg of nicotine gum than following acute abstinence and placebo gum. These results suggest that nicotine gum as a replacement therapy mitigates the effects abstinence may have on human cooperative exchanges.

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SMOKING CUES TRIGGER MORE CRAVING THAN AFFECTIVELY NEGATIVE STIMULI

A. Droungas, R. Ehrman, A. R. Childress, M. Semans, and C. O'Brien

It has been suggested that Pavlovian conditioning mechanisms underlie the maintenance of substance abuse and relapse. Consistent with this idea, smokers report greater craving for cigarettes in response to smoking cues compared to non-smoking stimuli. However, an alternative holds that smoking cues trigger more craving because they are more emotionally arousing. The current study compared reported craving in response to smoking cues and to negative stimuli with no smoking content. Twenty-six smokers viewed a video and then engaged in a task in each of three sessions. 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 "non-smoking" session the video was a nature documentary, and the subject sorted children's playing-cards. In each session subjects reported on their mood, desire to smoke, and nicotine high- and withdrawal-like feelings in response to the video and the task. Smokers reported more negative affect and less high-like feelings to the unpleasant stimuli compared to the smoking cues and the non-smoking stimuli. Smokers also reported a greater desire to smoke to the smoking cues than to either the unpleasant or the non-smoking stimuli, although both the smoking cues and the unpleasant stimuli produced equivalent increases in withdrawal-like feelings. Further inspection of the data revealed that eleven subjects reported comparable increases in desire to smoke and in withdrawal-like feelings in all three sessions (Nonspecific Responders). Nine of the remaining subjects reported greater desire to smoke and greater withdrawal-like feelings to the smoking cues than to the other stimuli (Specific Responders). Both groups reported more negative affect to the unpleasant compared to the non-smoking stimuli. Taken together, these data argue that: 1) Craving is not associated with increases in negative affect or feelings of nicotine-like high. However, it is related to feelings of nicotine-like withdrawal. 2) The response pattern of the Specific Responders is consistent with a Pavlovian interpretation. The response pattern of the Nonspecific Responders is produced by physiological withdrawal due to passage of time.

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The reference list will be made available from the senior author upon request.

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CALORIC RESTRICTION, KETONEMIA AND NICOTINE CONSUMPTION IN CIGARETTE SMOKERS

L. J. Cheskin, L. Wiersema, J. E. Henningfield, and D. A. Gorelick

Animal, and some human, studies find that diet influences (and can be influenced by) drug use. For example, 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 reported weight gain commonly associated with smoking cessation (U.S. Surgeon General 1988). There have been no controlled studies of the effect of caloric or carbohydrate (CHO) restriction on drug use by drug-dependent humans. This study addressed the issue in terms of nicotine dependence by measuring the effect of four different diets on cigarette smoking and craving in nicotine-dependent humans. Subjects were nine (six 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 [VAS]), mood (POMS), body weight, and urinary ketones were measured daily; expired breath CO 7 times daily; and resting metabolic rate (by indirect calorimetry) once weekly. Data from the last two days of each diet were analyzed by Wilcoxon paired signed-ranks test for cigarettes smoked and breath CO. Two-tailed alpha level = 0.05.

The low calorie (balanced) diet produced 7% more cigarettes smoked ($p < .05$) and 11% higher breath CO ($p < .02$) than the normal diet. The low calorie, low CHO diet produced 16% higher breath CO ($p < .02$) 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 effect).

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EFFECTS OF MARIJUANA ON SUBJECT RATINGS, MEMORY, AND MATCHING-TO-SAMPLE PERFORMANCE

S. M. Waits, J. D. Roache, and D. R. Cherek

This study examined the effects of smoking placebo or THC-containing marijuana cigarettes (1.75%, 3.58% delta-9 THC, w/w) on urinary cannabinoid levels, subject ratings, and performance measures. Subjects were four males who reported occasional marijuana use ranging from daily to 1 day/month. Cigarettes were smoked daily using a paced puffing procedure (1 puff/30 set x 10 puffs). Physiological, performance, and subject ratings were obtained before and repeatedly up to six hours after smoking. Subjects provided clean urine samples before each active dose was administered; placebo cigarettes were administered on other days.

Following an acute dose of THC-containing marijuana, urinary cannabinoid concentrations increased in a manner unrelated to THC concentration and returned to zero (<50 ng/ml) over 2-4 day period. Following four consecutive days of smoking 3.58% cigarettes, urinary concentrations reached a plateau by the fourth day and subsequently decreased to zero over a 4-6 day period.

The effects of marijuana were dose-related only for heart rate increases and several subject ratings. Marijuana-induced performance impairment was not dose-related. Short-term memory and simultaneous matching-to-sample performance was impaired by marijuana in all subjects. Memory impairments on a number recall task were greater with long delays (10 sec) than with short delays (0 sec) indicating a drug-induced forgetting over short time delays. Pattern matching-to-sample impairments showed greater effects with the more difficult discrimination conditions. Repeated administration of 3.58% delta-9 THC cigarettes across four consecutive days produced maintained drug impairments with no evidence of accumulation or tolerance to the effects of THC. Residual impairment on subsequent days was observed in two subjects, but only with the most difficult discrimination conditions of the matching-to-sample task.

This study reveals a technology for insuring clean urine samples in marijuana research studies, however, marijuana effects were not related to urinary concentration.

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MOTIVATIONAL EFFECTS OF MARIJUANA: HUMAN CHOICES TO WORK OR NOT WORK FOR REINFORCERS

D. R. Cherek and D. M. Dougherty

Human subjects were given the opportunity to earn points exchangeable for money by either pushing a button on a progressive-ratio schedule or by not responding and receiving points on a fixed-time schedule. During each experimental session, subjects began in the progressive-ratio schedule. Subjects had the option of switching to the fixed-time schedule by emitting ten responses on an appropriate button. Using these schedule contingencies, we examined the effects of smoking placebo or three potencies of marijuana cigarettes on the total number of responses, and response rate in the progressive ratio component, as well as the number of points earned and time spent in the progressive-ratio and fixed-time components.

Marijuana smoking produced a reduction in responding in the progressive ratio component and earlier escape to the fixed-time response independent point presentation. These effects were diminished by increasing the point value. These results are consistent with an interpretation of a "motivation-reduction" effect of marijuana.

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THE EFFECTS OF MARIJUANA ON HUMAN'S CHOICES TO COMPETE OR NOT TO COMPETE FOR REINFORCERS

D. M. Dougherty and D. R. Cherek

The effects of smoking marijuana on human subject's choices to earn monetary reinforcers by either competing with a fictitious opponent or by not competing and working alone were studied. To do this we modified Buskist and Morgan's (1987) competitive fixed-interval schedule to include another option, a non-competitive fixed-interval schedule. While on either schedule, for approximately two minutes at a time, the opportunity for a reinforcer became available after a fixed interval of time elapsed; the subject's first response after the reinforcer became available produced it. Under non-competing conditions, reinforcers were always available after each interval had elapsed. Under competing conditions, reinforcers were available intermittently based on a predetermined probability (ranging from .25 to .75) of delivery -- *i.e.* the probability of "winning". Results indicate that most subjects show strong preferences to earn reinforcers while competing, even when the density of reinforcers in this option is much less than that available in the non-competing alternative. And smoking marijuana effects competitive responding in the following ways: 1) rates of responding increase at low doses and decrease at moderate and higher doses; 2) choices to compete increase at low and moderate doses and decrease at high doses.

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ACKNOWLEDGEMENT:

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POLYMORPHISMS OF DEBRISOQUINE HYDROXYLATION AND MARIJUANA PREFERENCE AMONG SUBSTANCE ABUSING ADOLESCENTS

H. B. Moss, A. C. Mezzich, L. Murrelle, J. M. Perel, and B. G. Pollock

Polymorphisms of oxidative metabolism may have a role in drug abuse. We examined the relationship between phenotypic variations in debrisoquine (DBQ) hydroxylation (P4502D6) and marijuana preference among a group of male (n=88) and female (n=43) adolescents (15-19 years) who met DSM-III-R criteria for a Psychoactive Substance Use Disorder, and had some exposure to marijuana. Subjects identified their preferred drugs, and their recollection of subjective effects was elicited. After a monitored 72-hour drug abstinence interval, 10 mg of DBQ was orally administered and urine collected over 8 hours. Urinary DBQ and 4-hydroxy-DBQ were determined by HPLC, and metabolic ratios (MRs) were computed. MRs were clustered into Extensive (EM), Intermediate (IM) and Poor Metabolizer (PM) phenotypic groups by the group centroid method. Among males, no association was found between DBQ phenotype and marijuana preference. However, among females PM and IM metabolizers exhibited a distinct lack of preference for marijuana with 100% of those who preferred marijuana being EMs (Chi-square=3.24, df=2, $p<.05$). Significant inverse correlations between MR and measures of positive subjective effects of marijuana were also found among females. The results suggest that pharmacogenetic factors may be a component of the liability for abuse of specific drugs within defined populations.

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THE KAPPA OPIOID RECEPTOR ON THE R1.l THYMOMA CELL LINE ACTS THROUGH A GI PROTEIN TO INHIBIT ADENYLYL CYCLASE

D. M. P. Lawrence and J. M. Bidlack

We have demonstrated the presence of a high affinity κ opioid binding site on membranes prepared from the mouse R1.1 thymoma cell line (Bidlack *et al.,* 1992). This site has characteristics that are identical to brain κ receptors, such as inhibition of binding in the presence of mono- and divalent cations and guanine nucleotides (Lawrence and Bidlack 1992). We then tested whether the κ opioid receptor on R1.1 cell membranes, like brain opioid receptors, was coupled to adenylyl cyclase. The κ-selective agonist U50,488 stereoselectively inhibited basal and forskolin-stimulated cyclic AMP (cAMP) production by up to 40% in membranes prepared from R1.1 cells, with half-maximal inhibition occurring at 51 ± 14 nM (-)U50,488. The inhibition by (-)U50,488 was blocked by the κ-selective antagonist nor-binaltorphimine, but not by the irreversible p-selective antagonist ß-funaltrexamine or the δ-selective antagonist naltrindole. Other κ-selective agonists, including U69,593, dynorphin A (1-17), dynorphin B, and a-neo-endorphin, also inhibited cAMP production, with an order of potency that parallelled their K_i values for the inhibition of [^{3}H]U69,593 binding. The inhibition of adenylyl cyclase activity by (-)U50,488 was abolished in membranes prepared from R1.1 cells that were cultured with 20 ng/ml Bordetella pertussis toxin (PTX). Incubation of membranes with PTX and [^{32}P]NAD labelled a 41-kDa protein, as determined by SDS polyacrylamide gel electrophoresis followed by autoradiography. The molecular weight of the ADP-ribosylated protein is very similar to the size observed with G_i proteins from other tissues. In summary, these data demonstrate that the R1.1 thymoma cell line expresses a κ opioid receptor that is negatively coupled to adenylyl cyclase via a PTX-sensitive G protein (Lawrence and Bidlack, in press), supporting the notion that opioid receptors may play a role in immunomodulation.

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SEROTONIN IS NOT DIRECTLY INVOLVED IN MORPHINE-MEDIATED SUPPRESSION OF SPLENIC NK ACTIVITY

S. Mayo, J. Porter, and D.J.J. Carr

Previous studies have shown that morphine suppresses murine splenic natural killer (NK) activity by 30-50% through a- and ß-admnergic pathways. More recently, morphine (50.0 mg/kg) administration in mice results in a 2-fold increase in splenic serotonin levels. In mice preadministered phentolamine or doxazosin (a peripheral acting antagonist) splenic serotonin levels am not elevated following morphine (50.0 mg/kg) administration (Carr, unpublished observation). Both phentolamine and doxazosin antagonize morphine-mediated suppression of splenic NK activity (Carr, unpublished observation). Consequently, the role of serotonin as a modulator of splenic NK activity was investigated. Splenic lymphocytes from C57B1/6J female mice (4-6 wks old) were incubated with serotonin (10^{-5}-10^{-9} M) up to 120 min prior to assaying the cells for NK activity. The results (Fig. 1) indicate that serotonin has no direct effect on splenic effector cells mediating NK activity at all concentrations tested. These results suggest that serotonin is not the principal mediator eliciting immunosuppression following morphine administration in mice. However, the results do not exclude serotonin playing an indirect role either through the reuptake and modulation of other neurotransmitters in the spleen or possibly modifying immunocompetence directly in the presence of other neuropeptides or cytokines present in the splenic milieu. Future work will investigate the relationship between serotonin and morphine relative to immunocompetence using serotonin antagonist applied peripherally and centrally.

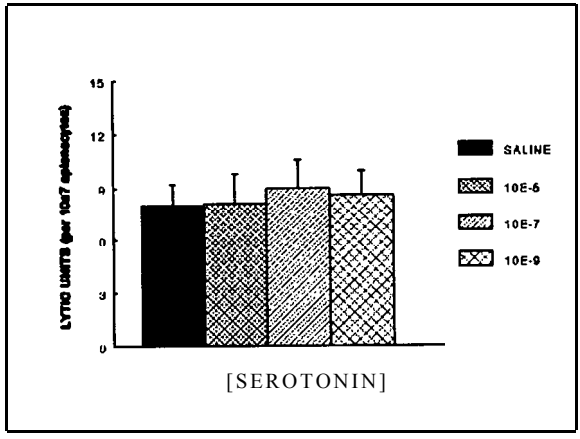

Figure 1 Serotonin does not modulate splenic NK activity.

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INFREQUENT OPIOID EXPOSURE IN RHESUS MONKEYS SUPPRESSES THE GENERATION OF ANTIGEN-DRIVEN KILLER CELLS IN ONE-WAY MIXED LYMPHOCYTE REACTIONS

D.J.J. Carr, H.H. Garza, L. Wilson, S. Ohkawa, O. Prakash, and C.P. France

Peripheral blood mononuclear cells (PBMCs) from rhesus monkeys receiving either saline (control, n=6), 3.2 mg/kg morphine daily (n=4) or various opioids only infrequently (twice/week, n=3) were assessed for the production of antigen-driven killer cells. PBMCs cultured for 4-5 days in the presence of irradiated (1500 rads) K033 or G966 (EBV-transformed rhesus monkey lymphocyte cell line insensitive to natural killer activity) were assayed on five separate occasions spanning 6 months for cytolysis of ^{51}Cr-labeled targets (K033 or G966). The results (Fig. 1) show a reduction in lytic units from PBMCs of infrequent opioid-exposed monkeys relative to controls. However, there was no difference in lytic units from PBMCs obtained from daily morphine-exposed monkeys relative to controls.

The target selectivity of the cultured antigen-driven effector cells was evaluated using the lymphokine activated killer (LAK)-sensitive cell line, DAUDI. Effector cells from all groups of monkeys lysed ^{51}Cr-labeled DAUDI cells in a conventional 4-hr ^{51}Cr-release assay to the same degree as that observed using the ^{51}Cr-labeled stimulator (K033 or G966) cells (data not shown). These results suggest the cytolytic effector cells generated *in vitro* ate antigen-independent corresponding to a LAK-like effector cell. Collectively, these results indicate infrequent opioid exposure affects immunocompetence specifically in the production of cytolytic cells which are known to regulate viral and tumor invasion.

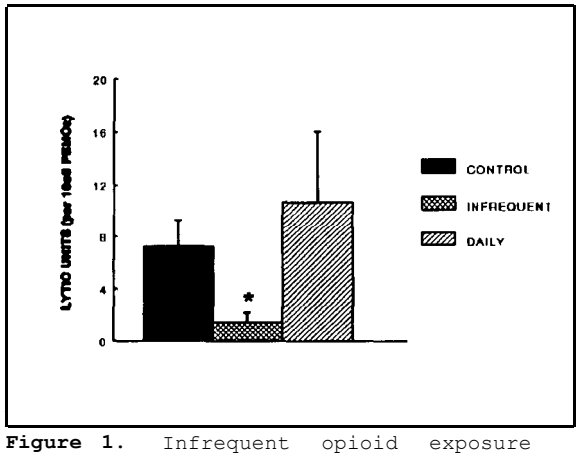

Figure 1. Infrequent opioid exposure suppresses antigen-driven cytolytic activity.

