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Randomized clinical trial of disulfiram for cocaine dependence or abuse during buprenorphine treatment

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ABSTRACT

Background: Disulfiram may be efficacious for treating cocaine dependence or abuse, possibly through inhibiting dopamine β-hydroxylase (DβH). Consequently, this randomized, placebo-controlled clinical trial of disulfiram during buprenorphine maintenance treatment evaluated the study hypothesis that disulfiram is superior to placebo and explored whether disulfiram response is greatest for participants with a single nucleotide polymorphism coding for genetically low DβH (T-allele carriers).
Methods: We randomized 177 buprenorphine-treated opioid dependent participants with cocaine dependence or abuse to 12 weeks of double-blind treatment with disulfiram 250 mg daily ($n = 91$) or placebo ($n = 86$). Of 155 participants genotyped, 84 were CC-homozygous, and 71 CT or TT genotypes. Primary outcomes included days per week cocaine use, number of cocaine-negative urine tests, and maximum consecutive weeks of cocaine abstinence. We analyzed an intention-to-treat comparison between disulfiram and placebo. We also explored potential pharmacogenetic interactions and examined treatment responses of four participant groups based on medication (disulfiram or placebo) by genotype (CC-homozygous or T-allele carrier) classification.
Results: Disulfiram participants reported significantly less frequent cocaine use; the differences in cocaine-negative urine tests or consecutive weeks abstinence were not significant. Frequency of cocaine use was lowest in disulfiram-treated T-allele carriers; differences in cocaine-negative urine tests or consecutive weeks abstinence were not significant among the four medication-genotype groups.
Conclusions: The findings provide limited support for the efficacy of disulfiram for reducing cocaine use and suggest that its mechanism of action may involve inhibition of DβH. Further studies of its efficacy, mechanism of action, and pharmacogenetics of response are warranted.
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1. Introduction

Cocaine abuse and dependence are significant public health problems, affecting an estimated 1.6 million Americans and 30–80% of opioid agonist maintained patients, including an increasing number treated in office-based settings with buprenorphine maintenance treatment (BMT; Arfken et al., 2010; Hubbard et al., 1997; Leri et al., 2003; Substance Abuse and Mental Health Services Administration, 2008). Cocaine use disorders are associated with a wide range of adverse health, social, family and legal consequences and, among opioid dependent patients, undermine the effectiveness of opioid agonist maintenance treatment and increase risk for HIV infection (Bux et al., 1995; Chaisson et al., 1989; Haddad et al., 2013; Hartel et al., 1995; Hunt et al., 1986; Joe and Simpson, 1995; Kolar et al., 1990; Kosten et al., 1987, 1988; Wasserman et al., 1998). Currently, there are no established pharmacological treatments for cocaine use disorders or adjuncitve pharmacological treatments for opioid agonist maintained patients with co-occurring opioid dependence and cocaine abuse or dependence.

Convergent epidemiologic, laboratory and clinical trial findings support the potential efficacy of disulfiram for treating cocaine use disorders, including some clinical trials with methadone maintained individuals and one small pilot study conducting during BMT (Baker et al., 2007; Bourdélat-Parks et al., 2005; Carroll et al., 2004, 1998; George et al., 2000; Hameedi et al., 1995; Kalayasiri et al., 2007; Major et al., 1979; McCance-Katz et al., 1998a,b; Oliveto et al., 2011; Pani et al., 2010; Petrakis et al., 2000; Schank et al.,

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2006; Schroeder et al., 2010). While initially evaluated because of the high co-morbidity of alcohol abuse among cocaine dependent individuals (Carroll et al., 1993, 1998), the effects of disulfiram on cocaine use are independent of reductions in alcohol use, suggesting that other mechanisms are involved (Carroll et al., 2004). One intriguing possibility is that disulfiram effects on cocaine use may involve inhibition of dopamine β- hydroxylase (DβH), which occurs at the same clinically relevant disulfiram concentrations as inhibition of aldehyde dehydrogenase (Mays et al., 1998). DβH catalyzes dopamine (DA) conversion to norepinephrine (NE); inhibition of DβH elevates the DA/NE ratio in mesolimbocortical dopaminergic and noradrenergic pathways (Goldstein et al., 1964; Karamanakos et al., 2001; Stanley et al., 1997).

Identification of a relatively common single nucleotide polymorphism (SNP) in the promoter region of the gene locus encoding DβH (locus name: DBH) (−1021C→T) has provided an opportunity to explore whether disulfiram's effects on cocaine result from inhibition of DβH and whether response to disulfiram is affected by DBH genotype. The CC homozygotes at the SNP have approximately 6–10 fold higher plasma DβH activity compared to TT homozygotes; CT heterozygous individuals have activity level that is midway between CC and TT homozygote individuals (Zabetian et al., 2001). Neuropsychiatric effects of disulfiram are more pronounced among individuals with lower baseline DβH activity or the SNP coding for lower DβH activity (Bourdélat-Parks et al., 2005; Ewing et al., 1977, 1978; Major et al., 1979). If disulfiram effects on cocaine use are mediated by its effects on DβH, T-allele carriers might have the best response to disulfiram, since disulfiram may reduce DβH activity to a sufficiently low level in these individuals to obtain clinically significant effects.

Because preliminary evidence for the efficacy of disulfiram for reducing cocaine use during buprenorphine maintenance treatment comes from only one small pilot study, we conducted a randomized, double-blind, placebo-controlled clinical trial of disulfiram with a substantially larger sample size of individuals with co-occurring opioid dependence and cocaine abuse or dependence receiving buprenorphine maintenance treatment. We hypothesized that disulfiram is superior to placebo. The study also explored whether the response to disulfiram 250 mg daily differed between T-allele carriers and CC-homozygous individuals.

