Disulfiram versus Placebo for Cocaine Dependence in Buprenorphine-Maintained Subjects: A Preliminary Trial

Tony P. George, Marek C. Chawarski, Juliana Pakes, Kathleen M. Carroll, Thomas R. Kosten, and Richard S. Schottenfeld

Background: We examined the effects of disulfiram versus placebo on cocaine dependence in buprenorphine-maintained subjects.

Methods: Opioid and cocaine dependent subjects (n = 20) were induced onto buprenorphine maintenance, then randomized to disulfiram (250 mg q.d.; n = 11) or placebo (n = 9) treatment for 12 weeks.

Results: Groups were comparable at baseline on demographic measures and on baseline measures of drug-use severity. Fifteen subjects completed the study, including 8 subjects randomized to disulfiram (72.7%) and 7 subjects randomized to placebo (77.8%). The total number of weeks abstinent from cocaine was significantly greater on disulfiram versus placebo (mean ± SD: 7.8 ± 2.6 vs. 3.3 ± 0.5, p < .05) and the number of days to achieving 3 weeks (24.6 ± 15.1 vs. 57.8 ± 7.7, p < .01) of continuous cocaine abstinence was significantly lower in disulfiram compared with placebo. The number of cocaine-negative urine tests during the trial were also higher on disulfiram (14.7) than on placebo (8.6); furthermore, subjects in the disulfiram group achieved consistently higher rates of cocaine-negative urine tests in each 3-week interval and the increase over time was faster in the disulfiram compared with placebo.

Conclusions: This preliminary study suggests the potential efficacy of disulfiram versus placebo for treatment of cocaine dependence in buprenorphine-maintained patients. Biol Psychiatry 2000;47:1080–1086 © 2000 Society of Biological Psychiatry

Key Words: Disulfiram, buprenorphine, cocaine, opioids, clinical trial

Introduction

The development of pharmacotherapies for cocaine dependence is of great importance, particularly in opiate-dependent individuals who have high comorbid rates of cocaine dependence, which may exceed 50% of the opiate-dependent population (Condelli et al 1992; Meandzija et al 1994). Cocaine use in these individuals is associated with continued illicit opioid use, intravenous drug use, and engagement in high-risk sexual activities that can increase the risk of HIV infection, as well as psychosocial, medical, and vocational difficulties and involvement in criminal activities (Condelli et al 1992; Kosten et al 1987). Despite intensive study, no pharmacologic treatment has proved efficacious for the treatment of cocaine dependence.

Converging evidence from clinical, epidemiologic, and human laboratory studies and from clinical trials have identified disulfiram as a potentially promising treatment for cocaine dependence. Disulfiram (Antabuse) is an inhibitor of aldehyde dehydrogenase, an enzyme involved in the breakdown of alcohol (ethanol). The accumulation of acetaldehyde produces an unpleasant reaction (nausea, vomiting, flushing, and, when severe, cardiac instability), which discourages alcohol use while subjects are administered this agent. The initial notion that disulfiram might be effective for the treatment of cocaine dependence came from observations of the high rates of alcohol abuse among cocaine-dependent patients and from clinical suggestions that alcohol may potentiate the effects of cocaine euphoria, produce disinhibition and impaired judgement, and function as a conditioned cue leading to cocaine use (Carroll et al 1993). In human studies, there is also evidence that concurrent use of cocaine and alcohol produces greater euphoria, augmented cardiovascular responses, and increased cocaine levels with the potential of increased toxicity, as well as production of the euphoric metabolite cocaethylene (McCance-Katz et al 1998b). Thus, by blocking alcohol use, disulfiram might also lead to reductions in cocaine use. Subsequent human...
laboratory studies suggested that disulfiram pretreatment may increase aversive stimulant (i.e., anxiety, dysphoria, paranoia) and cardiovascular responses to an intranasal cocaine challenge (Hameedi et al 1995; McCance-Katz et al 1998a, 1998c). This may relate to disulfiram’s inhibition of plasma esterases, which metabolize cocaine (Honjo and Netter 1969). Furthermore, disulfiram inhibits dopamine-β-hydroxylase (Caroldi and DeParis 1995; Goldstein et al 1964), and excessive dopamine release following cocaine use may be associated with increased anxiety and dysphoria rather than pleasurable and rewarding effects. This may lead to reduced cocaine use in the presence of disulfiram.

