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A Double Blind, Placebo-Controlled Trial that Combines Disulfiram and Naltrexone for Treating Co-Occurring Cocaine and Alcohol Dependence

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Abstract

BACKGROUND—This is a double blind, placebo-controlled trial that evaluated the efficacy of disulfiram, naltrexone and their combination in patients with co-occurring cocaine and alcohol dependence.

METHODS—208 patients were randomized to disulfiram (250mg/day), naltrexone (100mg/day), the combination, or placebo for 11 weeks. Outcomes were in-trial abstinence from cocaine and/or alcohol.

RESULTS—Few safety concerns were reported, although medication adherence was low in a number of patients for both medications, alone or in combination. In the primary analyses (GEE modeling), abstinence from cocaine as measured by cocaine-negative urines and days of self-reported abstinence from cocaine or alcohol did not differ between placebo and any of the medication groups. However, patients taking disulfiram (alone or in combination) were most likely to achieve combined abstinence from cocaine and alcohol. Secondary analyses revealed that patients taking the disulfiram-naltrexone combination were most likely to achieve 3 consecutive weeks of abstinence from cocaine and alcohol.

CONCLUSION—There was an association between disulfiram treatment and abstinence from cocaine and alcohol. More patients taking the disulfiram-naltrexone combination achieved 3 consecutive weeks of abstinence in treatment than placebo-treated patients.

Keywords

combining medications; cocaine; alcohol; disulfiram; naltrexone; clinical trial; medication nonadherence

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1. Introduction

Patients who have co-occurring cocaine and alcohol dependence comprise a large proportion of the cocaine-addicted population (Gossop, Manning, & Ridge, 2006b), and suffer more adverse addiction-related consequences, have greater psychosocial problems, are inherently inconsistent at showing up for treatment visits, and have higher rates of recidivism than patients dependent only on cocaine or on alcohol (Brady, Sonne, Randall, Adinoff et al., 1995; Carroll, Rounsaville, & Bryant, 1993; Flannery, Morgenstern, McKay, Wechsberg et al., 2004; Heil, Badger, & Higgins, 2001; Mengis, Maude-Griffin, Delucchi, & Hall, 2002). Also, concurrent use of cocaine and alcohol produces cocaethylene (Gossop, Manning, & Ridge, 2006a; Harris, Everhart, Mendelson, & Jones, 2003), an active transesterified metabolite associated with more lethality than cocaine alone (Pennings, Leccese, & Wolff, 2002) and toxicity (Harris et al., 2003; Hearn, Rose, Wagner, Ciarleglio et al., 1991; Pennings, Leccese, & Wolff, 2002).

Thus, this treatment-refractory population may require a pharmacological approach, added to traditional counseling, which effectively targets the potentially different neurobiology of the combination of cocaine and alcohol dependencies. Historically, there have been many attempts to test medications for the treatment of either cocaine or alcohol dependence alone. Presently, the Food and Drug Administration (FDA) has approved medications for treating alcohol dependence, but none have been approved for treating cocaine dependence (Vocci, Acri, & Elkashef, 2005). Notably, there have been few attempts to evaluate medications in clinical trials for treating the *co-occurrence* of cocaine and alcohol dependence.

One reasonable treatment approach of co-occurring cocaine and alcohol dependence, which has been tried but has thus far failed, is giving an FDA-approved alcohol-reducing medication (added to counseling) that will decrease alcohol drinking, and, in turn, indirectly promote cocaine abstinence. It is well known that the use of one addictive substance often leads to the use of another addictive one. However, two double-blind, placebo-controlled studies of 50mg/day of naltrexone, an FDA-approved medication for treating alcohol dependence, did not reduce alcohol or cocaine use in cocaine-alcohol dependent outpatients, compared to placebo treatment (Hersh, Van Kirk, & Kranzler, 1998; Schmitz, Stotts, Sayre, DeLaune et al., 2004). Nonetheless, some preliminary data have suggested that a higher dose of naltrexone (150mg/day) may be useful in reducing cocaine and alcohol use in cocaine-alcohol dependent patients (Oslin, Pettinati, Volpicelli, Wolf et al., 1999), but more so in men than in women (Pettinati, Kampman, Lynch, Suh et al., 2007).