2. Materials and methods

The study design was a single site, randomized, double-blind clinical trial comparing 12 weeks of treatment with disulfiram (250 mg daily) or placebo. Participants were inducted and stabilized on buprenorphine over a 2-week period, before being randomized to disulfiram or placebo. Participant recruitment, treatment and assessments were conducted between October, 2000 and February, 2004 in an ambulatory drug abuse treatment research clinic in New Haven, CT. The study was approved by the Human Investigation Committee, Yale University School of Medicine. All participants gave written informed consent. The study was registered with Clinical trials.gov (NCT00913484).

2.1. Participants, selection criteria, and recruitment

Participants age 18–45 were eligible if they met criteria for current opioid dependence and cocaine abuse or dependence, as assessed by the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 2000; Spitzer et al., 1992). Participants were excluded if currently physiologically dependent on alcohol; using metronidazole or clotrimazole; experiencing significant cardiovascular, renal, hepatic or neurologic illness or had liver enzymes (alkaline phosphatase or alanine transaminase) greater than three times the upper limit of normal; dangerous to themselves or others; psychotic; or considered at risk for suicide or violence. Because of the potential cardiac complications in disulfiram-treated patients who use cocaine and alcohol, participants were also excluded if they had any of the following cardiac risk factors: first degree family member with a history of myocardial infarction prior to age 60, a past history of myocardial infarction, hypertension (systolic blood pressure > 140 or diastolic blood pressure > 90), or EKG evidence of myocardial infarction or ischemia. Women were included if they agreed to adequate contraception and to monthly pregnancy testing. Fig. 1 (CONSORT Diagram) shows participant flow through the phases of the study; a total of 177 participants completed buprenorphine induction and stabilization and were randomized to treatment.

2.2. Randomization and blinding

A research pharmacist who had no direct contact with participants used a computer-generated simple randomization list to allocate participants to active or placebo disulfiram. The research pharmacist prepared active disulfiram 250 mg and matching placebo capsules by filling identical blue 00 capsules with Avicel (microcrystalline cellulose, NF) only or Avicel mixed with pulverized disulfiram 250 mg tablets, purchased from a local pharmacy, and dispensed the medications in individual medication bottles prepared for each participant. The medication labeling was identical for bottles containing active or placebo disulfiram. With the exception of the research pharmacist, none of the other research personnel or care providers had access to the randomization list, which was kept in the locked pharmacy office. All participants were advised that they might receive disulfiram, educated about alcohol–disulfiram interactions, and warned about using alcohol or alcohol-containing preparations.

2.3. Treatment procedures

Buprenorphine and active or placebo disulfiram were ingested by participants under direct observation at the clinic six days per week (Monday–Saturday); participants were provided a single-day's dosage of buprenorphine and active or placebo disulfiram for take-home medications for Sundays or holidays on the preceding day. All participants received one 8 mg SL buprenrophine mono tablet daily for the first three days, increased to two 8 mg SL tablets on days 4–7, and were then maintained on three 8 mg SL buprenorphine tablets (24 mg SL daily) through week 14. At the beginning of week 15, participants who did not want a referral for continuing buprenorphine or methadone maintenance or other available treatment began buprenorphine tapering at a rate of 4 mg every two days until the medication was discontinued and subjects were discharged. Participants received active or placebo disulfiram capsules daily beginning on the day of randomization and continuing through week 14. All participants also attended weekly manual-guided group drug counseling throughout the study period (Mercer and Woody, 1999).

2.4. Assessments

Substance use was assessed by weekly self-report, obtained by a trained research assistant, using a time-line follow-back methodology (Sobell et al., 1988, 1986) to assess days per week using illicit opioids, cocaine, other drugs or alcohol, and by urine toxicology testing. Urine samples were obtained three times per week (at times of medication dispensing), temperature checked to detect tampering, and analyzed using the Abbott Tdx system with cut off points >200 ng/ml for opioids and >300 ng/ml for cocaine metabolite and benzoylecognine. Breath alcohol was assessed weekly. Adverse medication effects and medical symptoms were assessed weekly using a 33-item symptom checklist developed for the study; the checklist included common medical symptoms (e.g., sore throat), symptoms associated with opioid agonist medications (e.g., sweating) or withdrawal (e.g., diarrhea), and known adverse effects of disulfiram (e.g., headache, lethargy, numbness or tingling of the extremities, or visual disturbances).

2.5. Genotyping

DNA (available from 155 participants) was extracted from whole blood using the method of Larhiri and Nurnberg (Lahiri and Nurnberger, 1991) or using a PAXgene blood DNA extraction kit (PreAnalytix Inc.). Genotype was determined by PCR amplification and restriction digestion with MwoI followed by size determination of digestion products by agarose gel electrophoresis as previously described (Zabetian et al., 2001). All genotypes were scored by two raters who were blind to treatment status.

2.6. Sample size

We planned to enroll 90 subjects in each treatment condition in order to have sufficient power (0.80) to detect low- to moderate-sized effects, as found in prior studies (Carroll et al., 1998; George et al., 2000; Petrakis et al., 2000), assuming a type I error of 0.05 (Cohen, 1988). Because of the population distribution of the DBH genotype, we anticipated that the sample size would be sufficient to explore but have low power to test definitively potential differences associated with genotype in response to disulfiram.

2.7. Statistical analysis

The primary outcomes, defined a priori, were frequency (the number of days per week) of cocaine use and the number of cocaine-negative urine tests in successive two-week intervals, and the maximum consecutive weeks of abstinence from cocaine, documented by urine toxicology testing. Secondary outcome measures included frequency (the number of days per week) of opioid use and the number of opioid-negative urine tests in successive two-week intervals, and the maximum

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