Two controlled clinical trials (Carroll et al 1993, 1998) and a case series (Higgins et al 1993) suggested that disulfiram can decrease both cocaine and alcohol use in subjects who abuse both substances and that its effect on cocaine use may occur independent of its effect on alcohol use. In an open-label pilot study of 18 subjects (Carroll et al 1993) comparing disulfiram with naltrexone in cocaine and alcohol abusing subjects, disulfiram (250 mg q.d.) led to significant reductions in percentage of days of cocaine and alcohol use and percentage of cocaine-positive urine tests compared with naltrexone (50 mg q.d.) treatment. Similarly, in an open label series, Higgins et al (1993) found that disulfiram 250 mg q.d. decreased cocaine and alcohol use. Recently, disulfiram (250–500 mg daily) was compared to a no-medication control in a randomized clinical trial evaluating three psychotherapies for cocaine-dependent, alcohol-abusing subjects (N = 122). There was a significant interaction of combining disulfiram with psychotherapy: Subjects receiving the disulfiram treatment significantly decreased their use of cocaine and alcohol and increased consecutive weeks of abstinence for both drugs (Carroll et al 1998).

There is also evidence that these effects of disulfiram on cocaine use may extend to opiate-dependent subjects (L. Petrakis et al, unpublished data, 1999). In a sample of 67 methadone-maintained subjects with concurrent cocaine dependence, disulfiram produced a significant reduction in self-reported cocaine use compared with the placebo group. Baseline alcohol use did not predict responses to disulfiram.

The high-affinity partial μ-agonist and κ-antagonist buprenorphine is a novel alternative to methadone for opiate dependence. Buprenorphine maintenance has been shown to be effective in reducing illicit opiate use (Johnson et al 1995; Kosten et al 1989; Ling et al 1998; Schottenfeld et al 1993; Strain et al 1994, 1996). Although some early animal (Mello et al 1989) and clinical (Kosten et al 1989) studies suggested that buprenorphine might be superior to methadone for reducing concurrent cocaine use in opiate-dependent patients, this advantage has not been supported in controlled clinical trials (Compton et al 1995; Schottenfeld et al 1997; Strain et al 1994).

Because buprenorphine is likely to be approved for the treatment of opiate dependence by the FDA in the near future, and may be widely used in primary care settings and in agnostic-maintenance programs, evaluation of agents with potential for the treatment of cocaine dependence is important in the setting of buprenorphine-maintenance treatment. In this preliminary study, we report on the adjunctive use of disulfiram versus placebo for cocaine dependence in buprenorphine-treated subjects.

Methods and Materials
We recruited 20 opiate-dependent subjects with concurrent cocaine dependence for this study. After providing informed voluntary consent, subjects were inducted onto buprenorphine sublingual tablets. All subjects signed an informed consent form verifying that they understood the consequences of using alcohol while taking disulfiram. Subjects were excluded from study participation if they had serious medical disorders that would preclude a trial of disulfiram (i.e., cardiovascular or cerebrovascular disease, psychotic disorders) or were using the antibiotic metronidazole, which is known to have disulfiramlike effects in the presence of alcohol use. Other exclusion criteria included 1) meeting DSM-IV criteria for alcohol or sedative-hypnotic dependence (unless detoxified before study entry); 2) use of psychotropic drugs such as antidepressants, mood stabilizers, or antipsychotic drugs; 3) current psychosis or suicidality and; 4) pregnancy as determined by β-HCG urine screening.