Another rationale, and a novel approach, to treating the co-occurrence of cocaine and alcohol dependence is to combine two medications, one of which will decrease cocaine use and the other of which will decrease alcohol use. In recent years, there have been a series of double blind, placebo-controlled clinical trials of combination medications for treating primarily alcohol *or* drug dependence in patients without concomitant psychiatric disorders (see, e.g., Ait-Daoud, Johnson, Prihoda, & Hargita, 2001; Anton, O'Malley, Ciraulo, Cisler et al., 2006; Kampman, Dackis, Lynch, Pettinati et al., 2006; Kiefer & Wiedemann, 2004), including adding disulfiram to naltrexone (Petrakis, Poling, Levinson, Nich et al., 2005), or to acamprosate – another FDA-approved medication for treating alcohol dependence (Besson, Aeby, Kasas, Lehert et al., 1998). The treatment strategy tested in the present study was combining two medications (added to twice weekly sessions of cognitive behavioral therapy) to treat patients presenting with dual cocaine and alcohol dependence. One medication was selected to reduce cocaine use (disulfiram – see below the rationale for doing so), and the second medication was selected to reduce alcohol use -- plus its FDA approval in 1994 for treating alcohol dependence (naltrexone).

Selecting a medication to reduce cocaine use was a more difficult task than choosing one to reduce alcohol use because there are no FDA-approved medications for treating cocaine dependence. However, recent controlled trials of several medications, namely, disulfiram, topiramate, modafinil, and others, suggested that some medications added to counseling may provide an advantage over placebo treatment for cocaine dependence (See respectively: Carroll, Fenton, Ball, Nich et al., 2004; Dackis, Kampman, Lynch, Pettinati et al., 2005; Kampman, Pettinati, Lynch, Dackis et al., 2004). To date, however, disulfiram has had more published articles than any other medication in support for its use in the treatment of cocaine dependence (see Carroll et al., 2004; Carroll, Nich, Ball, McCance et al., 2000; Carroll, Nich, Ball, McCance et al., 1998; Gossop & Carroll, 2006; Grassi, Cioceb, Dei Giudicib, Antonillia et al., 2007), particularly in men (Nich, McCance-Katzb, Petrakis, Cubellsa et al., 2004; Petrakis, Carroll, Nich, Gordon et al., 2000).

Disulfiram originally was approved in 1951 for promoting abstinence from alcohol, but it has been used only modestly since its approval to treat alcohol dependence (Suh, Pettinati, Kampman, & O'Brien, 2006). While disulfiram has an appeal in the context of the present study because of its known action in deterring alcohol use, it was selected for the present study primarily as a treatment for reducing cocaine use. Disulfiram's mechanism of action for reducing cocaine use is believed to be different from its mechanism for promoting abstinence from alcohol. Essentially, disulfiram's effect on decreasing alcohol use is that it inhibits the enzyme, aldehyde dehydrogenase, which is necessary for fully metabolizing alcohol, leaving an increased concentration of acetaldehyde, which causes unpleasant sensations (Suh et al., 2006). Potentially, disulfiram's mechanism of action for reducing cocaine use is that it inhibits dopamine beta-hydroxylase, an enzyme that normally converts dopamine to noradrenaline (Kosten, George, & Kosten, 2002; McCance-Katz, Kosten, & Jatlow, 1998a), and hence, increases the concentration of dopamine more than what is observed when cocaine is taken alone. Furthermore, disulfiram, when coupled with cocaine use, impedes cocaine metabolism by inhibiting plasma and microsomal carboxylesterases and plasma cholinesterase (McCance-Katz, Kosten, & Jatlow, 1998b). In some studies, the combination of disulfiram and cocaine have resulted in a higher than expected plasma-cocaine concentration, and a longer than expected cocaine-elimination half-life (Hameedi, Rosen, McCance-Katz, McMahon et al., 1995; McCance-Katz, Kosten, & Jatlow, 1998a). These effects of the disulfiram-cocaine interaction might result in an exacerbation of negative effects of cocaine, such as anxiety, paranoia, and cardiovascular response (McCance-Katz, Kosten, & Jatlow, 1998a, 1998b).

In a controlled clinical trial for treating cocaine dependence with disulfiram, Carroll and colleagues (Carroll et al., 2004) found that disulfiram significantly reduced cocaine use in patients with cocaine dependence. Of interest, however, disulfiram did not seem to provide the same advantage over placebo in reducing cocaine use in cocaine-dependent patients who regularly drank a substantial amount of alcohol. The results of this Carroll study, while encouraging for treating cocaine dependence, did not address how to treat the highly prevalent cocaine-dependent group with alcohol dependence.