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AFFILIATION:

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EFFECTS OF CHRONIC MORPHINE AND WITHDRAWAL ON ACUTE PHASE REACTANTS AND DIFFERENTIAL LYMPHOCYTE POPULATIONS IN SWINE

L. M. Schwandt, K. J. Schuh, and T. W. Molitor

The development of morphine dependence has been reported to have an important immunological component, To examine immune alterations during withdrawal, levels of acute phase reactants and circulating lymphocyte populations were studied in three swine chronically exposed to morphine and three controls. Acute phase reactants are a group of substances whose hepatic production is increased in response to mediators produced by activated lymphocytes and macrophages. Circulating lymphocyte populations change in response to immunologically relevant events as cells traffic to body regions where they are needed. Peripheral blood was collected at three time points: two hours before, 10 minutes after (during peak behavioral withdrawal), and 24 hours after naloxone injection. Three naloxone challenges were administered to all swine with a minimum of 72 hours between injections. Chronic morphine in swine produced somewhat higher levels of C-reactive protein relative to controls. FACS analysis indicated morphine produced a greater percentage of cells staining positive for CD4, CD8 and B cell markers.

Naloxone-precipitated withdrawal produced increases in the acute phase protein haptoglobulin and prevented a rise in C-reactive protein 24 hours after the naloxone, but they did decline over repeated sampling. While having no effect on CD4, CD8 or B-cell populations, withdrawal decreased macrophage numbers. Therefore, chronic morphine increases lymphocyte populations in swine, and morphine withdrawal increases acute phase proteins, indicating an immunological component to morphine dependence.

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DEVELOPMENT OF TOLERANCE TO MORPHINE IS ACCOMPANIED BY AN INCREASED SUSCEPTIBILITY OF THE IMMUNE SYSTEM TO STRESS

B. M. Bayer, X. Z. Ding, R. M. Brehio, S. Cha, and M. C. Hernandez

We have previously demonstrated that acute (2 hour) exposure to morphine (10 mg/kg) resulted in a 70-80 percent inhibition of mitogen-induced blood lvmphocyte proliferation. The purpose of the present study was to determine if the suppression of lymphocyte proliferation persisted following repetitive morphine administration. We further examined the consequences to the immune system of the combined exposure to a stressor and either acute or chronic morphine administration. Male rats were injected twice daily for four days with increasing doses of morphine ranging from 10 mg/kg to 40 mg/kg. By day five, morphine (10 mg/kg) administration was not accompanied by either analgesia or depressed blood lymphocyte proliferative responses, indicating the development of tolerance to both actions of morphine. Although restraint (30 minutes) was accompanied by analgesia and increased plasma corticosterone, no effect on lymphocyte proliferation was observed. When animals were exposed acutely to a combination of restraint and morphine (5 mg/kg), no significant differences were observed in the magnitude of suppression by morphine in unstressed or restrained animals. However, exposure of morphine-tolerant animals to restraint resulted in a 60 percent inhibition of lymphocyte responses in naive animals, these results indicate that the immune system of morphine tolerant animals may be more susceptible to inhibition upon exposure to a stressor.

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MORPHINE STIMULATES REPLICATION OF SIMIAN IMMUNODEFICIENCY VIRUS *IN VITRO*

R. Y. Chuang, L. F. Chuang, and K. F. Killam, Jr.

Intravenous drug users are among the high risk groups of Acquired Immunodeficiency Syndrome (AIDS) victims. Nevertheless, needle-sharing alone cannot account for the reportedly high levels of infectivity. The blood volumes transferred by shared needles are rather small (<.75 µl) and even opioid addicts who did not share needles showed substantial rates of seropositivity to human immuno-deficiency virus (HIV), the etiology of AIDS. Since most opioids are themselves immuno-modulatory and immuno-compromising, opioids have been considered as a co-factor contributing to the secondary opportunistic infections of AIDS patients. The present study was undertaken to determine whether, in addition to their immunomodulatory effect, short-acting opioids such as morphine may directly promote virus growth and hence accelerate the process from viral exposure to the development of AIDS.

Simian immuno-deficiency virus (SIV)-infected human CEM x174 cells were employed in this study. SIV is an animal lentivirus closely related to HIV. Infection with SIV was found to induce cytopathic effects on CEM x174 cells. The results of this study showed that syncytium formation of SIV-infected CEM x174 cells was significantly enhanced in the presence of morphine sulfate, with a concomitant increase in the presence of morphine sulfate, with a concomitant increase in the activity of cellular reverse transcriptase and in the expression of SIV p27 core antigen. Parallel establishment of the viability of morphine-treated cells indicated that morphine protects against cell lysis induced by SIV so that replication and production of SIV particles continue and exceed that of cells without morphine treatment. Therefore, using an *in vitro* system, our studies demonstrated a direct opiate effect on simian AIDS virus proliferation.

Further studies showed that morphine-induced delayed cell lysis *in vitro* correlated well with *in vivo* observations that peripheral blood mononuclear cells isolated from morphine-dependent rhesus macaques displayed a lesser degree of programmed cell death by apoptosis during SIVmac infection. These studies suggest that modification of the biological properties of HIV-infected cells by morphine may be one of the mechanisms by which opioids exacerbate the progression of AIDS in drug abusers. The results of our studies may provide a model tissue culture system for evaluating the potential interaction between opioids and the progression of AIDS/simian AIDS.

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EFFECT OF CHRONIC OPIOID TREATMENT ON SIMIAN IMMUNODEFICIENCY VIRUS INFECTION IN RHESUS MONKEYS

L. F. Chuang, K. F. Killam, Jr., and R. Y. Chuang

INTRODUCTION:

Through the use of a simian model for the Acquired Immunodeficiency Syndrome (AIDS), the present investigation was conducted as a controlled, longitudinal study to evaluate the correlation between the chronic administration of opioids and its effects on cell-mediated and humoral immune functions after Simian Immunodeficiency Virus (SIV) infection of rhesus monkeys. Eight experimental rhesus monkeys, including three saline-treated, three morphine-treated and two L-alpha-acetylmethadol (LAAM)-treated monkeys were infected with SIVmac239, a molecular clone of SIVmac. This presentation describes our observations of monkey survival rate up to 15 months post-infection.

RESULTS:

Inoculating the monkeys with SIV reduced the mitogen response of T cells. A constant decline in the ratio of CD4+/CDS+ cells in the infected animals was observed. While autologous CDS+ cells of all animals were found to inhibit SIV replication, the CD8+ lymphocytes of the morphine-dependent animals showed a differential inhibitory effect toward the replication of autologous SIV due to the occurrence of significant viral mutation in the morphine-dependent animals. Furthermore, it was shown that the opioid-dependent monkeys had a lower titer of neutralizing antibodies than non-dependent monkeys. Autologous SIV isolated from the three morphine-treated animals also showed resistance/partial resistance to AZT inhibition. In all of the animals studied, chronic administration of opioids was certainly not effective in controlling the diarrheal state seen after SIV infection.

Up to 15 months post-infection, determination of the monkey survival rate showed that opioid-treated animals appeared to be more susceptible to SIV infection than saline-treated animals. Three of the five opioid-treated animals had died while the other two were undergoing chronic diarrhea, opportunistic infections, and/or tumor formation. In contrast, of the three saline-treated, SIV-infected monkeys, two of the macaques were exhibiting chronic diarrhea (a sign of SIV infection) while the other saline monkey was displaying consistent weight gain. In addition, the plasma of this animal was loaded with antibodies against SIVmac239. These observations suggest that this saline-treated macaque may have escaped the consequence of viremia.

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DELTA^9-TETRAHYDROCANNABINOL INHIBITION OF TUMOR NECROSIS FACTORα PRODUCTION BY RAW264.7 MACROPHAGES

K. Fischer-Stenger, D. A. Dove Pettit, and G. A. Cabral

Delta^9-tetrahydrocannabinol (Delta^9-THC), the major psychoactive component of marijuana, has been shown to be immuno-suppressive and to alter macrophage soluble cytolytic activity. The purpose of this study was to determine whether Delta^9-THC inhibited this function by altering tumor necrosis factorα (TNFα) production. The RAW264.7 macrophage cell line was used to produce macrophage conditioned medium (MØCM) containing TNFα which lysed L929 tumor cells. RAW264.7 macrophages were exposed to Delta^9-THC for 48 hours and were triggered with lipopolysaccharide (LPS) for 2 hours to 24 hours. Cytotoxicity assays demonstrated that MØCM produced by RAW264.7 macrophages exposed to 10^{-5} M Delta^9-THC was deficient in tumoricidal activity. Immuno-precipitation with an anti-TNFα antibody confirmed that RAW264.7 macrophages produced, and secreted, TNFα after triggering with LPS. In the presence of 10^{-5} M Delta^9-THC, less TNF was present in MØCM while intracellular levels of TNFα remained unaffected. Northern analysis revealed that Delta^9-THC had no effect on levels of TNFα messenger RNA (mRNA) from RAW264.7 macrophages triggered with LPS for 2 hours, 4 hours, or 6 hours. Although, slightly less TNFα mRNA was detected after triggering of cells with LPS for 24 hours. These results indicate that Delta^9-THC has no major effect on TNFα message. Radiolabel pulsing and pulse-chase experiments revealed that the intracellular conversion of the 26 kDa presecreted form of TNFα to the 17 kDa secreted form was inhibited by the drug. These results indicate that Delta^9-THC suppresses soluble macrophage tumoricidal activity, at least in part, by decreasing the intracellular conversion of presecretory TNFα to its 17 kDa secretory form.

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DELTA-9-TETRAHYDROCANNABINOL INHIBITION OF RAW MACROPHAGE TUMORICIDAL ACTIVITY IS DEPENDENT UPON THE ACTIVATION STIMULUS

D. Burnette-Curley and G. Cabral

We have shown that peritoneal macrophages obtained from mice treated *in vivo* with Bacillus Calmétte-Guérin (BCG) and delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, are impaired in their ability to effect cell contact-dependent cytolysis of tumor cells, amoebae, and virus-infected cells. However, these cells are able to bind their targets, suggesting that THC inhibits the induction and/or secretion of cytolytic molecules. We have employed an *in vitro* model system consisting of effector RAW264.7 macrophage-like cells and target murine tumor cells, susceptible to different macrophage cytolytic mechanisms, to determine whether THC exerts its effects on distinct macrophage killing pathways. RAW264.7 cells were treated with 10^{-5}M, 10^{-6}M, 10^{-7}M, or 10^{-8}M THC and were activated for 4h with 10 U/ml IFN-g plus 100 ng/ml LPS or with 1 µg/ml LPS. Cells, then, were employed in a chromium release assay using mouse L929 fibroblasts and P815 mastocytoma cells as targets. L929 cells are TNF-sensitive and nitric oxide (NO·)-resistant whereas P815 cells are TNF-resistant and NO·-sensitive. Results demonstrate that the protocol employed for macrophage activation is important in determining the effects of THC. TNF-dependent cell contact-dependent killing of macrophages was inhibited at both high and low concentrations of THC (10^{-5}M-10^{-7}M). Twenty hour conditioned medium (20h CM) obtained from macrophages treated with 10^{-5}M THC contained decreased levels of TNF when assayed using a TNF-specific enzyme-linked immunosorbent assay (ELISA). In contrast, L-arginine-dependent cell contact-dependent killing, in which NO· is the effector molecule, was inhibited only at high THC concentrations (10^{-5}M). Macrophage activation with IFN-g plus LPS overcame this drug-induced inhibition. Levels of NO^-_2 produced by RAW cells treated with IFN-g plus LPS or by LPS alone were assessed using the Griess reagent. Decreased levels of NO^-_2 were produced in response to activation with LPS but not with IFN-g plus LPS. These results indicate that at the higher drug concentrations (*i.e.,* 10^{-5}M). THC exerts a generalized inhibition of macrophage cell contact-dependent cytolytic activities. In contrast, at lower drug concentrations (*i.e.,* 10^{-7}M), THC specifically inhibits TNF-mediated killing.

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ASSOCIATION OF PERINATAL COCAINE WITH LEAD AND TOBACCOEXPOSURE

D. R. Neuspiel, M. Markowitz, and E. Drucker

Tobacco, lead and cocaine each has suspected effects on fetal growth and brain development. Yet, despite the environmental co-occurrence of these agents, studies of purported effects of cocaine in pregnancy have neither measured lead nor quantified tobacco exposure in mother or infant. Social, environmental or nutritional factors associated with poverty may explain a cocaine-lead association. Cocaine users may be exposed to higher doses of both active and passive tobacco smoke than non-users. In this study, exposure to these agents and their effects on fetal growth were assessed in 18 cocaine-exposed and 46 random non-exposed dyads. Umbilical cord blood lead and urine cotinine and creatinine levels were determined and all mothers were queried about tobacco use. Higher lead levels were noted in cocaine-exposed newborns. Ratios of cotinine to creatinine were higher in cocaine users than non-users, whether or not they admitted cigarette smoking. Crude means of birth weight, head circumference and length were lower in cocaine-exposed newborns, but these effects were attenuated after control for lead and cotinine by multiple linear regression. Future studies of *in utero* cocaine effects should consider more precise measures of other toxic exposures known to co-exist among cocaine users.

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PRENATAL COCAINE DIFFERENTIALLY ALTERS POSTNATAL NEUROENDOCRINE RESPONSES TO A 5-HT RELEASER AND 5-HT AGONISTS IN MALE AND FEMALE RAT PROGENY

G. Battaglia, T. Cabrera, A.D. Levy, Q. Li, and L.D. Van de Kar

Serotonin (5-HT) plays a trophic role in fetal brain development. Functional 5-HT uptake has been reported in growth cones of developing neurons. Since cocaine blocks 5-HT uptake, our hypothesis is that cocaine-induced perturbations of fetal 5-HT levels may produce long-term functional deficits in brain 5-HT systems. In STUDY I, gravid dams received 0.9% saline or (-)cocaine (15 mg/kg, s.c., b.i.d) from GD 13 - GD 20. Litters were culled to 9 and all progeny fostered to untreated lactating dams. Prenatal cocaine produced no changes in litter size, gender distribution, birth weights, crown-rump lengths or anogenital distances in progeny of either gender. Subcutaneous administration of cocaine has been reported, in some treatment paradigms, to produce skin "lesions" which may result in an increased "stress" in the dams. Since some investigators have proposed that this effect might complicate any interpretation of postnatal data, we evaluated stress hormone responses in dams at 3 days postpartum. There were no differences between saline- and cocaine-injected dams in either basal levels of ACTH and corticosterone or levels of the same hormones following stimulation by the 5-HT releaser, p-chloroamphetamine (PCA). These data indicate that the subcutaneous administration of cocaine did not result in long-term effects on stress hormone levels in the pregnant dams. Progeny in STUDY I, received saline or the 5-HT releaser, PCA (8 mg/kg i.p.) and trunk blood was collected 60 minutes later for RIA of plasma hormones. In postnatal day (PD) 70 male progeny, prenatal cocaine significantly attenuated PCA-induced stimulation of renin (-50%) and ACTH (-43%), but not corticosterone. In PD 30 female progeny, stimulation of ACTH and corticosterone, but not renin, was attenuated by prenatal cocaine. Since these data suggested possible gender differences STUDY II compared male and female PD 30 progeny for changes in neuroendocrine responses to directly acting 5-HT_{1A} (8-OH-DPAT, 0.5 mg/kg, s.c.) and 5-$HT_{2/1C}$ (DOI, 2 mg/kg, s.c.) agonists. Prenatal cocaine potentiated 5-HT_{1A}-mediated stimulation of ACTH (+28%) and renin (+54%) in male, but not female progeny. In contrast, the 5-$HT_{2/1c}$-mediated stimulation of ACTH and renin was potentiated in both male and female progeny by prenatal cocaine. These data demonstrate: (1) long-term functional alterations in progeny 5-HT systems following prenatal exposure to cocaine and (2) gender differences in cocaine's ability to alter 5-HT receptor-mediated hormone responses.