During the first 2 days of buprenorphine induction, subjects received 8 mg on Days 1 and 2, 16 mg during Days 3 to 5, and 24 mg from Day 6 onward using an 8 mg sublingual tablet preparation supplied by the Medications Development Division at the National Institutes on Drug Abuse (NIDA). At the beginning of Week 2, subjects were randomized to either disulfiram (250 mg) or matching placebo for a total of 12 weeks, and these were dispensed daily with buprenorphine. Subjects and the research staff were blind to medication assignment. All subjects also were advised that they might receive disulfiram, advised about alcohol-disulfiram and cocaine-disulfiram (i.e., anxiety, dysphoria, paranoia; Hameedi et al 1995) interactions and warned about potential interactions if using other preparations containing alcohol (e.g., cosmetic products containing alcohol) while they participated in the study.

All subjects participated in weekly, 1-hour, group drug-counseling sessions that provided education about disulfiram treatment, enhanced motivation for abstinence from cocaine and heroin use, provided drug refusal and coping skills training, and encouraged motivation to participate in self-help groups (e.g., Narcotic and Alcoholics Anonymous).

Urine toxicology testing was conducted three times weekly, and breathalyzer tests were given to subjects at periodic random intervals. At the end of the 12-week study period, study medications (disulfiram and placebo) were discontinued, and buprenorphine was tapered over a 2-week period. Subjects were offered entry into the clinical methadone-maintenance program,
naltrexone, or discharge at study completion. A three-panel qualitative urine toxicology screen (Abbott Laboratories [Abbott Park, IL] TDX system) for the major cocaine metabolite (benzylecgonine), opioids, and benzodiazepines was used, with detection thresholds of 300 ng/mL for cocaine and 200 ng/mL for opioids.

Primary outcome measures included 1) mean number of weeks of abstinence from cocaine, 2) number of days to achieving 3 weeks abstinence from cocaine, and; 3) the number of cocaine-negative urine tests during the 12-week trial. Secondary outcomes included treatment retention and self-reported cocaine, heroin, and alcohol use.

Statistical Analysis

Statistical analyses were conducted on the intention-to-treat sample. Chi-square and t tests were used to compare the two groups with regard to baseline characteristics. Differences in subject retention were analyzed using chi-square. Drug-use patterns over time were analyzed using mixed model procedures in SAS 6.12 statistical package (SAS Institute, Cary, NC). This procedure is particularly suitable for repeated measures designs with missing data, and it allows for a variety of within-subject covariance structures and unequal variance and covariance structure across time. It provides tests of the overall between-subject effects and tests of fixed and random effects, and it also allows for variance components analysis that can provide tests of specific pattern of results. In this study, we conducted tests of the overall differences between the two medication groups, repeated measures analysis, and variance components analysis using the mixed model procedure.

A chi-square analysis was used to evaluate the medication effect on the proportion of subjects who achieved 3 or more consecutive weeks of abstinence. ANOVA procedures were used to compare the time to 3 or more consecutive weeks of abstinence, as well as the total number of weeks abstinent between each group.

A total of 645 out of the 740 (87.1%) possible urine samples, had subjects provided the single baseline and thrice weekly urine toxicology samples for the 12 weeks of the study, were obtained on the 20 subjects in the intention-to-treat sample. To obtain a continuous outcome measure for urine toxicology results, data was grouped into four 3-week intervals (total of 9 urine samples per interval), and the number of negative urine tests in each of the three week intervals was calculated. We accounted for missing urine toxicology data by the following method: Rather than impute missing urines to positive, we utilized the number of negative urines during the trial for each subject as the outcome measure. Thus, each subject contributed a discrete number of negative urines to this outcome, rather than a proportion.

Results

Characteristics of Treatment Groups

Eleven subjects were randomized to disulfiram 250 mg q.d. (n = 11) and nine subjects to daily inactive medication (n = 9). The baseline characteristics of subjects enrolled in this study are presented in Table 1. There were no differences between groups on all baseline measures. There were substantial rates of intravenous drug use. None of the subjects were employed, and more than 80% were unmarried. Treatment retention between the study groups was comparable, with 8 out of 11 (72.7%) completing disulfiram treatment compared with 7 out of 9 (77.8%) completing placebo treatment \( \chi^2(1) = 0.07, p = .80 \). Alcohol use at baseline was negligible in both groups (Table 1).