With respect to the treatment in the present study for the patient's alcohol dependence, the daily, oral version of naltrexone was selected to be given in combination with disulfiram. Naltrexone is an opioid receptor antagonist that has been found in a number of trials to reduce heavy drinking in alcoholics. (See review by Pettinati, O'Brien, Rabinowitz, Wortman et al., 2006). A preponderance of evidence from pre-clinical and clinical studies suggest that the therapeutic effect of naltrexone in alcoholism stems from its ability to attenuate alcohol-induced euphoria (O'Malley, Jaffe, Chang, Schottenfeld et al., 1992; Volpicelli, O'Brien, Alterman, & Hayashida, 1990) by inhibiting the release of beta-endorphin (Volpicelli, Watson, King, Sherman et al., 1995). Notably, naltrexone may also have direct therapeutic effects on cocaine use, independent of its effects on alcohol consumption, although to date, clinical trials

have not proven its effectiveness in reducing cocaine use at the 50mg/day dose (Hersh, Van Kirk, & Kranzler, 1998; Schmitz et al., 2004). Furthermore, studies have failed to demonstrate that naltrexone has an effect on cocaine euphoria in humans (Sofuoglu, Singha, Kosten, McCance-Katz et al., 2003; Walsh, Sullivan, Preston, Garner et al., 1996). Nonetheless, pre-clinical studies have demonstrated that cocaine releases beta-endorphin (Beakeland, Lundwall, Kissin, & Shanahan, 1971), and that naltrexone and other opioid antagonists reduce rates of cocaine self-administration in animals (Paille, Guelfi, Perkins, Royer et al., 1995; Pelc, Verbanck, Le Bon, Gavrilovic et al., 1997; Sass, Soyka, Mann, & Zieglgansberger, 1996). Chronic exposure to both alcohol and cocaine result in dynorphin upregulation (Dackis & O'Brien, 2003), which may contribute to dopamine hypoactivity in both conditions (De Witte, Littleton, Parot, & Koob, 2005; Fuller & Gordis, 2004; Suh et al., 2006). This neuroadaptation may be reversed by naltrexone's antagonism of kappa-opioid receptors, by which dynorphin inhibits dopamine activity. In summary, the present study evaluated in a controlled clinical trial the effect of treating cocaine-alcohol dependence with the combination of disulfiram and naltrexone added to twice weekly sessions of cognitive behavioral therapy.

2. Methods

2.1 Patients

The patients were 208 men and women between the ages of 18 and 65 who had a DSM-IV diagnosis of both cocaine and alcohol dependence. Patients with dependence on substances other than cocaine and alcohol, except nicotine addiction, were excluded. Patients needed to have used in the month before treatment a minimum of \$100 worth of cocaine and drank an average of 12 standard alcoholic drinks a week. Psychiatric exclusion criteria included active psychosis, mania, dementia, or the need for treatment with psychiatric medications. Medical exclusion criteria included pregnancy, breastfeeding, active hepatitis, and significant hepatocellular injury. If clinically indicated, patients had to successfully complete outpatient alcohol detoxification, i.e., achieve 3 days of abstinence from alcohol, before starting study medication. The study was approved by the University of Pennsylvania's Institutional Review Board, and all patients who were included in the study had signed informed consents prior to screening.

2.2 Procedures

Patients were treatment-seeking cocaine users recruited through community advertisements and professional referrals. Those patients who appeared to meet criteria in a telephone interview were invited to the Treatment Research Center (TRC) for a screening evaluation. Eligible patients entered a 13-week trial that included a 2-week pre-treatment/screening phase and an 11-week randomized medication phase.

During the 4 years of recruitment for this trial, 434 cocaine-alcohol dependent patients were invited to screen for this study. Of these, 342 (79%) signed consent and agreed to begin screening. There were 97 consented patients (28%) who never returned after signing consent for the first screening session. Of those remaining (245 consented patients), 37 (15%) were excluded during the screening period based on the specific eligibility criteria: 10 were excluded for medical reasons (e.g. taking disallowed medications, significantly elevated blood pressure or higher than 3.5 times normal liver function tests), 18 were excluded for not meeting cocaine and/or alcohol dependence diagnostic criteria, and 9 were excluded for disallowed psychiatric diagnoses (e.g. bipolar disorder or psychosis), or for concomitant opiate abuse or dependence. The remaining 208 patients entered the randomized medication phase of the trial.