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THE EFFECT OF PRENATAL COCAINE EXPOSURE ON THE ACQUISITION OF COCAINE-INDUCED CONDITIONED TASTE AVERSIONS

C. M. Ferrari and A. L. Riley

Although the effects of prenatal cocaine in both animals and humans are well documented (see Dow-Edwards 1991). one area that has received little attention is the effect of prenatal cocaine exposure on subsequent sensitivity to cocaine. In the limited work in this area, prenatal cocaine has been reported to decrease subsequent responsivity to cocaine (Heyser, Goodwin, Moody & Spear 1992; Heyser, Miller, Spear & Spear 1992; Meyer, Sherlock & MacDonald 1992; Sobrian, Burton, Robinson, Ashe, James, Stokes & Turner 1990). The present study extended this analysis of changes in the behavioral sensitivity to cocaine by assessing cocaine toxicity in animals prenatally exposed to cocaine. Specifically, 60-day old pups (born of mothers that received subcutaneous (SC) injections of 20 mg/kg cocaine twice daily during gestational days 7 - 19, inclusive) were given 20-minute access to saccharin followed by a SC injection of cocaine (0, 18, 32 or 50 mg/kg) for a total of four conditioning trials. The rate and asymptotic level of cocaine-induced aversions in this group were compared to that in pups born of mothers fed the amount consumed by cocaine-treated mothers and in pups born of mothers administered the cocaine vehicle. During aversion training, all pups acquired dose-dependent aversions with no differences among the breeding conditions. That is, prenatal cocaine had no affect on the ability of pups to acquire cocaine-induced taste aversions. The basis for the differences in the present study and those reporting changes in behavioral sensitivity to cocaine following prenatal cocaine exposure is not known, although the effects of prenatal cocaine in general are dependent upon a variety of factors, including sex, time since prenatal exposure, time since training and the specific task in which the effects are evaluated. Any one (or any combination) of these factors may also be important in the effects of prenatal cocaine on subsequent behavioral sensitivity to cocaine.

References available upon request from senior author.

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COMPARISON OF MATERNAL CHARACTERISTICS AND PERINATAL OUTCOME FOR COCAINE USING WOMEN IN RESIDENTIAL OR OUTPATIENT TREATMENT

K. A. Kaltenbach, M. Comfort, and A. Smith

This study is part of an ongoing National Institute on Drug Abuse Research Demonstration Project investigating the efficacy of residential versus outpatient treatment for pregnant cocaine using women. At enrollment subjects must be pregnant (<24 weeks gestation), cocaine (non-opiate) using women, 18 years of age or older. Both residential and outpatient treatment programs include comprehensive obstetrical and psychotherapeutic services. This preliminary report consists of 35 women enrolled in the project who have delivered; residential treatment (MSP) n=19, outpatient treatment (OPS) n=16. The x age for MSP women was 30, for OPS mothers 31 (*NS*). There were no differences in gravida, parity, or whether mothers had custody of older children. Differences were found in education: MSP x 12.4 years, OPS x 10.7 years (p=.001). When assessed at intake no differences were found between groups on the Beck Depression Scale, the Internal Control Index, or in psychiatric diagnosis, but the MSP mothers scored higher on the Everyday Stressors Index (p=<.005). Seven infants were premature (4 MSP, 3 OPS), however, there were no differences in GA (MSP mean=38.1 weeks, OPS mean=37.5 wks). Mean length of post-partum hospital stay for term infants was 4 days, for pre-term 27 days. Birthweight for pre-term infants did not differ by maternal drug group (MSP x=2130, OPS x=1780) but a trend was found for term infants (MSP x=3340, OPS x=2990, p=.052). None of the infants were SGA. Associations among maternal and infant outcomes will be discussed in terms of service utilization and length of treatment.

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COMPREHENSIVE DAY TREATMENT IMPROVES OUTCOMES FOR PREGNANT DRUG USING WOMEN

E. R. Brown, M. Jay, A. Chaudhury, H. Kayne, B. Zuckerman, and D. Frank

We report results for the first 58 women enrolled in an ongoing randomized trial comparing a neighborhood based comprehensive day treatment outpatient program to the standard hospital based multiple clinic approach. At intake women were an average of 27 years old, had four prior pregnancies with two living children often not in their custody. Fifty-eight percent were high school dropouts, 40% had been physically or sexually abused during the current pregnancy; 82% were women of color, We hypothesized that a treatment program providing drug treatment, prenatal, and pediatric, would result in decreased drug use, increased retention in drug treatment, and improved perinatal and parenting outcomes. Women in the comprehensive day treatment program had: (1) a 50% decrease in drug use severity at 12 months post-partum as measured by the Addiction Severity Index; (2) a 50% decrease in low birthweight infants and (3) increased parenting skills as measured by the infant's performance on the HOME scale.

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THE NIDA "PERINATAL-20" TREATMENT RESEARCH DEMOSTRATION PROGRAM

E. Rahdert and L. Finnegan

The "Perinatal-20" refers to a NIDA-funded treatment research demonstration grant program comprised of twenty experimentally controlled, quasi-experimental, and clinical correlative studies that focus on the treatment of drug abusing women of childbearing age (predominantly pregnant or postpartum), with and without their children. Most are five-year projects, with ten awarded support in October 1989, the other ten in October 1990. The primary aim of each project is to evaluate a specific approach to treating addicted women, whether they are mothers or mothers-to-be. A secondary aim is to examine the effects of maternal drug abuse on the offspring. Most of these treatment programs are comprehensive by design, offering a continuum of care that includes a broad array of therapeutic and supportive services to addicted women, their children, and sometimes other family members.

By December 1992, the Perinatal-20 studies had enrolled more than 2000 women, including pregnant or parenting teenagers, and over 1000 infants and children. Of the women, 7% were teenage (less than 18 years) and 79% between 18 and 34 years of age. Sixty percent reported cocaine as their primary drug-of-abuse. Among the adults (eighteen years and older) 75% were African American. This is in contrast to the adolescent sample which was 38% African American, 33% Hispanic, and 21% Non-Hispanic white. Other statistics that appear of clinical interest are the 62% who were unemployed, the 61% who did not finish high school, and the 86% who did not have a supportive marital partner (never-married, widowed, divorced, or separated).

The high number of subjects that ultimately will be enrolled, plus the many commonalities across the twenty therapeutic approaches, induced extensive collaboration among the multi-disciplinary group of Perinatal-20 investigators. Together they formed a work group that generated a list of variables and related measures by which to define their subjects and report treatment outcomes. Another work group generated a standardized descriptive checklist for use by each project in order to more precisely characterize the treatment and services that are to be delivered. And lastly, investigators with their key staff continued to meet on a semi-annual basis to identify, discuss, and share potentially viable solutions to the many complex problems associated with the technical methodology of conducting research in what might be called the "real life clinical settings" represented in the Perinatal-20 treatment research program.

AFFILIATION:

National Institute on Drug Abuse

REGRESSION EQUATION FOR DETERMINING AND INDIVIDUALIZING NICOTINE PATCH DOSE TO OPTIMIZE SERUM NICOTINE REPLACEMENT DURING TREATMENT FOR TOBACCO DEPENDENCE

D. P. L. Sachs, E. A. Person, A. G. Bostrom, and M. D. Hansen

At the 1991 CPDD Meeting we presented findings, using 6-month data, from a N = 220, randomized, double-blind, placebo-controlled trial showing that nicotine patch therapy effectively treated tobacco dependence, both initially, while the patient used nicotine patch, and long term, after stopping treatment. (Mean serum venous cotinine replacement provided by the patch in successfully-treated patients who used the patch daily was 50% of the venous blood level during smoking.) We also presented subgroup analysis showing differential treatment response for men and women. In an effort to better understand these differences, we carried out a series of multiple linear regression analyses on the 1-year data for those active patch patients who were sustained nonsmokers for the entire 18-week treatment period and whose daily diaries indicated correct patch use. Since this number was only 25 men and 35 women, we lacked sufficient power to chose the predictive factors based on statistical reasons; hence, we chose them for theoretical reasons. This led to the development of the regression equations below. Venous serum cotinine in ng/ml for ***men*** during patch treatment is predicted by:

$$Cot_{RxM} = 338.66864 - BMI \bullet 9.34216 - \#PkYrs \bullet 0.75199 + Age \bullet 0.40385 + Cot_{Smok} \bullet 0.08776 + FTQ \bullet 2.79601$$

($r = 0.7654$, $p = 0.0064$). where BMI = Body Mass Index (in kg/M^2), #PkYrs = # of Pack-Years Smoked = # Years Smoked • # Cigarette Packs Currently Being Smoked/Day, FTQ=Fagerström Tolerance Questionnaire Score (0- 11 scale; 0-6 ≅ low dependent, 7-11≅ high dependent), Age = Age (in years), & Cot_{Smok} = Venous Serum Cotinine (in ng/ml) During Baseline Smoking. Cot_{Rx} for ***women*** during patch treatment is predicted by:

$$Cot_{RxF} = 129.93686 + BMI \bullet 3.93846 + \#PkYrs \bullet 0.02047 - Age \bullet 2.25053 + Cot_{Smok} \bullet 0.31122 - FTQ \bullet 12.00131 + MP \times BMI \bullet 1.79433$$

($r = 0.6944$, $p = 0.0071$). where MP × BMI = Menopausal Status × BMI (MP = 0 ≅ Pre-menopausal; MP=1 ≅ Post-menopausal). For example, a 60-year-old man with a 50 pack-year smoking history, a Cot_{Smok} = 100 ng/ml, and a BMI = 20 kg/M^2, would have a predicted Cot_{Rx} on one 30 cm^2 nicotine patch of 167 ng/ml (167% replacement). But if he weighed more, with BMI = 35, then predicted Cot_{Rx} would fall to only 27 ng/ml (27% replacement) - substantial under-dosing. These equations suggest that nicotine patch dose should be adjusted up or down based on the above, 5, pre-treatment factors for men (6 for women) to enable them to achieve adequate therapeutic serum levels during nicotine patch treatment. Regular use of this equation in clinical practice could substantially boost nicotine patch effectiveness, since fewer patients would be under-dosed and more would, consequently, receive sufficient treatment.

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BENZODIAZEPINE DETOXIFICATION USING FLUMAZENIL

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Preclinical studies suggest that the benzodiazepine (BZ) antagonist flumazenil (FLU) in single doses can reverse BZ dependence. This ongoing study aims to investigate the efficacy of FLU for detoxifying patients from BZ agonist drugs. Barbiturate pretreatment is being employed to attenuate the induced acute withdrawal which accompanies FLU use in BZ dependent patients.

METHOD:

Nine BZ-dependent methadone maintained inpatients thus far have participated. After symptom stabilization on alprazolam, five patients received FLU 1.5 mg IV over 15 minutes and four patients placebo (PLA). Phenobarbital (PBS) is administered PO 2.5 hours prior to FLU/PLA. Subsequent to FLU/PLA, alprazolam is abruptly discontinued via single blind placebo substitution. Abstinence symptoms are rated using the Ribicoff Abstinence Rating Scale (RARS) for the next ten days.

RESULTS:

Peak minus baseline RARS scores appear lower (24±15 vs 38±14, $p=.20$, Student's t-test, two-tailed) and "PRN" BZ use has been lower (0.6±0.9 vs 4.0±2.9 mg/10d aprazolam equivalent, $p<.05$, Student's t-test, two-tailed) after FLU than after PLA. FLU administration in conjunction with PBS has been medically well-tolerated.

DISCUSSION:

The preliminary data from these nine patients is promising. Flumazenil may be able to assist in the detoxification of benzodiazepine dependent patients.

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STRATEGIES FOR EVALUATING DRUG ABUSE PHARMACOTHERAPY

D. C. Shockley, T. Ansah, J. W. Cornish, and E. S. Onaivi

Despite the intensified research into the biological basis of drug dependency and addiction, drug abuse continues to be a medical problem and effective treatment regimen continue to be elusive. A range of compounds from different chemical groups that are known to have abuse liability are reclassified and approaches to drug abuse pharmacotherapy are presented. The different pharmacotherapeutic concepts for the treatment of drug dependency are known to be based on agonist, mixed agonist-antagonist, antagonist, substitution or deterrent principles. Some of these concepts are based on the craving and relapse that occur while trying to quit from the use of drugs that lead to dependency.

In the present preclinical studies, the effects of flunarizine, a calcium channel entry blocker, on cocaine induced motor activities were determined in rats and mice. The influence of flunarizine on the withdrawal anxiogenesis following the twice daily administration and abrupt cessation from cocaine treatment was also determined in a separate cohort. In the clinical setting, the research subjects were men scheduled for the treatment of cocaine, alcohol, or opiate dependency or cocaine pharmacotherapy in methadone maintained patients. For the opiate studies, the focus was on replacement treatment while the action of specific agents in reducing craving and decreasing the effects of alcohol have been evaluated (see Meyer 1992. Arch Gen Psychiatry 49: 900-904 and Alterman *et al.,* 1992. Drug and Alcohol Dependence, 31:19-29, 1992). The outcome variables included retention in treatment groups and relapse or abstinence.

The preclinical correlates determined in the present studies demonstrated that cocaine induced locomotor activity and stereotype behavior could be inhibited in mice but not in the rats. However, in both rats and mice, the withdrawal anxiogenesis which was still present 48 hr after withdrawal from cocaine was blocked by flunarizine. The results of the urine specimen analysis and self-report measures were not always similar in the clinical situation. The urine analysis of the abused substances and metabolites may however, provide an indication of drug abuse pharmacotherapy. As different classes of drugs of abuse activate different neurotransmitter systems in the CNS, it is unlikely that an unidentified common pathway exists for drug dependency. If this was the case, it may be easy to treat drug dependency in the clinic. Thus, polydrug abuse and the involvement of multiple systems in drug dependency may require the development of novel multifaceted approaches in the management of drug dependency. It was therefore concluded, that in evaluating the therapeutic potential of novel compounds, a number of factors including species variation, combinations with nonpharmacologic interventions, and appropriateness of the test should be considered.

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ACUTE AND CHRONIC AMANTADINE PRE-TREATMENT ATTENUATE SOME OF COCAINE'S EFFECT IN HUMAN SUBJECTS

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

Amantadine is an anti-viral and anti-Parkinson drug. It exerts its therapeutic effects primarily by releasing dopamine and norepinephrine from neuronal storage sites and delaying the reuptake of these transmitters into synaptic vesicles. The present study was conducted to assess amantadine's effectiveness in altering the reinforcing properties of cocaine. Both an acute and chronic (5 day) study were planned. Healthy adult male and female volunteers, ages (21-35) provided informed consent for either **a** three-day acute or a five day chronic study. On each acute study day subjects received either placebo, 200 mg or 400 mg of amantadine syrup. Three hours later all subjects snorted 0.90 mg/kg of cocaine. Compared to placebo, both doses of amantadine attenuated the cocaine-induced elevation in heart rate in male subjects. Subjects receiving the 200 mg of amantadine reported feeling less high on a visual analog scale at 10 and 30 minute post cocaine than the placebo and 400 mg groups. Subjects in the 200 mg group experienced a modest delay in reporting cocaine effects. The 400 mg dose of amantadine may be as effective as the 200 mg dose; however, the high dose resulted in an increase in physical unpleasantness on the ARCI Scale which may have masked its efficacy. These data demonstrate that an acute dose of amantadine (200 mg) effectively suppresses some of the behavioral and physiologic effects of cocaine.