Tolerability and Safety of Disulfiram in Buprenorphine-Treated Subjects

In general, disulfiram appeared to be well tolerated by subjects in this study, and there were no reports of disulfiram reactions with alcohol use. No direct liver toxicity of disulfiram treatment was observed during the study as assessed by monthly monitoring of liver function tests. Two subjects in disulfiram and one in the placebo group reported alcohol use during the trial, and none of these subjects completed the study.

Effects on Cocaine Use

The total number of weeks abstinent for cocaine was significantly higher for disulfiram than it was for the placebo group (7.8 ± 2.6 vs. 3.3 ± 0.5, \( p < .05 \)). The proportions of subjects achieving 3 weeks abstinence (45.5% vs. 44.4%) was comparable for disulfiram and placebo groups \( \chi^2(1) = 0.02, p = .96 \). The mean (± SD) for time (in days) to 3 weeks free from cocaine use (24.6 ± 15.1 vs. 57.8 ± 7.7, \( p < .05 \)) was significantly reduced for disulfiram vs. placebo.

The mean (± SD) number and mean (± SD) proportion respectively of cocaine-negative urines during the entire trial (see Figure 1 for individual subjects results between
groups) and during each 3-week interval (out of a maximum of 9) of the 12-week trial (Figure 2) was higher in the disulfiram (3.66 ± 3.78; 40.7% ± 42.0%) versus the placebo (2.14 ± 3.15; 23.8% ± 35.0%) group, but this difference was not statistically significant \( F(1,18) = 1.30, p = .27 \). The number of cocaine-negative urine samples in successive 3-week intervals increased significantly over time in both groups \( F(3,18) = 13.36, p < .01 \), but the interaction between medication \( \times \) time was not significant \( F(3,18) = 1.75, p = .19 \); Figure 2). In post hoc analyses of the pattern of results, using the mixed models procedure with time as a continuous variable, there were consistent and statistically significant effects of medication condition \( F(2,18) = 11.53, p < .05 \), time \( F(1,18) = 13.36, p < .05 \), and a significant quadratic interaction [i.e., a curvilinear trend over time; \( F(1,18) = 5.15, p < .05 \)]. As seen in Figure 2, subjects in the disulfiram group obtained consistently higher numbers of cocaine-free tests, subjects in both groups increased the rates of cocaine-free tests over time, and the increase in the number of cocaine-free tests was more rapid in the disulfiram group than in the placebo group.

**Effects on Opiate Use**

There were no significant differences in the total number of weeks of opiate abstinence in disulfiram versus placebo groups (8.0 ± 2.8 vs. 6.0 ± 3.7, \( p = .37 \)). The proportion of subjects attaining 3 [63.6% vs. 88.9%; \( \chi^2(1) = 1.68, p = .19 \)] consecutive weeks of opioid-free urines were comparable between disulfiram and placebo groups.

As illustrated in Figure 3, there was a trend for the numbers of opiate-negative urine samples to increase over time \( F(1,18) = 3.76, p = .07 \). The mean (± SD) number (and mean [± SD] proportion) of opiate-negative urines during each 3-week interval during the 12-week trial was 5.00 ± 1.03 (55.6% ± 11.4%) in the disulfiram versus 4.94 ± 0.93 (54.9% ± 10.3%) in the placebo group. Using the mixed models procedure, there were no significant effects of medication \( F(1,18) = 0.20, p = .97 \), time \( F(3,18) = 2.49, p = .09 \), or medication \( \times \) time interaction \( F(3,18) = 0.96, p = .43 \). As seen in Figure 2, there were no consistent differences favoring either group.
Self-Reported Cocaine and Heroin Use during the Trial

The results of weekly self-reported cocaine and heroin use by subjects at baseline and during the trial is reported in Figure 4. Disulfiram appeared to reduce cocaine use (Figure 4A) but not heroin use (Figure 4B) (in bags/day) compared with placebo.