2.2.1 Design—Randomized patients were assigned to 250mg/day of disulfiram (DISULF; n=53), 100mg/day of naltrexone (NTX; n = 52), the combination of disulfiram and naltrexone

(DISULF+NTX; n=49), or to double placebo (PLAC; n=54). Patients received their first dose of randomized medications in the 3rd week of the study, following 2 weeks of screening. Patients were assigned for the first 2 days of the 11-week treatment phase to receive either 50 mg/day of naltrexone or placebo in the morning; and, then on the 3rd day of the treatment week, 100 mg/day of naltrexone or placebo in the morning. Patients were also assigned to receive 250 mg of disulfiram, starting in the first treatment week on the 5th day. In the 4th week of treatment, patients who tolerated the medications would be prescribed the maximum doses of 250 mg/day of disulfiram (or matching placebo) and 100 mg/day of naltrexone (or matching placebo). Patients were continued at these daily dosages of each medication or placebo through to end of 11 treatment weeks, or Week 13 since signing consent. In the last 2 weeks of the trial, both medications were tapered, and pharmacotherapy was completed by the end of Week 11 (Week 13 since signing consent). All patients received the same number of pills (active medication and/or placebo pills), regardless of group or week of treatment. Study medication was dispensed in clearly labeled blister cards at a once-a-week medical evaluation visit.

The disulfiram target dose of 250mg/day is the one that is recommended in its label. Naltrexone's recommended daily dose is 50mg/day, but for this study we chose a target dose of 100mg/day because this higher daily dose will last longer in patients—better ensuring the medication's action in patients if they tend to be medication nonadherent; also, our prior studies suggested that doses higher than 50mg/day may result in better outcomes in patients with the combination of cocaine and alcohol dependence (Oslin et al., 1999; HM Pettinati et al., 2007). In addition to medication or placebo pills, participants received twice-weekly individual cognitive-behavioral therapy (CBT) utilizing the CBT therapy manual and supporting materials that were developed for the National Institute on Alcohol Abuse and Alcoholism Project MATCH (Kadden, Litt, Cooney, & Busher, 1992). The basic format was accepted, although specific procedures were adapted for treatment of both cocaine and alcohol dependence by our group. CBT was provided by Master's-level therapists with training in delivering CBT. Therapists received weekly supervision by a doctoral-level therapist with over 15 years experience in treating cocaine dependence. In addition, individual therapy sessions were audiotaped and a random sample of tapes from each therapist was listened to by the therapists' supervisor to address any CBT drift.

2.2.2 Measures—Psychiatric diagnoses were obtained by master's level clinicians using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1995). Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Pre-treatment laboratory testing included a chemistry screen, bilirubin, complete blood count, urinalysis, urine pregnancy testing and a 12 lead EKG. Breathalyzer readings were collected at each visit throughout the study to ensure that research data were not collected from patients with a positive breathalyzer.

The primary in-trial outcome measure of daily alcohol use was the patient's self-report collected via the Timeline Followback method (TLFB) (Sobell & Sobell, 1992). The TLFB is a 15–30 minute, semi-structured interview that uses the recall of critical life events and a personalized calendar to prompt recall of alcohol drinking frequency (days) and quantity (number of drinks per day) during the inquiry period (up to 90 days). The recalled information on alcohol use is recorded for each day on the personalized calendar. The TLFB method has been adapted by our laboratory, including the personalized calendar, to also collect information from the patient about daily use of cocaine or other abused drugs. Thus, a similar procedure was used in this study to recall daily use of cocaine, plus dollars worth of cocaine used per day. The TLFB was administered by a research technician, who had received training in administering the TLFB. The TLFB was given in screening to record use of alcohol and cocaine in the 3 months immediately preceding treatment entry. Use information was also collected

for each day in treatment, updated at each research visit to create a continuous daily record of cocaine and alcohol use or abstinence in the 3 months prior to treatment and all during the treatment period. A 30-day alcohol and drug use self-report was also collected at a single follow-up visit that was scheduled for 6 months after the end of the trial to assess the patient's status following treatment. Urine drug screen (UDS) tests were obtained 3 times weekly during the 2 screening weeks and the 11 weeks while in treatment.

Urine collection was not observed but urine specimen temperature was monitored. A urine specimen was also collected at a single follow-up visit that was scheduled for 6 months after the end of the trial to assess the patient's status following treatment. Urine specimens with lower than 90 degrees, or greater than 100 degrees, Fahrenheit were not accepted. (Fewer than 1% urine specimens were outside this range). Specimens were analyzed for benzoylecgonine (BE) by fluorescent polarization assay. Specimens were analyzed qualitatively ≥ 300 ng/ml of BE was considered drug-positive, indicating recent cocaine use.