In the chronic study, subjects were given 100 mg (bid) amantadine capsules for four consecutive days. On the fifth day subjects received a 0.90 mg/kg dose of cocaine. There were significant gender differences in the response to cocaine's cardiovascular effects as well as the number of episodes of euphoria. In general, males reported an increase in euphoria episodes and reported feeling "higher" after cocaine administration than did females. These differential responses between male and female users and acute and chronic amantadine treatment may be important factors in deciding which treatment program will be more efficacious.

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COMPARISON OF OPEN-LABEL PHARMACOTHERAPIES FOR COCAINE DEPENDENCE

E. Leon, T. Llosa, I. D. Montoya, N. Kreiter, K. Preston, and D. A. Gorelick

The effectiveness of pharmacotherapies for cocaine dependence has remained controversial, resulting in clinicians' use of a variety of medications. This study presents findings from open-label treatment of 179 cocaine-dependent (DSM-IIIR criteria) outpatients (with no other illicit drug dependence) at a private clinic in Lima, Peru. Patients were 95.7% males, mean (S. D.) age 23.5±2.5 years, mestizos 70%, native-Peruvians 20%, Asians 7%, whites 2%, and blacks 1%. Seventy percent smoked coca paste, 29% intranasal, and 1% injected. Group mean characteristics (range) were age 21.5-27 years, number of coca paste cigarettes smoked per binge 16-22.4, length of cocaine use 32-88 months, frequency of cocaine use 8-12 days/month, length of longest abstinence 9-39 days, number of relapses per month 3.6-6 and time since last use before treatment 3-5.8 days. Patients received a medication based on when they entered treatment, in the following order (mean daily dose [mg], scheduled duration of treatment [weeks]: 27 anti-depressants (clomipramine, naprotiline) (150, 13), 40 bromocriptine (7.5, 13), 52 amino-acid mixture (L-tryptophan, L-tyrosine, vitamins) (3100, 13), 23 coca tea (16.4, 52), 22 carbamazepine (481.6, 8). All 15 patients with current psychosis received sulpiride (100, 13). Patients were treated by the same therapeutic team, with two-thirds receiving weekly individual counseling. Clinical data were obtained by self-report, confirmed, in most cases, by weekly interview with a close relative. Statistical analyses were done by pair-wise t-test (continuous variables) or chi-square test (categorical variables), with 2-tailed alpha level + .05 (uncorrected for multiple tests).

All medications, except sulpiride, were associated during treatment with significantly longer longest-abstinence and fewer relapses per month than were self-reported before treatment. During treatment, sulpiride had the shortest longest-abstinence and most relapses per month (perhaps because of co-morbidity), while amino-acids had the fewest relapses. No significant medication side-effects were observed. Most dropouts were reported due to relapse; none were due to medication.

These tentative findings suggest that several different medications (amino-acid mixture, bromocriptine, carbamazepine, anti-depressants, coca tea), but not sulpiride, may have efficacy, in conjunction with counseling, in the treatment of cocaine dependence. However, several methodologic limitations raise cautions: open-label, non-random design, no urine toxicology data, significant baseline differences in some patient characteristics, and differing treatment periods.

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PREDICTING COCAINE USE IN A FLUOXETINE DOUBLE BLIND TRIAL

H. M. Rhoades, J. Schmitz, J. Grabowski, and R. Elk

Studies of specific treatments in heterogeneous populations of cocaine dependent patients have produced mixed results. Identification and precise definition of critical determinants (predictors) should contribute to better matching of patients to treatment, which should then produce improved results. We have examined our data, collected from a heterogeneous population of cocaine dependent patients (N=155) in a twelve week, randomized, double-blind, placebo-controlled study of fluoxetine, for possible predictors.

Statistical Analyses: Three sets of exploratory analyses were conducted: 1) A multiple regression analysis to predict change in proportion of cocaine positive urines. 2) A discriminant analysis to identify variables which could be used to classify patients into those who completed versus dropped out early. 3) A multiple regression analysis to predict change in strength of desire to use drugs.

The multiple regression predictors of change in cocaine positive urines included: ASI composite scores for Employment and Medical problems (positively associated with higher proportions of cocaine); Eysenck Extraversion scale (positive association); Hamilton Anxiety scores (negative association); the 2 Clinic Visit per week condition was associated with more cocaine positive urine screens than was the 5 Clinic Visit per week condition; and the Clinic Visit condition interacted with both Intake urine screen and Hamilton Anxiety scores.

The discriminant function analysis of those subjects who dropped out early versus those who completed found: The live visits per week condition; the greater dose of fluoxetine; the younger a subject; the less the interviewer rated ASI Alcohol Severity score; and the greater the ASI Alcohol Composite score (item derived); were associated with greater probability of study non-completion (all significant at $p<.05$).

The predictors of change in Strength of Desire to Use Drugs included: Two ASI Composite scores, Family Relationships (associated with decreased desire) and Medical Status (associated with greater desire); subject reported desired to quit (negatively associated with desire, i.e., the more desire to quit, the less the strength of desire); negative association with Spielberger - State scores; cocaine positive intake urine screens were positively correlated; attending clinic only twice per week was associated with increased desire to use drugs. Intake urine screen status and Clinic Visit frequency interacted with regard to predicting desire to use drugs.

The results of these analyses indicate that homogeneous subgroups of cocaine dependent patients may be identified.

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THE PROGNOSTIC SIGNIFICANCE OF ANTISOCIAL PERSONALITY DISORDER IN THE TREATMENT OF COCAINE DEPENDENCE USING PHARMACOTHERAPY

J. Leal, D. Ziedonis, and T. Kosten

PURPOSE AND METHODS:

This study analyzed the treatment outcome of 94 cocaine-abusing methadone patients according to the presence or absence of antisocial personality disorder (ASP). Previous studies suggest that individuals with ASP have a worse prognosis than those without ASP. Our study was a 12-week, randomized, double-blind pharmacotherapy trial in cocaine abuse treatment using Desipramine (150mg daily, n=30), Amantadine (300 mg daily, n=33) and placebo (n=31). We compared the treatment outcome differences in the non-ASP versus ASP patient groups according to retention rates, percentage of cocaine free urines, and money spent on cocaine.

RESULTS AND CONCLUSION:

The 12 week retention rates were lower for the ASP group (ASP 61% vs non-ASP 87%). Although there was no significant difference in the percentage of cocaine-free urines between the ASP vs. non-ASP patients (9% vs. 18%) during the first two weeks, during the last two weeks the non-ASP patients showed a significantly greater percentage of cocaine-free urines (30% vs. 7%). Furthermore, the ASP patients did not show any significant change during treatment in the amount of money spent on cocaine, while the non-ASP patients had a significant decline in dollars spent ($t=4$, $df=74$, $p<.01$).

The ASP patients on medication (53%) had worse retention than those on placebo (75%). The placebo treated patients in both the ASP and non-ASP groups showed no significant difference in percentage of cocaine-free urine toxicologies over the course of treatment. However, cocaine-free urines in the medicated non-ASP group increased from 15% to 32% compared to the medicated ASP group which actually decreased from 14% to 10%.

Based on our findings, antisocial personality disorder is a poor prognostic factor for treatment retention and continued cocaine abuse with medication improving treatment outcome for the ASP patients, but not for the non-ASP patients.

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A DOUBLE-BLIND COMPARISON OF CARBAMAZEPINE AND PLACEBO FOR TREATMENT OF COCAINE DEPENDENCE

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This study evaluted the clinical safety and effectiveness of the anti-convulsant carbamazepine (CBZ), along with counseling, for outpatient treatment of cocaine dependence. Inclusion criteria: males or females 21 - 50 years old, current cocaine dependence (DSM-IIIR criteria), and $\geq$ 14 g of cocaine use in prior three months. Exclusion criteria: current dependence on other psychoactive substances except caffeine or tobacco, illiteracy, severe or uncontrolled psychiatric or medical symptoms, pregnancy, lactation, or women of child bearing potential not using a medically accepted method of birth control, or diastolic blood pressure greater than 95 mm Hg. Patients signed a written consent and were not paid for their participation in this study.

CBZ was given double-blind as follows: week 1: 200 mg/day, week 2: 400 mg/day, week 3: 600 mg/day, week 4: 800 mg/day, week 5: 600 mg/day, week 6: 400 mg/day, week 7: 200 mg/day, week 8: placebo. Patients visited the clinic three days each week to provide a urine-drug test, ingest one medication dose, and receive additional medication to last until the next scheduled visit. Twice a week subjects had standardized cognitive/behavioral individual counseling.

Eighty-one applicants consented to participate. Results from 62 evaluable patients (placebo = 34, CBZ = 28) who received medication for $\geq$ 1 week mean (SD) age 33.2+5.4 years, males 49 (79.0%), blacks 42 (67.7%), whites 19 (30.7%), Native Americans 1 (1.6%), years of education 12.7±1.8, full-time employed 49 (79.6%). The commonest lifetime DSM-IIIR diagnoses were ASP 18 (29%), phobia 16 (25.8%) and PTSD 8 (12.9%). The two groups did not differ significantly in sociodemographic characteristics or psychiatric comorbidity. Biweekly CBZ plasma level monitoring indicated good medication compliance, with all CBZ patients reaching a CBZ blood level $\geq 5.6 \pm 0.8$ ug/ml during the 4th week of treatment.

Both groups showed increased urines negative for cocaine, decreased self-reported cocaine use (money spent and grams used), and decreased Beck and SCL-90R scores, with no significant difference between CBZ and placebo. Increased BP (10%), headache (5%), and elevated ALT (5%) were the commonest side-effects, none medically serious. There were no frequency or severity differences between CBZ and placebo. This study does not support the efficacy of CBZ for outpatient treatment of cocaine dependence, although it appears safe at these doses in this setting.

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METHYLPHENIDATE (MP) FOR INITIAL TREATMENT OF COCAINE DEPENDENCE AND A MODEL FOR MEDICATION EVALUATION

J. Grabowski, J. Schmitz, J. D. Roache, H. Rhoades, R. Elk, and D. L. Creson

Agonists and antagonists have been used to treat drug dependence but success has been limited with medications for cocaine dependence. Equivocal or negative results have been reported with several agents. No uniquely effective agent has been identified paralleling methadone, buprenorphine, or naltrexone as used for opiate dependence. Methylphenidate was examined earlier with variable results in special populations (Khantzian 1984; Kleber *et al.,* 1985). An agonist may enhance retention and treatment in cocaine dependent patients but the model should be further examined.

We are examining MP as a mode1 for initial agonist treatment for cocaine dependence. Patients previously treated unsuccessfully in a double blind fluoxetine study (Grabowski *et al.,* 1993) were randomly assigned to placebo or MP in a double blind trial. Outpatients receive either placebo or 20mg sustained release (s.r.)+ 5 mg standard dose preparation in the morning at the clinic. They also receive placebo or 20 mg s.r. as an afternoon "take home" dose. Adherence to afternoon dosing was monitored with an electronic dispenser bottle that recorded opening. Pretreatment safety, and behavioral, cognitive, and physiological response measures were undertaken in two full day sessions in our Human Behavioral Pharmacology Laboratory (HBPL). This was followed by two weeks monitoring and stabilization phase, and then an eight week treatment phase in our Addictive Behaviors Clinic (ABC). Quantitative analysis of urinary benzylecgonine levels was monitored with two urine samples weekly. Standard intake and weekly self-report measures were obtained in the HBPL.

Sample size to date (three placebo and four MP patients) is too small to draw conclusions. However, these data show no untoward effects in MP treated subjects. Patient response and retention have been favorable. Reported "desire to use" cocaine and "preoccupation with use" decreased in the MP group. Enhanced performance was observed even at this low dose of MP. Nonsignificant increases in blood pressure and heart rate appeared. There was no statistically significant difference in abstinence (cocaine free urines) and no obvious change in quantitative urine screens in either group; these data are being further examined. One MP patient dropped out in week one; no other patients departed. Study of higher doses in a larger and homogeneous patient population is planned.

While the utility of MP or the agonist mode1 is not yet resolved, this study demonstrates a unique combination of laboratory and clinic resources for medication development. The approach permits rapid sequential evaluation of individual safety and effects. followed by evaluation of treatment effectiveness in drug dependent patients. Also the data clearly indicate that agonists do not present problems and may be of use in treatment.

REFERENCES: Request from senior author

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BROMOCRIPTINE, DESIPRAMINE, AND TRAZODONE ALONE AND IN COMBINATION TO COCAINE DEPENDENT PATIENTS

R. I. H. Wang, J. Kalbfleisch, J. K. Cho and M. Forbes

To date, there is no successful pharmacotherapy in the treatment of patients with cocaine dependence. The purpose of the present study was to evaluate the treatment outcome when bromocriptine, desipramine or trazodone is given alone or in combination to patients with cocaine dependence, hopefully taking care of three known neurotransmitter systems, dopamine, catecholamine and serotonin.

Adult male subjects with a history of regular use of cocaine were screened on the day of admission for detoxification or the following day to participate with informed written consents in this randomized double-blind, active placebo controlled, parallel group study. Patients were assigned to one of the five following treatment groups receiving one identical capsule twice a day with a total daily dose of 2.5 mg bromocriptine(B), 100 mg desipramine(D), 100 mg trazodone(T), a combination of 1.25 mg bromocriptine, 50 mg desipramine, and 50 mg trazodone(C), or a very low dose of diphenhydramine served as active placebo(P).

Patients were evaluated at regular intervals using standard and special rating forms for anxiety (WARS) and depression (SADS). They were also checked for side effects and symptoms of cocaine withdrawal (CWAS).

Forty-three of 59 patients completed two weeks of study. Mean cocaine withdrawal ratings (CWAS) improved significantly ($P<.01$) at week 2 compared to baseline for groups B,D,T, and combination(C) but not for placebo(P).

The mean anxiety ratings (WARS) also improved significantly ($P<.01$) at week 2 compared to baseline for groups B,D,T, and combination(C) but not for placebo(P).

Compared to baseline, groups B and T showed significant reductions in mean depression ratings at the end of week 2; the placebo group (P) however, also showed a significant reduction in mean depression at the end of week 2. The incidence of side effects was low and not statistically different among the five groups. Comparison of change scores (from baseline to two weeks) between groups showed that B and D differed from placebo ($P<.05$) for withdrawal ratings (CWAS) and T and D differed from placebo ($P<.05$) for anxiety ratings (WARS). The placebo group contained three early dropouts, while each of the other four groups had only one early dropout. This was not factored into statistical analysis. Further work should be carried out using higher doses of bromocriptine, desipramine and serotonin alone and in combination.

References available upon request.

AFFILIATION:

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FLUPENTHIXOL AND DESIPRAMINE TREATMENT OF CRACK USERS: DOUBLE BLIND RESULTS

E. Khalsa, P. Jatlow, and F. Gawin

Clinical research has demonstrated that tricyclic antidepressants facilitate abstinence in outpatient cocaine abuse if they are given in correct time and dosage ranges. Preclinical research demonstrates that decrements in reward responsivity follow chronic stimulant administration, and clinical observations show that anhedonic symptoms can perpetuate cocaine abuse even in the absence of other major depressive symptoms. Oral medications appear to be less effective for "crack" abuse because cocaine smokers present increased psychological devastation compared to earlier abusers of cocaine (mainly intranasal users) and thus have very poor compliance to oral medication regimens. A previous open study reported that flupenthixol decanoate (10-20 mg/q/2 wks) facilitated abstinence in outpatient crack cocaine abusers who had not responded to multiple prior attempts of non-pharmacological treatment. We are conducting the first double-blind comparison of placebo, desipramine, and flupenthixol in 90 crack cocaine abusers. Preliminary results were presented at the 1992 CPDD meeting. Assessments are now completed for almost 3/4ths of the sample (n=63). Subjects met DSM-III-R criteria for cocaine dependence and received desipramine (n=20), flupenthixol (n=22), or placebo (n=21) for six weeks in a double blind design. Minimal psychotherapy was provided to better isolate pure neuropharmacological effects from psychosocial intervention and to better approximate the realities of urban treatment.