Discussion

In this small sample study of buprenorphine-maintained patients with concurrent opioid dependence and cocaine use, disulfiram was well tolerated, demonstrated safety compared with placebo, and was associated with a significant increase in the total number of weeks abstinent and a reduced number of days to achieving 3 weeks abstinence from cocaine compared with placebo. Furthermore, there was also a trend for the rates of cocaine-negative urine tests to be higher in the disulfiram-treated group. These findings are consistent with three clinical trials supporting the efficacy of disulfiram for treating cocaine abuse (Carroll et al 1993, 1998; I.L. Petrakis et al, unpublished data, 1999). At trial endpoint, subjects in both disulfiram and placebo groups had similar proportions of cocaine-negative urines, but the acquisition of cocaine-free urines was faster in the disulfiram group (Figure 1). The convergence of rates of cocaine-free urines at trial endpoint may reflect administrative pressures on subjects to reduce their illicit cocaine use by the time of trial completion because failure to do so typically leads to difficulties with readmission to our clinical programs. Nevertheless, during a substantial period of the trial, cocaine-negative urines are increased in the disulfiram versus placebo groups, and this appears to represent a specific pharmacologic effect of disulfiram on cocaine dependence.

The effect size of the difference between the two medication groups was calculated at 0.44 (Cohen’s d), based on the difference in the number of cocaine-free urines in disulfiram versus placebo groups, which is consistent with a moderate effect size. Accordingly, to detect significant overall differences between the study groups, a sample size of 83 subjects in each group would have been necessary, given the moderate effect size calculated from these results and assuming power (1-β) of 0.80 and α error = 0.05. The overall reductions in both cocaine and illicit opioid use over the 12-week trial are consistent with previous studies showing time-dependent reductions in drug use during maintenance treatment with comparable buprenorphine doses (Schottenfeld et al 1993, 1997). Our previous studies have indicated that buprenor-
Phen was no more effective than methadone in reducing concurrent cocaine use (Schottenfeld et al 1997), consistent with findings from other investigators (Strain et al 1994a).

The mechanism of disulfiram effects in reducing cocaine abuse in this study is probably independent of effects of alcohol use because there was little alcohol use at baseline or during the study in either group. Disulfiram’s mechanism of action may relate to 1) inhibition of plasma esterases, which metabolize cocaine (Honjo and Netter 1969), or 2) inhibition of dopamine-β-hydroxylase (DBH; Caroldi and DeParis 1995; Goldstein et al 1964), with resultant aversive responses to cocaine abuse (i.e., anxiety, dysphoria, and paranoia) produced by excessive dopamine levels, leading to a compensatory decrease in cocaine use. Genotypes of the DBH locus that predict high and low enzyme activity recently have been identified (Cubells et al 1998), and it is possible that there also may be genetic differences in treatment responses to disulfiram. Accordingly, subjects with lower DBH activity would be predicted to have enhanced responses to disulfiram for reducing cocaine use, and this hypothesis will be tested in future studies.

Despite the small sample size of this study, the results of the current study suggest the potential efficacy of disulfiram treatment for cocaine use during buprenorphine-maintenance treatment. Given the evidence from human laboratory studies (Hameedi et al 1995; McCance-Katz et al 1998a, 1998c) and the effectiveness of disulfiram for cocaine dependence in clinical trials (Carroll et al 1993, 1998; I.L. Petrakis et al, unpublished data, 1999), larger controlled studies of disulfiram for treatment of cocaine dependence are planned in buprenorphine-maintained subjects, and the combination of buprenorphine and disulfiram may be an effective combination for the problem of combined cocaine and opioid dependence.

This study was supported in part by Grants Nos. R01-DA-09413 (RSS), K12-DA-00167 (TPG), and P50-DA-04060 and P50-DA-09250 (TRK) from the National Institute on Drug Abuse and by a National Alliance for Research on Schizophrenia and Depression Young Investigator Award (TPG).

References


Schottenfeld RS, Pakes J, Ziedonis D, Kosten TR (1993): Buprenorphine: Dose-related effects on cocaine and opioid