Cocaine abstinence was determined for each week by 3 weekly cocaine negative urine samples. If any samples during a given study week were positive for BE or missing, the week was coded as non-abstinent. For alcohol, abstinence from alcohol for a given study week was determined by self-report derived from the TLFB method. Any alcohol use during a given study week resulted in that week being coded as a non-abstinent week.

In addition to examining cocaine and alcohol outcomes separately, we also chose to evaluate outcomes that reflected the combination of both alcohol and cocaine use. One of these outcomes involved creating an abstinence index that combined the separately constructed cocaine and alcohol use/non-use, and then repeating outcome analyses with this index as the primary outcome measure. A secondary analysis with this combined abstinence index compared the number of patients who were able to achieve 3 consecutive weeks of continuous abstinence from both alcohol and cocaine while in treatment. The latter measure has been used in a number of studies because it is thought to represent a primary goal of short-term treatment, which is to get patients to achieve a stable period of continuous abstinence. Abstinence from cocaine for approximately 3–4 consecutive weeks has been shown to be predictive of long-term cocaine abstinence (Carroll, Rounsaville, Gordon, Nich et al., 1994; Kosten, Morgan, Falcione, & Schottenfeld, 1992). We, therefore, evaluated the proportion of patients in each of the four treatment groups (DISULF, NTX, DISULF + NTX, PLAC) that were able to attain 3 consecutive weeks of abstinence from both cocaine and alcohol while in treatment.

Other measures included the Hamilton Rating Scales of Depression (Hamilton, 1960) and of Anxiety (Hamilton, 1959). They were administered at pre-treatment and at the end of treatment to measure the number of mood and anxiety symptoms. Adverse events were measured at each medical evaluation visit using the Systematic Assessment for Treatment Emergent Effects (Rabkin, Markowitz, Ocepek-Welikson, & Wager, 1992).

2.3 Statistical Analysis

The main analyses in this paper were by intention-to-treat. The two primary outcome measures were: 1) abstinence from cocaine; and 2) abstinence from alcohol. In addition, a combination measure of abstinence from both cocaine use (based on UDS) and alcohol use (based on TLFB) was also created for both primary and secondary analyses. Secondary outcomes included abstinence from heavy drinking (defined as drinking 5 or more standard drinks in one day for men and 4 or more for women). The patients were initially compared on a variety of demographic and pre-treatment characteristics, using logistic regression for categorical characteristics, and linear regression (ANOVA) for continuous characteristics, to assess how well the randomization had balanced patient characteristics across the four treatment groups.

Primary and secondary outcomes were analyzed using generalized estimating equations (GEE) models. The models included terms for use status during the pre-randomization phase, medication group (disulfiram present/absent; naltrexone present/absent), together with linear and quadratic time effects, and some group by time interactions. In fitting these models to the data, terms were included if they were significant at the 5% level, and lower order effects contained in a significant interaction effect were also included. Empirical (sandwich) standard errors were used to assess significance. Thus, the primary outcome analyses did not include additional covariates, but characteristics that showed significant imbalance across the groups were considered for inclusion as covariates in supplementary analyses.

With respect to the repeated binary outcomes of abstinence from cocaine, alcohol, and both, missing weeks were imputed as positive/use, which is a standard practice in clinical trials for which cocaine abstinence is a primary outcome (Shoptaw, Kintaudi, Charuvastra, & Ling, 2002). The protocol called for three urines to be collected per patient each week, yielding a possible 39 urines per patient, 6 during the 2-week pre-randomization phase, and 33 during the 11-week treatment phase. GEE approaches work best when the data are in the form of a smaller number of repeated measurements for each of many patients (Sharples & Breslow, 1992), so we chose to reduce the number of time points per patient by coding each of the 11 weeks as a use or non-use week, rather than including each urine per week in the model. Using weeks as the time units of analysis, rather than visits, also reduces the risk of overestimating drug use due to BE carryover. The urines submitted during the pre-randomization phase were used to determine use/non-use status prior to randomization, and this status was included as a covariate in the GEE model. To assess the sensitivity of the results to the imputation of missing urines/weeks as positive/use, we re-ran the analyses with missing observations ignored, and also performed pattern-mixture analyses. Our pattern-mixture analyses compared subjects that provided complete data versus data from those that prematurely left the study or provided only partial data (Hedeker & Gibbons, 1997; Park & Lee, 1999). Pattern-mixture models augment the GEE models described above by including a variable describing the pattern of missing data in the study as a main effect and as an interaction effect with the group and time variables. This allows us to model differences in longitudinal behavior across missing data patterns, and to assess whether there are group by missing-pattern interaction effects. In our models, we used a binary variable as an indicator of missing pattern, distinguishing between subjects who provided complete data and those who missed at least one visit. As each of these groups included at least two time points, this allowed us to examine the influence of missing pattern on rate of change over time. As the results of the “missing = use” and “missing = ignored” analyses were virtually identical, we report on the “missing = use” and pattern-mixture analyses only.