Engagement in treatment through a third visit was very poor for placebo, and increased to 6 fold in the medication groups (5 vs 30+%). Both medications were significantly superior to placebo on reduction in cocaine use, dyscontrol over cocaine urges, craving for cocaine, Beck depression scores, and Hopkins Symptom Checklist 90 scores.

Our results thus far show that flupenthixol and desipramine in "crack" abuse facilitate engagement in treatment in the context of minimal psychotherapy. Flupenthixol decanoate and desipramine were equally superior to placebo in maximizing symptom reduction.

Our data also suggest that pharmacotherapy, alone, is usually an inadequate treatment for "crack" dependence. Unless enriched psychotherapies, pharmacotherapies, or psychotherapy + pharmacotherapy interactions produce much higher initial retention, it may be necessary to hospitalize abusers to initiate abstinence.

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EFFECTS OF HALOPERIDOL ON CONDITIONED COCAINE CRAVING

S. E. Hall, C. A. Crawford, K. Delucchi, and S. M. Hall

Recently it has been hypothesized that dopamine release contributes to the ability of cues previously conditioned to cocaine (such as cocaine paraphernalia) to elicit cocaine craving. To evaluate the role of dopamine in human cocaine craving, we administered under double blind crossover conditions a single dose of haloperidol or placebo to experimental subjects prior to cue exposure. Since subjective measures such as craving are difficult to define we also evaluated measures of anxiety (anxiety, irritability, nervousness) and the neurochemical measures homovanillic acid (HVA), cortisol, and adrenocorticotrophic hormone (ACTH). In the ten patients studied to date there was a highly significant effect of cues on the placebo day, both on subjective measures of craving and on anxiety. In addition there was an increase in ACTH approaching significance ($p=.1016$). On the haloperidol day no significant change was observed on any subjective (craving and anxiety) or neurochemical (ACTH) measure. Directly comparing the placebo and active days there was a significant difference between haloperidol and placebo on measures of anxiety, one measure of craving and an effect approaching significance on ACTH ($p=.1172$). In addition, analysis of serum HVA and cortisol levels taken one hour following cue presentation showed increases approaching significance ($p=.1094$ for both) on the placebo day but not the active day. ACTH showed a statistically significant decrease ($p=.0313$) one hour post-cues on the haloperidol day but not the placebo day.

The ability of haloperidol to antagonize completely the anxiogentic effects of cocaine cues is consistent with a large literature supporting the anxiolitic properties of haloperidol. Given the small number of patients studied to date we believe the data is consistent with the hypothesis that haloperidol can antagonize all measures of cue reactivity. These data directly support the hypothesis that dopamine release may be important to cocaine craving and contradict the earlier “dopamine depletion” hypothesis of craving. In addition, the finding that cocaine cues are anxiogenic has important implications for the development of novel anxiolytic pharmacotherapies to promote cocaine abstinence.

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MONOAMINE UPTAKE INHIBITORS ALTER COCAINE PHARMACOKINETICS

S. R. Tella and S. R. Goldberg

Clinical evidence suggests that various monoamine uptake inhibitors may be useful in the treatment of cocaine abuse. However there is contrary evidence suggesting that these drugs may exert adverse influences on cocaine's behavioral, physiological and toxic effects. For example, it has been reported that desipramine may enhance some of cocaine's adverse behavioral effects and its cardiovascular toxicity in humans (Fischman *et al.,* 1990). Pretreatment with various monoamine uptake inhibitors, namely desipramine, fluoxetine and GBR 12909 has been shown to potentiate the discriminative stimulus effects of cocaine in rats (Cunningham and Callahan 1991). Further, pretreatment with mazindol has been reported to potentiate the acute lethal and convulsant effects of cocaine in rodents (Jaffe *et al.,* 1989). The basis for the potentiating effects of monoamine uptake inhibitors on cocaine's behavioral, physiological and toxic actions are not known.

In the present study, we investigated in conscious rats instrumented with arterial and venous cannulas, the time courses for changes in plasma levels of cocaine and its major metabolite benzoylecgonine after an i.v. bolus injection of 3 mg/kg cocaine and the pharmacokinetic interactions between cocaine and several monoamine uptake inhibitors. Plasma levels of cocaine reached 1276 ± 53 ng/ml 0.5 min after injection and then rapidly declined to 768±110 ng/ml by 2 min; thereafter, decline of plasma cocaine levels was relatively slow. Plasma benzoylecgonine levels were low at 0.5 and 2 min following cocaine injection but increased gradually over the next 25 min. Pretreatment with the norepinephrine-selective uptake inhibitors desipramine and nisoxetine, the serotonin-selective uptake inhibitor fluoxetine or the dopamine-selective uptake inhibitor GBR 12909 all enhanced plasma levels of cocaine 0.5 min, but not 5 min after cocaine injection compared to that of a control group. The enhancement of plasma cocaine levels by GBR 12909 was greater than that produced by desipramine, nisoxetine or fluoxetine. With the exception of the high dose (10 mg/kg) of GBR 12909, these agents did not significantly alter plasma levels of benzoylecgonine measured either 0.5 or 5 min after cocaine injection. These results indicate that monoamine uptake inhibitors can alter cocaine pharmacokinetics and that the interaction is not due to a change in the biotransformation of cocaine. Central monoamine uptake sites may serve as rapid distribution sites for cocaine and, thus, may play a role in this pharmacokinetic interaction.

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EFFECTS OF DOPAMINE UPTAKE INHIBITORS ON BEHAVIORAL AND TOXIC EFFECTS OF COCAINE

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Drugs with mild psychomotor stimulant effects have been suggested as potential cocaine (COC) abuse treatment agents. Clinical success with these compounds has thus far been inconsistent or complicated by side-effects. A strategy for the discovery of medications for the treatment of COC dependence could make use of the non-selectivity of certain dopamine uptake inhibitors. The non-dopaminergic actions of these compounds could function to mask or dampen the behavioral effects normally characteristic of drugs which block dopamine uptake. In the present experiment, the abilities of GBR 12935, benztropine (BEN), and ifenprodil to mimic, block, or enhance the behavioral and toxic effects of COC were compared. GBR 12935, is a potent dopamine uptake inhibitor with high selectivity for the dopamine uptake site. BEN, a structural hybrid of GBR 12935 and COC, is a potent dopamine uptake inhibitor with prominent muscarinic antagonist activity and is in clinical use for Parkinson's disease (Cogentin). Ifenprodil inhibits dopamine uptake at concentrations comparable to those observed with COC. In addition, ifenprodil binds to sigma sites and to the polyamine regulatory site of the NMDA glutamate receptor subtype.

COC, GBR, and BEN increased locomotor activity and enhanced the locomotor effects of COC in mice. Although IFEN neither increased activity nor augmented the stimulatory effect of COC, IFEN attenuated the stimulant effects of COC at doses that did not reduce spontaneous activity when given alone. Fixed-interval responding of rats was increased by all drugs except IFEN. With the exception of IFEN, all drugs fully substituted for COC in rats discriminating 10 mg/kg COC from saline. However, only GBR significantly enhanced and none of the drugs blocked the discriminative stimulus effects of COC. Only COC and GBR produced convulsions in mice when given alone; only GBR significantly enhanced the convulsant effects of COC in mice.

In contrast to the generally uniform behavioral effects of dopamine uptake inhibitors, non-selective inhibitors of dopamine uptake exhibited striking differences in the profile of behavioral effects compared to cocaine and the more selective compound, GBR 12935. Benztropine had low efficacy as a psychomotor stimulant, displayed a reduced ability to enhance behavioral effects of cocaine, and did not exhibit the toxic effects of cocaine either when given alone or in conjunction with cocaine. These observations combined with its safe clinical use, suggest that benztropine may be a reasonable candidate for clinical evaluation in the treatment of cocaine dependence.

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EFFECT OF DOPAMINE RECEPTOR ANTAGONISTS ON COCAINE-INDUCED SUBJECTIVE EFFECTS: A NATURALISTIC CASE STUDY

D. C. Ohuoha, J. W. Maxwell, J. L. Cadet and R. B. Rothman

A variety of data provide compelling evidence that mesolimbic do amine (DA) mediates the reinforcing effects of cocaine in animals, including the fact that DA receptor antagonists attenuate its reinforcing action. However, the applicability of the DA hypothesis to humans is problematic. For example, it is well known that schizophrenic patients on antipsychotic medication abuse cocaine, and it is not uncommon to come across patients who use cocaine while on their medication yet still experience cocaine-induced euphoria. The present study was undertaken to determine the relationship between the dose and type of antipsychotic medication used and a patient's report of the subjective effects of cocaine. Patients who participated in this pilot study were admitted to the acute care hospital at St. Elizabeths Hospital, Washington, DC, for an acute exacerbation of either Schizophrenia (N = 9) or Bipolar Disorder (N = 1) complicated by cocaine dependence. All patients in this study were being treated with either haloperidol decanoate or fluphenazine decanoate (average dose was 5 to 15 mg po equivalents per day). Only patients whose records indicated that they had received their medication as scheduled participated in the study. All patients had been prescribed benztropine for prevention of extrapyramidal side effects (average dose of 2-4 mg per day), and the one patient with bipolar disorder was also taking lithium and carbamazepine. While on the inpatient unit, the patients were retrospectively administered the POMS and a custom-designed questionnaire (the "CDQ"). Patients were instructed to answer the questions under two conditions: how they felt for the five minutes preceding their use of cocaine, and how they felt over the next 30 minutes. This generated a set of "before" and "after" ratings. All patients were also asked if the cocaine made them feel high. All patients reported that the cocaine made them very high., and that they experienced intense cocaine-craving both before and after using cocaine. Analysis of the POMS and CDQ revealed a number of highly significant changes. Viewed collectively with other studies, these retrospectively gathered data suggest that DA D2 receptors do not mediate the subjective and reinforcing effects of cocaine in humans.

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DISULFIRAM THERAPY IN PATIENTS ABUSING COCAINE AND ALCOHOL

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The majority of patients in treatment for cocaine dependence also abuse alcohol. The present investigation is an ongoing study of the effects of adjunct disulfiram therapy during outpatient behavioral treatment for cocaine dependence. Subjects were 16 adults who met DSM-III-R criteria for cocaine dependence and alcohol abuse. All subjects had $\geq$ 2 weeks on and off disulfiram. Patients ingested 250 mg disulfiram 2-3 times a week under staff supervision and were given take-home doses to complete a scheduled daily intake. While causality for effects can not be inferred because patients often determined when disulfiram therapy was terminated, disulfiram therapy was associated with significant reductions in alcohol and cocaine use. Patients reported significantly fewer drinking days and drinks per occasion, and demonstrated a > two-fold decrease in cocaine-positive urinalysis results while on versus off disulfiram therapy. These results suggest that disulfiram may be a useful adjunct medication in patients who abuse alcohol and cocaine. However, controlled trials will be necessary to adequately evaluate the direct contribution of disulfiram therapy to these outcomes.

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DISULFIRAM TREATMENT OF COCAINE ADDICTION

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An open label study with eighteen outpatients with a history of concurrent alcohol and cocaine use found that disultiram treatment resulted in significantly fewer days of cocaine use in addition to more prolonged periods of alcohol abstinence compared to naltrexone, suggesting some efficacy of disulfiram in the treatment of cocaine addiction. This finding is intriguing as disulfiram has been associated with psychosis but no toxic interactions between disulfiram and cocaine have been reported. We conducted this study to investigate the safety and possible interactions between cocaine and disultiram.

METHOD: Eight cocaine dependent patients participated in four test days during which they received active or placebo disulfiram 250 mg orally followed one hour later by active or placebo cocaine 2mg/kg intranasally in a 2 by 2 design. Patients were assessed by using the visual analog scales along with physiological measurements and plasma cocaine levels over 180 minutes.

RESULTS: Active cocaine elevated the mean peak blood pressure and pulse in both active and placebo disulfiram groups but no difference was observed between the active and placebo disulfiram groups. Cocaine induced "High" and "Rush" between the two groups was also insignificant. There does appear to be about a 50% reduction in mean peak cocaine craving and increased mean peak scores on "Nervousness" and "Paranoia" ratings in the active disulfiram pretreated group. These differences were not statistically significant. Three patients became quite nervous and paranoid possibly due to the combination.

DISCUSSION: The major finding of this study is that disulfiram 250 mg is medically well tolerated but may increase nervousness and paranoia when given concurrently with cocaine which may reduce cocaine craving. Psychosis associated with disulfiram, probably due to inhibition of dopamine beta hydroxylase, an enzyme responsible for conversion of dopamine to norepinephrine leads to increased concentration of dopamine. Cocaine further increases the dopaminergic activity possibly leading to enhanced paranoia.

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INDUCTION OF ALCOHOLICS ON NALTREXONE: A PILOT STUDY

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Naltrexone is undergoing study as a pharmacological adjunct to psychosocial treatment of alcohol dependence and abuse. Most clinical experience with naltrexone has been with treatment of opiate abusers. To examine naltrexone induction effects in patients being treated for alcoholism, we conducted an open-label study of naltrexone in ten inpatients. The mean age of subjects was 42.3 years (SD. 9.7). Four subjects were female, six were male. Nine subjects were white; one was black. Symptom side effects were measured with the Symptom Checklist-90 (SCL-90). Following detoxification from alcohol and collection of baseline measures, subjects were administered 10 mg of naltrexone. Naltrexone dose was increased 10 mg each day until subjects were receiving 50 mg daily. For the duration of the study, subjects remained on 50 mg/day. Subjects completed the SCL-90 daily before they received their next naltrexone dose.

RESULTS:

None of the ten subjects had severe symptoms or mood disturbances during the study. Some subjects reported mild, transient, naltrexone induction side effects, such as drowsiness, nausea, headache, hot and cold flashes, and dry mouth. Graphic analysis of daily SCL-90 positive symptom total scores (the positive symptom total is the number of symptoms that the subject reported out of a possible 90) showed that eight of ten subjects had fewer symptoms while on naltrexone than at baseline. One subject had the same number of symptoms, and one subject had a slight increase in the number of symptoms. All subjects continued naltrexone after discharge from the hospital and participated in weekly follow-up evaluations for one month. No subject discontinued naltrexone because of adverse effects. None reported relapse to alcohol use.

CONCLUSION:

With the naltrexone induction and maintenance schedule used in this study, naltrexone was well-tolerated by subjects undergoing treatment for alcoholism. Most patients had fewer symptoms while on naltrexone than at baseline.

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A DOUBLE-BLIND STUDY OF MAZINDOL FOR THE TREATMENT OF COCAINE ABUSE IN NEWLY ABSTINENT COCAINE ABUSING METHADONE-MAINTAINED PATIENTS: A PRELIMINARY REPORT

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

Mazindol is a dopamine reuptake inhibitor which may be useful for ameliorating dysphoric states consequent to initiation of abstinence from chronic cocaine use. Previous research has suggested that mazindol's utility may be limited by side-effects such as jitteriness when administered to subjects who are concurrently self-administering cocaine. We conducted a double-blind study of mazindol for the treatment of cocaine abuse in methadone-maintained patients abstinent from cocaine abuse for two weeks. To minimize side-effects, a 1 mg dose of mazindol was chosen. To date. 30 subjects have oarticioated in the study, 11 males and 19 females. Subjects' mean age was 36 years. Subjects had been using cocaine an average of 11 years, and opiates an average of 12 years. Frequency of cocaine use was between four and seven times per week. Patients received 1 mg of mazindol or matching placebo with their daily methadone dose for 12 weeks. Patients also participated in once weekly relapse prevention group therapy sessions. A behavioral contingency which lowered methadone dose 10 mgs for submitting a positive cocaine urine screen was also in place. Outcome measures included three times weekly urine screens for benzoylecgonine and the Beck depression inventory.

Subjects reported no interactions between mazindol and methadone or cocaine. Three subjects in the mazindol group and one subject in the placebo group dropped out of treatment due to side-effects.

During the course of the study, we observed that rates of cocaine use were relatively low for all subjects, suggesting that the psychological interventions may be overriding a possible pharmacotherapy treatment effect. We therefore conducted a preliminary examination of the data after 30 patients had completed the study. This examination, reported here, revealed that the active medication group submitted 16 percent positive cocaine urine screens and the placebo group 25 percent. Subjects assigned to placebo also tended to report higher depression scores. These differences were not statistically significant; however, this may have been the result of the low statistical power with only 30 subjects. Given the low rates of cocaine use among these long-term illicit drug users, we have decided to continue to enroll subjects into this study. With greater statistical power these data may suggest a role for mazindol, in combination with psychological interventions, for relapse prevention to cocaine abuse in newly abstinent subjects.

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A REPORT ON 10 YEARS OF EXPERIENCE WITH QUANTIFIED URINES IN SUBSTANCE ABUSE TREATMENT AND PHARMACOLOGIC TRIALS

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Quantified urine analyte levels, first employed in the substance abuse field in smoking cessation studies (Russell and Feyerabend 1975; Jacob *et al.,* 1981), are being employed as a potential useful outcome measure in pharmacological trials of cocaine abuse (Batki *et al.).* Levels of the cocaine metabolite benzoylecgonine (BE), expressed as nanograms per milliliter of urine per mg of creatinine, are oresented from 7,675 urine samples collected from 2,519 VA psychiatric patients; 3,177 urine samples from 218 patients in three controlled trials of bromocriptine, desipramine, and buproprion for cocaine dependence; and 17,038 urine samples from 244 patients in a controlled trial of buprenorphine and methadone for opiate dependence. Laboratory methodologies included fluorescence polarization immunoassay, radioimmunoassay, gas-liquid chromatography with nitrogen-phosphorus detection, high-pressure liquid chromatography with diode array, ultraviolet, and electrochemical detection, and gas-chromatography-mass spectroscopy.

Summary: There was a spectrum of BE positive urines (BE+) across the four trials. The BE+ rates were similar for the two pharmacological trials for cocaine abuse in non-methadone patients (bromocriptine=36.1%, desipramine=37.8%). The BE+ value of 56.7% in a general population of methadone-maintained patients contrasted with the 90.8% BE+ rate in methadone-maintained patients selected to receive buproprion for cocaine-dependence. Outcome of medication trials for cocaine abuse/dependence will likely be tempered by the rate of cocaine use in the study population. The appearance of characteristic patterns of BE levels across the four trials was independent of the percentage of BE+ urines within each trial. Shifts from one pattern to another might reflect pharmacologic activity not otherwise discernible with traditional qualitative urine measures.

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PSYCHIATRIC MORBIDITY, ANTISOCIAL PERSONALITY DISORDER, AND TREATMENT RESPONSE IN METHADONE MAINTENANCE PATIENTS

R. P. Mattick, J. Bell, and W. Hall

Previous research has suggested that psychiatric morbidity has a negative relationship to outcome in methadone maintenance treatment (MMT), although the association has not always been observed. It was hypothesised that the presence of symptoms of Antisocial Personality Disorder (ASPD) would have a negative relationship to outcome in MMT, an effect that would be strengthened by the presence of symptoms of an affective disorder, and global psychopathology. Patients in MMT in Australia were studied as a part of a larger project on the prevalence of psychiatric disorders and their relationship to outcome. Continued drug use, HIV risk-taking behaviours (drug use and sexual behaviour). and continued criminal activities during treatment were assessed. ASPD was diagnosed using the Diagnostic Interview Schedule, and the presence of Axis 1 disorders was diagnosed using the Composite International Diagnostic Interview schedule (n=271). There was a significant surfeit of current depressive (odds ratio = 6.89), anxiety (panic disorder odds ratio = 9.71; social phobia odds ratio = 16.99), and ASP (odds ratio = 44.83) disorders found, compared to general population estimates. Other disorders did not show elevated rates in the six months prior to interview.

Regression analyses were conducted (n = 225) to determine the relationship between ASPD symptoms, depressive symptoms, global psychopathology, daily methadone dose, the clinic attended, years dependent, gender, and four methadone maintenance therapy outcomes (continued heroin use, HIV risk taking behaviour, criminal behaviour, and methadone dose level). Continued heroin use was predicted by current dose, and by the program identifier variable (*i.e.,* the clinic attended), but not by psychopathology. HIV risk taking behaviour (total score, sexual risk, and injecting risk) were unrelated to any of the predictor variables. Criminal behaviour was predicted by ASPD symptoms and the program identifier variable. Methadone dose level was predicted by ASPD symptoms, but not by other variables. In summary, from these results, it appears that psychopathology has a relatively small role in determining outcome in methadone maintenance treatment.

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ACUPUNCTURE AS AN ADJUNCT TO SERVICES PROVIDED AT METHADONE TREATMENT FACILITIES

T. R. Jackson, E. W. 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 is 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, most multiply drug dependent, are being recruited. This sample is being drawn from clients newly admitted to methadone treatment at Evergreen Treatment Services, a non-profit methadone treatment center and the VA Medical Center Addiction Treatment Center, Outpatient Unit. These subjects, while receiving standard methadone treatment, are randomly assigned to either specific or non-specific acupuncture treatment. The subjects and all research and clinical staff are blind to the condition assignment; only the acupuncturist providing the treatment is aware of the condition. A five point acupuncture protocol is being used and a point detector is used to differentiate needle placement between the two conditions. Acupuncture sessions are held once daily prior to dosing. Subjects are encouraged to undergo acupuncture treatments daily for two weeks, five days per week (totaling ten acupuncture treatments), after which treatment is available on a daily voluntary basis. Data concerning subjects' attendance at methadone treatment services, methadone dose level, drug screen urinalysis and breathalyzer results, attendance at acupuncture sessions, and reasons for discharge from treatment are gathered from client charts. Questionnaires regarding mood, physiological responses to acupuncture, and withdrawal symptoms are administered to subjects immediately prior to and following each acupuncture session. Participants complete self-rating scales on drug use and cravings and withdrawal symptoms weekly. The blind assignment for this project has not been broken. Between the two sites, we have been able to recruit into the study 36.5% of the clients eligible. Volunteers differ from refusers in race and employment status: Volunteers show a significantly higher level of employment than refusers (40.9% of volunteers are employed, 17.4% of refusers are employed [$\underline{X}^2=8.5$, p=.003]). Whites are significantly more likely to volunteer than non-whites (of those volunteering 20.5% are non-white, 39.5% of defusers are non-white [$\underline{X}^2=4.8$, p=.02]).

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NEUROPSYCHOLOGICAL SCREENING IN A METHADONE CLINIC

D. Voirin, D. A. Calsyn, C. Fleming, A. J. Saxon, and E. A. Wells

This study used screening tests to examine the level of neuropsychological functioning in a sample of 344 clients entering methadone maintenance treatment. At treatment entry, clients were administered the Rey Auditory Verbal Learning Test (AVLT), the Trail-Making Test (A and B), and The Addictions Severity Index (ASI). Clients (n=269) were administered these measures again at a 12 month follow-up. AVLT and Trail-Making scores were converted to standard scores for age and gender and then classified as impaired if greater than one standard deviation below the nonnative mean. AVLT false positives were considered impaired if greater than 0. Impaired and not impaired clients were compared on demographic characteristics, level of pre-treatment drug use, and treatment retention. All comparisons between the impaired and not impaired subjects were done based on scores at intake, follow-up, and change between intake and follow-up. Level of neuropsychological impairment was not different for level of education. However, as age increased, the number of words recognized on a narrative paragraph of the AVLT at intake decreased. Performance on Trails A at intake and follow-up and on Trails B at intake also decreased as a function of age. Gender effects were found for level of impairment on the AVLT: Female clients were more impaired in ability to recall verbal information at intake and follow-up (intake: females, 52.3%. males, 34.7%; follow-up: females, 52.3%, males, 30.5%), and also differed from males in change in impairment between intake and follow-up with no females changing impairment status. Male clients were more likely to falsely recognize information that was not presented at both intake (males, 34.4%, females, 17.5%) and follow-up (males 42.6%, females, 30.1%). Race effects were found for level of impairment on the AVLT: African Americans were more impaired on total number of words recalled (50.9%) and presence of false positives on the recognition task (47.9%) than white clients (total recalled, 34.9%, false oositives, 26.5%) at intake. African American clients also improved at a greater rate than whites after intake and were not different on level of impairment at follow-up. Race effects were also found for level of impairment on Trails B: African American clients were more impaired (74.3%) than white clients (45.6%) at intake. Similar to the AVLT results, African American clients improved at a greater rate than whites after intake and were not different on level of impairment at follow-up. No effects for self-reported pre-treatment drug use were found for males. Contrary to expected findings, less extensive pre-treatment use of marijuana use was associated with greater confabulation on the AVLT recognition task. Greater confabulation on the AVLT recognition task was found to be related to decreased treatment retention for males.

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RELIABILITY OF SEQUENTIAL NALOXONE CHALLENGE TESTS

T. J. McMahon, M. I. Rosen, A. Margolin, M. **J. Kreek, E. A. Wallace, S. W. Woods, H. R. Pearsall, and T. R. Kosten**

Efforts to identify new pharmacologic agents for the treatment of opiate withdrawal might be enhanced by the availability of a within-subjects research design. If there is adequate test-retest reliability, naloxone challenge tests could be used to test new medications by comparing their ability to attenuate naloxone-precipitated withdrawal with that of placebo. This study was designed to determine the test-retest reliability of three naloxone challenge tests done with the same opiate-dependent individual.

Method: Five opiate-dependent males were admitted to an inpatient setting, stabilized on methadone 25mg po QD, and challenged with naloxone 0.2 mg IV on three consecutive days.

Results: Two-factor ANOVA indicated that test-retest with the same individual and challenge number accounted for more than 80% of the variance in six dependent measures. Test-retest correlation coefficients for all dependent measures exceeded .65. Physiologic measures tended to be more reliable than subjective and objective ratings of withdrawal. There was a consistent trend for withdrawal to be slightly more severe during the first challenge.

Conclusions: Sequential naloxone challenge tests show a high degree of stability, and the method shows promise for testing new treatments for opiate withdrawal. In order to control for greater withdrawal during the first challenge, treatment conditions should be balanced within the challenge sequence.

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PROLONGED ADJUNCTIVE CLONIDINE USAGE IMPROVES TREATMENT OUTCOMES FOR OPIOID ADDICTS GIVEN NALTREXONE

D. Sikowitz, D. M. Ziedonis, M. Hayes, and T. Kosten

PURPOSE AND METHODS:

The usage of the opioid antagonist naltrexone in the treatment of opiate dependence has been limited in the general addict population because of poor compliance and retention. Addicts leave treatment often complaining about residual opioid withdrawal and psychiatric symptoms. Clonidine is an effective and relatively safe agent in the management of opiate withdrawal and continued usage may help during naltrexone induction.

In this two week outpatient open pilot study we compared the treatment outcomes of 30 patients treated as usual in our naltrexone program (50 mg Naltrexone qd) versus eighteen patients treated with naltrexone (50 mg qd) and adjunctive clonidine (0.1 mg BID). Assessments included opiate withdrawal symptoms (opiate withdrawal symptom checklist) and psychiatric symptoms (Beck Depression Inventory and the Spielberger State and Trait Anxiety Inventory).

RESULTS AND CONCLUSIONS:

Addicts in the study were 75% male, 73% single, 31 years old, 11 years of education, 35% employed, 50% with legal problems, and 65% white. The clonidine/naltrexone group had better treatment retention (83% versus 67%) than the naltrexone alone group. While in treatment, the clonidine/naltrexone group had better medication compliance (97% versus 60%) and therapy compliance (97% versus 53%). Patients receiving clonidine reduced their symptoms of opioid withdrawal by 34% (82 to 54 on opiate withdrawal scale), depression by 36% (14 to 9, BDI score) and anxiety state by 18% (51 to 42).

Two weeks of adjunctive clonidine (post detoxification) may improve retention and compliance in a naltrexone treatment program. Adjunctive clonidine further reduced symptoms of opiate withdrawal, anxiety, and depression. This study is limited in design, and double blind studies should be done in the future.

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BUPRENORPHINE: RAPID AND SLOW DOSE-REDUCTIONS FOR HEROIN DETOXIFICATION

C. Pycha, R. B. Resnick, and M. Galanter

Buprenorphine reduces severity of opioid withdrawal symptoms and has been reported to be comparable to methadone in ambulatory heroin detoxification (Bickel *et al.,* 1988). Furthermore, only mild withdrawal symptoms or none at all had been observed following abrupt or rapid discontinuation after its daily administration for 24-58 days (Jasinski *et al.,* 1978; Mello *et al.,* 1982; Kosten and Kleber 1988; Fudala *et al.,* 1990). However, heroin craving and abstinence symptoms developed during gradual dose-reductions (10% BIW) in 28 of 29 subjects who had been maintained for 8-12 weeks on 1.5-8.0 mg/day buprenorphine (Resnick *et al.,* 1992). The present study was designed to assess the contribution made by rate of buprenorphine dose reductions to the outcome of ambulatory heroin detoxification.

Fifty-eight heroin dependent subjects were stratified into low-dependence ($50 heroin/day or less) and high-dependence (>$50 heroin/day) groups. They received an initial dose of buprenorphine that blocked abstinence symptoms and were randomized (2:1 ratio) to receive, single-blind, a rapid (N=39) or slow (N=19) dose-reduction schedule, followed by placebo for ten days. Outcome was measured by retention in treatment and heroin use.

Mean time on buprenorphine was nine days (range: 7-13) for the rapid group and 28 days (range: 22-37) for the slow group. The groups were comparable in age, level of dependence and years addicted. Dropout rates were 64% and 79% in the rapid and slow groups respectively. The greater dropout rate in the slow group could be attributed to the longer treatment time and increased opportunity for relapse. Heroin use was not significantly different between the groups. Outcome success was not related to rate of dose reductions and appeared limited to highly motivated individuals. At three months follow-up, six subjects were abstinent (three from each group). For four of the six abstinent subjects this was their first treatment episode, a finding consistent with our previous observation that buprenorphine treatment is accepted by many heroin addicts who otherwise would remain untreated because of refusal to receive methadone.

REFERENCES:

Available from senior author.

ACKNOWLEGMENT

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BUPRENORPHINE MAINTENANCE: REDUCED DOSING FREQUENCY

R. B. Resnick, C. Pycha, and M. Galanter

Buprenorphine has been acceptable and efficacious for many heroin addicts who refuse methadone maintenance (Resnick, *et al.,* 1992), a finding of considerable public health importance. Furthermore, in doses up to 8 mg/day, it has been comparable to methadone in reducing heroin craving and use. In contrast to methadone, however, where doses may be dispensed for self-administration at home, take-home buprenorphine has not been authorized and patients have been required to attend the clinic 7 days per week. Although medication diversion is thereby eliminated, it imposes a hardship on patients that may compromise compliance in long-term treatment and penalizes those who prefer buprenorphine to methadone. Based on a report that subjective effects of buprenorphine leveled off at 16 mg and then decreased at 32 mg, with blood levels that were both dose- and time-related (Walsh, *et al.,* 1992). we explored administering higher doses less often than daily, as a way to reduce the frequency of clinic attendance without the need to dispense take-home medication.

Thirty-one heroin abstinent subjects maintained on buprenorphine 4-16 mg/day for 1-12 months, received double their daily dose administered every two days. Nineteen subjects also received a triple dose, administered every three days. One subject maintained for 72 hours on a triple dose of 24 mg, received a quadruple dose of 32 mg on two separate occasions. Subjects were evaluated for abstinence symptoms and changes in subjective drug effects.

Abstinence symptoms (anergia and restlessness) emerged 30-40 hours after 8 mg in two of four subjects who had been receiving 4 mg/day; within 72 hours after both 32 mg doses in the subject who had no abstinence symptoms for 72 hours after 24 mg; and within 72 hours after a triple dose in seven of nineteen subjects. No other subjects reported abstinence symptoms within 48 hours (after 8-32 mg) or 72 hours (after 12-32 mg). One subject maintained on 6 mg/day reported increased agonist effects after receiving 12 mg, but not after 10 mg. Twenty-nine of the 31 subjects have had continued heroin abstinence with dosing every 48-72 hours (3-4 days per week). The gratitude expressed for the reduced clinic attendance required, suggests that compliance in long-term buprenorphine maintenance may be improved for subjects receiving 4-16 mg/day, without the need to dispense take-home medication.

REFERENCES:

Available from senior author.

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A BEHAVIORAL TREATMENT FOR OPIOID DEPENDENCE DURING A BUPRENORPHINE DETOXIFICATION: A PRELIMINARY REPORT

W. K. Bickel, L. Amass, S. T. Higgins, R. A. Esch, and J. R. Hughes

In this clinical trial a behavioral treatment program for opioid dependence was compared to standard counseling typical to that provided during methadone treatment. Thirty-nine patients (19 behavioral and 20 standard) were randomly assigned to treatment during a 26-week detoxification with buprenorphine (a new synthetic opioid that may have more desirable effects than methadone treatment). All subjects received their buprenorphine 7-days a week at the clinic and provided urine samples 3 times per week which were analyzed for the presence of opioids. The behavioral treatment consisted of community reinforcement and contingency management approaches originally developed for the treatment of cocaine dependence (Higgins *et al.,* 1991, 1993). The methadone style counseling was based on the results of a survey of counseling provided as part of methadone treatment (Ball *et al.,* 1990). Data from 37 patients have been analyzed. Eighty-two percent of the behavioral treatment group and 78% of the standard treatment group remained in treatment for at least 8 weeks. Fifty-three percent of the behavioral treatment group and 17% of the standard treatment group remained in treatment for the entire 26 weeks. Fifty-six percent of the behavioral treatment group and 16% of the standard treatment group provided 8 weeks of continuous opioid abstinence. Thirty-three percent of the behavioral treatment group and 5% of the standard treatment group provided 13 weeks of continuous opioid abstinence. These preliminary data suggest that the behavioral treatment program, originally developed for the treatment of cocaine dependence, can be employed in the detoxification of opioid dependent patients.

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COGNITIVE FUNCTION IN DUALLY DEPENDENT OPIATE AND COCAINE USERS BEFORE AND AFTER BUPRENORPHINE OR PLACEBO TREATMENT: A P300 ERP STUDY

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

The relationship between cognitive impairments and opiate dependence has been infrequently studied. Even though it has been suggested that chronic heroin and cocaine abuse may lead to neuropsychological and cognitive impairments, the findings in the literature have been contradictory. The present study was conducted to assess cognitive function before and after detoxification from heroin and cocaine and to investigate whether buprenorphine treatment is more effective than placebo in reversing the disruptive effects of detoxification. Fifteen male volunteers between the ages of 25-40 meeting 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 a 12-day detoxification period consisting of a 6-day methadone detoxification and a 6-day drug-free period, and then on the 15th day of either buprenorphine (12 mg/day) or placebo treatment. Testing consisted of an auditory oddball paradigm involving a discrimination between a frequent (800 Hz) and a rare (1600 Hz) tone at 60dB SPL. There were no significant differences in P300 amplitude, latency, or topographic distribution between the drug-dependent subjects and matched controls on the admission day. Following detoxification there was a significant decrease in P300 amplitude in the drug-dependent group when compared to controls ($p < .01$). During this second visit self-reported signs of withdrawal were minimal. Buprenorphine treatment significantly reversed the P300 amplitude decrement following detoxification while placebo-treated subjects continued to show depressed P300 amplitudes. Reduced P300 amplitude following methadone detoxification at a time when subjective reports of withdrawal are minimal may represent a marker of low levels of withdrawal which persists beyond more overt behavioral signs and symptoms. The finding that buprenorphine treatment reverses the withdrawal-induced decreases in P300 amplitude further demonstrates that event-related potentials are a sensitive tool for studying the neurophysiological correlates of drug dependence and withdrawal.

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BUPRENORPHINE AND NALOXONE INTERACTIONS IN METHADONE MAINTAINED PATIENTS

S. Welm, R. T. Jones, J. Mendelson, S. Batki, and R. Upton

Sublingual buprenorphine appears useful for the treatment of opiate dependence. A sublingual dose formulation of buprenorphine effective for the treatment of opiate addiction but significantly dysphoric or unpleasant to discourage use when taken parenterally would be advantageous. One promising formulation is a combination of buprenorphine and the opiate antagonist naloxone in a fixed dose ratio.

Patients on methadone maintenance represent a population with a high potential for parenteral drug abuse and, therefore, huprenorphine abuse. To assess abuse liability of buprenorphine and buprenorphine/naloxone combinations, six methadone maintenance patients (40-60 mg/day) received i.v. huprenorphine (0.2 mg), naloxone (0.1 mg), buprenorphine and naloxone in combination (huprenorphine 0.2 mg, naloxone 0.1 mg) or placebo. One male subject quit the experiment after three sessions because of unpleasant drug effects.

Buprenorphine alone produced no significant physiologic or subjective effects. Naloxone alone produced marked opiate withdrawal symptoms. Buprenorphine in combination with naloxone produced characteristic physiologic and subjective opiate antagonist-like signs and symptoms. In four of six subjects, the combination formulation produced more intense withdrawal than naloxone alone. The abuse liability of buprenorphine/naloxone combinations in methadone maintenance patients appears to be less than buprenorphine alone.

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DEVELOPMENT OF A BUPRENORPHINE-NALOXONE COMBINATION DRUG FOR THE TREATMENT OF DRUG ADDICTION

C. N. Chiang and R. Hawks

Buprenorphine is currently being developed in a sublingual dosage form for the treatment of drug addiction. Because the abuse of buprenorphine sublingual tablets marketed for analgesia has been reported, an important consideration in the development of this drug as a "take-home" medication for drug abuse treatment is to minimize its diversion potential.

One approach is to incorporate a short-acting antagonist of low sublingual bio-availability in the formulation. Naloxone has been selected for the combination product because its bioavailability (less than 10%) following the sublingual route of administration is much lower than that of buptenorphine (55%) and there are precedents for the use of naloxone to reduce the parenteral abuse potential of narcotic analgesics *e.g.* buprenorphine, pentazotine, tilidine. An analgesic combination of buprenorphine and naloxone is currently marketed in New Zealand. The development of the combination product of buprenorphine and naloxone is consistent with FDA's combination drug policy (21 CFR 300.50), which allows the addition of one or more drugs to an effective agent, in order to minimize. abuse potential.

NIDA's ongoing development program for this combination product includes developing stable, palatable and efficacious formulations (liquid unit doses), carrying out clinical pharmacology studies for the determination of the optimal dose ratio of buprenorphine and naloxone in the combination product, and conducting limited clinical trials. Preliminary data from studies of buprenorphine and naloxone in methadone maintained patients, in subchronic buprenorphine patients and in heroin addicts indicate that a combination of buprenorphine and naloxone at a dose ratio of 1:1 will be aversive for intravenous use by methadone maintained patients and by moderately/highly opiate-dependent heroin addicts but will remain efficacious for sublingual use by buprenorphine maintained patients. Studies are ongoing to finalize the dose ratio for the combination product.

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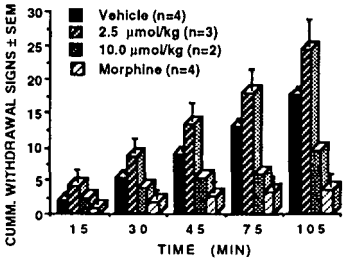
DYNORPHIN-(2-17) SUPPRESSED WITHDRAWAL IN MORPHINE -DEPENDENT RHESUS MONKEYS

E. R. Bowman and M. D. Aceto

Previous studies in this laboratory demonstrated that dynorphin-(1-13) or Dyn-(1-13) as well as Dyn-(1-10), but not Dyn-(1-8), Dyn-(1-6) and α-endorphin, suppressed withdrawal behavior in maximally dependent rhesus monkeys (Aceto *et al.,* Eur. J. Pharmacol. 83, 1982 and Aceto *et al.,* Fed. Proc. 42, 1983). In order to extend these findings and to determine whether or not deletion of the tyrosine (tyr)-residue was essential for suppression of withdrawal in our animal model, the present studies were initiated. As shown in the fig below, an intravenous dose of 10 μM of Dyn-(2-17) suppressed withdrawal behavior.



These results confirm that the tyr-residue is not critical for activity in the Dyn series (N. M. Lee and A. E. Takemori, U. Minnesota, personal communication) and are in accord with previous observations that short peptide fragments such as Dyn-(1-6) and Dyn-(1-8) are inactive or less potent. They also suggest potential clinical uses for this and other active Dyn-peptides in the pharmacotherapy of pain, and tolerance to and dependence on opioids.

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NIMODIPINE TREATMENT OF OPIATE WITHDRAWAL

M. I. Rosen, E. A. Wallace, H. R. Pearsall, G. K. Aghajanian, S. W. Woods, and T. R. Kosten

INTRODUCITON: Nimodipine, a centrally-acting L-type calcium-channel blocker, has been shown to attenuate opiate withdrawal in preclinical studies. We examined the effects of nimodipine on naloxone-precipitated opiate withdrawal, and its efficacy for detoxification from methadone.

METHODS: Six opiate-dependent subjects were hospitalized and stabilized on methadone 25 mg daily. On three separate days, 24 hours after the previous methadone dose, patients received in a blinded, randomized sequence single doses of either placebo, nimodipine 30 mg, or nimodipine 90 mg (p.o.). One hour later, patients received naloxone 0.8 mg intramuscularly and withdrawal severity was assessed by an observer every five minutes for the next 60 minutes. Results: Mean peak withdrawal severity (0-60 rating scale) by nimodipine dose was placebo: 20.3+/-7.9; nimodipine 30 mg: 19.0+/-11.2; nimodipine 90 mg: 15.3+/-6.9 mg. Repeated measures ANOVA of peak withdrawal scores by nimodipine dose was not significant: $F(df\ 2,5)=1.29$, $p>.05$. Nimodipine was well tolerated, without significant cardiovascular effects.

CONCLUSION: Although nimodipine did not produce statistically significant attenuation of naloxone-precipitated opiate withdrawal at the doses tested, the data suggest that higher nimodipine doses may be efficacious. Pilot data utilizing nimodipine for detoxification of methadone-maintained patients will also be presented.

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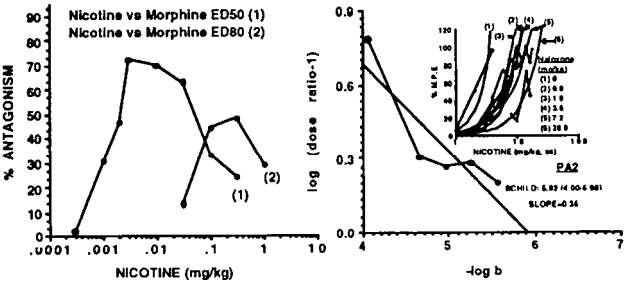
NICOTINE'S OPIOID AND ANTI-OPIOID INTERACTIONS: POSSIBLE ROLE IN MAINTAINING SMOKING BEHAVIOR

M. D. Aceto, S. M. Scates, Z. Ji, and E. R. Bowman

Preliminary data from this laboratory suggested an intimate involvement of nicotine (NIC) with the opiate system, *i.e.,* NIC antagonized morphine (MOR)-induced antinociception and, in turn, naloxone (NAL) antagonized NIC-induced antinociception in mice (Aceto *et al.* NIDA Monog. 34, 1981 and Tripathi *et al,* J.P.E.T. 221, 1982). We decided to investigate further these intriguing leads. As shown in the fig. on the left, at lower doses, NIC antagonized MOR-induced antinociception. The effect was highly dose-specific. In addition, as shown in the fig. on the right, Nic antinociception which occurred at much higher doses was antagonized non-competitively by Nal as shown in the Schild plot.



This raises the possibility that nicotine may activate the anti-opiatergic system at low doses and at high doses the opiatergic system. These results may explain, in part, nicotine's role in maintaining smoking behavior.

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NICOTINIC ANTAGONISTS: IN VIVO EFFECT ON CALCIUM AND VOLTAGE-CALCIUM CHANNEL

M. I. Damaj, S. P. Welch, G. A. Patrick, and B. R. Martin

There is evidence that mecamylamine and dihyro-ß-erythroidine (DBE), potent nicotinic antagonists with no apparent common structure similarities, could be acting on different sites to modulate central nicotine receptors. The aim of this study was to examine the *in vivo* interaction (using antinociception as a model) of mecamylamine and DBE with calcium and voltage-calcium channels, thought to be involved in nicotinic receptor activation. Male ICR mice received intrathecally (i.t.) 10 µg (0.061µmol)/animal of mecamylamine or 20 µg (0.06µmol)/animal of DBE 5 min before treatment with one of the following drugs given i.t. : calcium, (±)-BAYK8644, thapsigargin and A23187. The antinociceptive effect was measured by the tail-flick method. Free intracellular calcium $[Ca^{2+}]_i$ measurements were performed in spinal synaptosomes by spectrofluorescence using fura-^{2} as an indicator. Pretreatment with mecamylamine completely blocked the antinociceptive response of calcium, (±)-BAYK8644 and thapsigargin, while the A23187 effect was reduced to 50% MPE. DBE, did not significantly reduce the antinociceptive effect of all the agents tested. Furthermore, nicotine (10µM) induced a rise in $[Ca^{2+}]_i$ in spinal synaptosomes (41% increase in basal) which was not reduced by 10 or 100 µM of mecamylamine. These results combined with the fact that mecamylamine does not compete for the [^{3}H]-nicotine binding site suggest that this antagonist is not acting directly on the nicotine agonist site. Mecamylamine may be acting on calcium-dependent mechanisms involved in the intracellular signaling process such as calmodulin, calmodulin-dependent protein kinase, modulation of the release of endoplasmic reticulum calcium by a direct action on IP_3 receptors or Ca^{2+}-dependent ATPase. It could also, however, be exerting its antagonistic property by altering a second messenger, resulting in intracellular calcium modulation.

Dihydro-ß-erythroidine, on the other hand, seems to act directly on the nicotine receptor. Indeed, DBE has been reported to compete for [^{3}H]-nicotine binding site on a nanomolar range and our experiments shows that its i.t. administration did not reduce the andnociception induced by diverse drugs which increase intracellular calcium such as thapsigargin, calcium and (±)-BAYK 8644.

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THE USE OF SCANNABLE CASE REPORT FORMS IN SUBSTANCE ABUSE TREATMENT TRIALS

D. Jerger, J. Wilkins, V. von Raffay, J. Gold, D. Levine, and D. Gorelick

In order to eliminate the need for terminal or card punch data entry, specialized case report forms were developed to be electronically scanned on a National Computer Systems (Columbia, PA) OpScan 5 optical mark recognition (OMR) scanner and introduced into a NIDA-funded, controlled clinical trial of desipramine in the treatment of schizophrenics with cocaine dependence. All forms, completed using pen, included locator and demographic information, the Addiction Severity Index (ASI), the Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), the Hamilton Depression and Anxiety Inventories (HAM-D and HAM-A), the Profile of Mood States (POMS), and the Strauss/Carpenter Prognostic Scale. IBM-compatible computers were configured and programmed to decode the information from each scanned form, perform validity checks on the acquired data, and convert the information into Paradox (Borland Intl., Scotts Valley, CA), a relational database.

For further analysis, the data was transferred into appropriate formats for statistical applications including SAS, BMDP, and SPSS. Data entry was performed daily; the scanning system was programmed to reject forms improperly completed. Therefore, errors, including missing data, inappropriate additional responses, or missing patient, date, or evaluator codes were brought to the attention of the evaluator while the subject was still available and the evaluator had recall of the interview.

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IDENTIFYING PROGRAM VARIABLES FOR MATCHING DRUG ABUSERS TO TREATMENT PROGRAMS

M. L. Polinsky and Y. I. Hser

The matching of drug users to treatment programs has long been viewed as an important factor in optimizing treatment outcome. Past studies have generally focused on matching drug abuse severity to treatment modality (inpatient versus outpatient). Other program variables such as service type and intensity, staffing, and philosophy may also be useful.

As part of an ongoing study attempting to improve matching users to local programs, a mail survey is being conducted to determine potentially useful program variables for matching. Drug treatment programs for adults in Los Angeles County, a 4,000 square-mile area, have been identified by review and comparisons of several sources (*e.g.,* the National Drug Treatment Unit Survey and the California Alcohol and Drug Data System listings) and by word of mouth and observation.

In December 1992, survey booklets were mailed to 367 programs that provide treatment services for adult drug users (excluding those which require a primary diagnosis of alcoholism and those which provide only assessment, referral, or self-help). Treatment centers with multiple program components were asked to complete separate booklets for individual modalities. The survey booklet includes questions regarding organizational structure, program capacity and philosophy, client populations served, service type and intensity, staff qualifications and caseload, and capability and willingness to serve clients with special needs.

A preliminary analysis of 184 booklets included responses from all program types: 10% hospital inpatient, 15% residential, 34% outpatient drug-free, 15% outpatient methadone maintenance, 18% outpatient detox. and 8% day treatment. The programs had been in operation an average of 10.5 years and 61% had annual budgets of mote than $250,000. Program size and specialization varied extensively, although 40% of all the programs reported feeling able to serve almost any type of client, regardless of the primary drug of abuse, chronic impairments, or pregnancy status. Differences among program types were evident in the kinds and intensity of approach, followed by individual counseling. Self-ratings of perceived quality of treatment staff and overall program did vary with counseling services getting higher ratings over referral, medical, and psychiatric services.

Plans are to complete the survey; perform further analyses, including information about program staffing, client eligibility, admission procedures, and discharge policies; and to use the information to test and refine a system of matching clients to treatment programs.

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COMPUTERIZED CLINICAL SIMULATIONS FOR DIAGNOSIS AND TREATMENT OF ADDICTION TO PRESCRIPTION DRUGS: A DEMONSTRATION

P. K. Horvatich and S. H. Schnoll

The Medical College of Virginia in collaboration with the National Board of Medical Examiners (NBME) has developed three computer-based simulations (CBX) to teach the prescribing of drugs with abuse liability. The clinical cases for these simulations include pain management, attention deficit disorder and anxiety disorder which are used to emphasize the appropriate prescribing of the opioid analgesic, stimulant and sedative-hypnotic drug classes respectively. Because of the problem-solving nature of clinical case simulations are an effective instructional strategy. CBX cases, developed during the past 20 years and used for evaluation purposes by the NBME, are conducted in an uncued environment in which more than 2000 treatment orders can be made in free text. In addition, in CBX cases "patients" respond to treatment in a realistic manner, making the NBME's svstem one of the most complex medical simulations to date. The MCV cases on prescription drugs are used primarily for presentation/discussion to large groups of primary care physicians during a two-day continuing medical education course on prescription drugs. However, these simulations also are appropriate for small group tutorial and self-instructional purposes. The purpose of this session will be to describe and demonstrate the computerized clinical simulations described above, in the large group presentation format.

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BRAIN MAPPING OF THE REWARD SYSTEM: A DATABASE OF CONNECTIONS OF THE VENTRAL STRIATUM

M. G. Laubach, D. P. Friedman, L. J. Porrino, and D. J. Woodward

Progress in understanding the primate visual system has been accomplished through the construction of a database for corticocortical connections of the visual areas (Felleman and Van Essen 1991). In attempting to understand the neurobiology of the reward system, we have constructed several information management structures for connections of the rat ventral striatum. A connectivity matrix and a connectivity table were constructed using the Quattro Pro program to document reported projections from the cerebral cortex and thalamus to the ventral striatum. The Adobe Illustrator program was used to construct annotated circuit diagrams for ventral striatal connections. Our analysis visualizes sub-territories within the ventral striatum which are distinguished by the cortical and thalamic projection topography.

Future work will use intelligent data structures to further document all afferent and efferent connections of the ventral striatum. Our goal is to provide a means for generating testable hypotheses of ventral striatal function based on anatomic information.

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RESILIENCY AND INVULNERABILITY AS PROTECTIVE FACTORS IN SUBSTANCE ABUSE RESEARCH

W. A. Rhodes and E. G. Singleton

The historical focus of problem-oriented research like addiction science is on persons who are at-risk for experiencing difficulties and who are vulnerable to developing pathology. Research has essentially overlooked the potential contribution of studying protective factors -- those characteristics of individuals who overcome predisposing conditions that contributed to their drug problem or shielded them from abuse and dependence.

The concept of resiliency has been used to describe both types of persons. This presentation introduces the distinctions between resiliency and invulnerability, explores the shortcomings of a deficits approach to substance abuse research, and places the study of protective factors in context. Further study of wellness could improve the imbalance.

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POLICY ISSUES IN ANALGESIC EDUCATION AND REGULATION: FEAR OF ADDICTION IS A BARRIER TO THE USE OF OPIOID ANALGESICS IN CANCER PAIN MANAGEMENT

D. E. Joranson and A. M. Gilson

A significant impediment to the management of cancer pain with opioid analgesics throughout the world is the exaggerated fear of addiction. This fear is prevalent among the public, patients, health care professionals and regulators. The source of this belief appears to be a misconception that the presence of physical dependence or tolerance to opioids in a person are sufficient to produce addiction. In fact, the World Health Organization's (WHO) initial conception of addiction focused on the physiologic ability of morphine-like drugs to produce dependence.

Later, WHO substituted "drug dependence" for "addiction", and defined it primarily as a psychic state characterized by compulsive behavior. However, a physiologic interpretation of addiction has permeated medical education and regulation, and little has been done to change public attitudes, professional training and public policy. Efforts to address this problem at the international, national and state level will be discussed.

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NEUROPSYCHOLOGICAL DEFICITS IN SUBSTANCE ABUSERS: LEVELS OF DIAGNOSIS MODELS

A. M. Horton, Jr.

This paper reviews critical papers on the assessment of neuropsychological deficits in substance abusers and suggests assessment instruments for three diagnostic levels. These levels of diagnosis are screening, classification and treatment selection. Brief neuropsychological test batteries *(i.e.,* less than thirty minutes) are proposed for each level. Essentially, the suggested screening procedure utilizes the Trail Making Test, the Mini-Mental State Examination (Folstein, Folstien, & McHugh 1975), and the Abstraction portion of The Shipley Institute of Living Scale (SILS) (Shipley 1967).

The classification instrument is a short form of the Brain Age Quotient (BAQ) devised by Ralph M. Reitan (1973), based on a three subtest set (Trail Making Test Part B, Block Design and Digit Symbol subtests) (Horton & Anilane 1986). The two major considerations in treatment selection for drug addicts from a neuropsychological point of view are their abilities to encode and retain verbal and non-verbal information *(i.e.,* short-term memory abilities) and their ability to deal with abstract principles and form concepts *(i.e.,* executive functions). The Russell Version of the Wechsler Memory Scale (WMS) (1975) and the Category Test of the Halstead-Reitan Neuropsychological Test Battery (Reitan & Wolfson 1985) are the suggested tests.

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MATERNAL AND INFANT CONTRIBUTIONS TO JOINT ATTENTION: PHASE 1 OF A COMPARISON BETWEEN COCAINE-EXPOSED AND NON-EXPOSED INFANTS AND THEIR MOTHERS

M. Margulies, S. Hamel, and D. Neuspiel

The present study was designed to compare mother-infant interaction and shared visual attention to toys in a sample of cocaine-exposed and non-exposed one-year-olds and their mothers. In phase one of this study, infant and maternal contributions to mother-infant interaction and shared visual attention to a toy were analyzed with a sample of 19 non-exposed infants and their mothers during two minutes of free play. Both mother and infant were rated on quality of affect and degree of responsiveness. Outcome measures included a global rating of the quality of mother-infant interaction, and duration of shared visual attention to toys (joint attention). Maternal and infant affect were highly correlated as were maternal and infant responsiveness. Maternal responsiveness was more highly correlated with both the global rating and joint attention than was maternal affect. Infant responsiveness was more highly correlated with joint attention than was maternal responsiveness ($r = .67$ vs. $r = .50$). Joint attention and the global rating were also highly correlated. A regression analysis indicated that infant responsiveness was the only significant contributor to time spent in joint attention. These. findings support a model of mutual responsiveness and reciprocity: high levels of responsiveness in each member of the dyad resulted in optimal interaction ratings and joint attention outcomes. Since the joint attention measure is a relatively objective measure, it might serve as a more sound outcome measure of mother-infant interaction. The infant clearly plays an important role in determining whether joint attention ensues by virtue of his or her ability to remain focused on a toy even when the mother attempts to redirect attention elsewhere. A mother's sensitivity to her infant's focus of visual attention, that is, maintenance of it rather than redirecting attention to a different toy, indirectly influences joint attention outcomes. There is a need for intervention programs that teach mothers ways to optimally respond to their infants' cues and to support their infants' ability to focus on objects and learn about the environment, particularly for mothers of high-risk infants. Data collection from a parallel sample of cocaine-exposed infants and mothers is in progress. These data will be compared with data from the present sample in phase two of the study.

AFFILIATION:

Medical and Health Research Association of New York City, Inc., National Development and Research Institutes, Inc., New York, NY, University of Pittsburgh, Pittsburgh, PA, and Albert Einstein College of Medicine, New York, NY

THE NALOXONE CONJUNCTIVAL TEST: AN UNDERUSED TOOL? A REVIEW OF THE AVAILABLE DATA

M. Auriacombe, J. W. Cornish, L. Skoble, and C. P. O'Brien

BACKGROUND:

There is currently no simple and morbidity-free procedure available to determine a state of opiate dependence in patients. There is preliminary evidence, however, that the naloxone conjunctival test, which consists of instilling a drop of a saline solution of naloxone hydrochloride into a subject's eye, causes significant homolateral mydriasis (anisocoria) in the eye of a chronic opiate dependent subject and not in that of a non-dependent subject.

METHOD:

We reviewed the international literature on the naloxone conjunctival test using the Medline database and a manual search of major scientific journals specialized in the field of substance abuse.

RESULTS:

Up to December 1992, we uncovered six articles dealing specifically with the use of opiate antagonist ophthalmic solutions in populations of chronic opiate addicts. Four of the articles reported the occurrence of mydriasis when a solution of naloxone is used in opiate addicts. Two of the articles reported that there was no differential change in pupil size when the naloxone solution is used; however one study used a much weaker and the other a much stronger solution of naloxone than reported in the other studies.

CONCLUSION:

From our review of the literature, it appears that the naloxone conjunctival test holds great promise as a simple and morbidity-free method of testing for chronic opiate addiction, that it should be further studied and that its usage should eventually develop.

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DEVELOPMENT OF GLUTAMATERGIC ANTAGONISTS: NEW TREATMENTS FOR OPIATE ADDICTION

B. H. Herman, F. Vocci, D. Majewska, and P. Bridge

Recent preclinical research suggests that drugs which antagonize N-Methyl-D-aspartate (NMDA) receptors inhibit opiate tolerance and dependence. NMDA receptors have been shown to be involved in functions that may be components of addiction including neuroprotection. There are five major research efforts implicating the glutamatergic system in opiate addiction. (1) Investigations indicating that the non-competitive NMDA receptor antagonist, MK-801, inhibits morphine tolerance and withdrawal symptoms in mice (Tanganelli *et al.* 1991) rats *(e.g.,* Rasmussen *et al.* 1991; Trujillo and Akil 1991), and guinea pigs (Tanganelli *et al.* 1991). A major disadvantage with the clinical use of drugs like MK-801 is that they can precipitate phencyclidine (PCP)-like behavior *(e.g.,* Rasmussen *et al.* 1991) and also can be neurotoxic *(e.g.,* Olney *et al.* 1989). However, there are pharmacological alternatives which share the beneficial effects of these drugs but do not appear to have similar severe side effects. (2) The competitive NMDA receptor antagonist, LY274614, inhibits morphine dependence in rats (Rasmussen *et al.* 1991), and reverses the development of morphine tolerance in opiate dependent rats (Tiseo and Inturrisi 1993). LY274614 appears to have less PCP-like side effects than MK-801 (Rasmussen *et al.* 1991). (3) The nitric oxide synthase rats (Kimes *et al.* 1991) and blocks opiate tolerance and even reverses mu opiate withdrawal symptoms in mice (Kolesnikov *et al.* 1993). (4) Glycine antagonists have been reported to block NMDA-induced convulsions (Koek and Colpaert 1990). (5) Mao *et al.* (1992) have found that GM1 gangliosides reduce experimental pain in rats. Further investigations are indicated on the effects of NMDA antagonists on opiate addiction.

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NIDA PRECLINICAL COCAINE TREATMENT DISCOVERY PROGRAM (CTDP)

C. Hubner, A. Reid, J. Biswas, H. Sorer, J. Terrill, and D. McCann

NIDA/MDD's mission is to develop medications for the treatment of drug addiction. One of the MDD's goals is to identify potential treatments for the medical management of cocaine abuse. As part of this effort, a Cocaine Treatment Discovery Program (CTDP) has been established to discover compounds which either substitute for cocaine with weaker effects or block cocaine's effects. This is achieved by testing compounds through a decision-based screening program. This screening program consists of *in vitro* biochemical analyses (dopamine transporter binding, inhibition of dopamine uptake) and *in vivo* pharmacological evaluations (mouse locomotor activity, rat drug discrimination, rat self-administration). A compounds advancement through the screening program is dependent on results at each stage of testing. Additional capabilities for compound characterization, including an in vitro biogenic amine activity profile, primate drug discrimination and primate self-administration studies are also available for "promising" compounds. These tests are performed through NIDA contracts or interagency' agreements awarded to SRI International, Texas College of Osteopathic Medicine, Harvard School of Medicine, NIDA/Addiction Research Center, NIH/NIDDK and the Washington D.C. Veteran's Administration.

The CTDP currently has a special interest in testing compounds with the following activities: compounds which act at the dopamine or serotonin transporters, full or partial dopamine agonists, dopamine antagonists which are unlikely to produce extrapyramidal side effects, 5-HT1C, 5HT2 or 5-HT3 antagonists, sigma ligands and calcium channel antagonists. The CTDP is also interested in evaluating compounds which affect dopaminergic systems through novel mechanisms. The CTDP has been acquiring these types of compounds for testing from a wide variety of sources including academic institutions, commercial chemical companies, government laboratories, pharmaceutical companies and the NIDA Drug Supply Program. Over the past three years ~350 compounds have entered the CTDP program.

CTDP data that has been generated on compounds in the public domain are being entered into the MDD Database. This structure-activity database, which is accessible to interested scientists on a dial-up basis, contains chemical information in a MACCS (Molecular Design Ltd) system and biological data in an Oracle system. The MDD Database serves as a tool to assist in the design of novel compounds for potential use as drug abuse treatment agents.

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