We also assessed the effects of medication adherence and medication exposure on the comparisons of medication groups. We used the number of pills taken over number of pills prescribed for an individual patient while in treatment (measure of medication adherence), and the number of pills taken over the maximum number of pills available to any given patient who completed the full 11 weeks of treatment (medication exposure). Beyond the intent-to-treat analysis, this study repeated the same sets of analyses for the subset of patients who took at least 80% of the medication while in treatment, as well as for those “exposed” to 80% of medication taken by completers. While these analyses are not bias-protected by the initial randomization, they provide a useful measure of whether overall medication effects are affected by nonadherence while in treatment, as well as by poor exposure to a full course of pharmacotherapy.

3. Results

3.1 Demographic and Pre-Treatment Alcohol and Cocaine Use

The average age of the patients for the N=208 sample was approximately 41 years old. Most were African American men (88.9%) and most smoked crack cocaine (78.9%). The mean number of years of education completed for the sample was 12.3 years. On average, patients had said they had in the month prior to treatment used cocaine 45.8% of the days, and drank alcohol on 56% days, with 48.8% heavy drinking days in the same pre-treatment month.

Overall, the four study groups, DISULF, NTX, DISULF-NTX, and PLAC were very similar in demographics and pre-treatment alcohol and cocaine use characteristics (see Table 1).

3.2 Treatment Attendance

Records of patient self-reported cocaine and alcohol use via the TLFB were complete for 85.1% of the sample. The patients on average attended 9.7 or 44% of a possible 22 CBT sessions, and attended at least one CBT session a week for a mean number of 6.2 or 56% of 11 weeks. There were no significant differences in either the mean number of CBT sessions or mean number of weeks where a CBT session was attended across the four groups. The percent of patients per treatment group who discontinued treatment before the end of the trial were: 22.6% DISULF, 32.7% NTX, 40.8% DISULF + NTX, and 40.7% PLAC. *Chi-square* tests showed no significant difference in discontinuation rates across the four groups (Pearson *chi-square* = 5.2, *df* = 3, *p* = 0.16).

3.3. Medication adherence while in treatment and medication exposure to full 11-week trial dosage

Medication adherence and exposure measures were based on pill counts, using returned blister cards and discussion with the patient at weekly intervals. Medication adherence was defined as the percentage of pills ingested based on the number prescribed while the patient was in the trial. Medication exposure is defined as the percentage of pills ingested based on the number of pills that comprised the “planned maximum dose”, i.e., the amount of pill taking expected in patients who completed 11 weeks of treatment and were 100% adherent over the 11-week trial.

There were 45.8% of patients who took 80% of their pills while in treatment, and this rate was comparable for all four treatment groups (*chi square* = 4.79, *df* = 3, *p* = 0.19), and there were also no differences in naltrexone versus disulfiram adherence rates in patients while in treatment.

Only 35.1% of the patients received 80% or more of the maximum possible number of disulfiram pills, compared to 58.7% of naltrexone, suggesting that patients received more exposure to naltrexone than disulfiram, although the difference in medication exposure rates between the two medications was not significant (*chi square* = 3.2; *df* = 3, *p* = 0.36). Nonetheless, the medication adherence and exposure rates indicated only a modest exposure to these medications in this trial, preventing us from conducting a meaningful post-hoc exploratory analyses of outcome results with only those patients who had either taken 80% of the medications while in the trial or had been exposed to at least 80% of the medications overall.

3.4 Primary and Secondary Outcome Analyses

Some key in-trial and end-of-trial variables representing cocaine and alcohol use, mood and anxiety are listed for informational purposes for all four groups in Table 2. Outcome analyses focused primarily on the urine drug screen results and self-reported cocaine and alcohol use, and these analyses are described below. As Table 2 shows, rates of self-reported abstinence

for cocaine, any drinking, and heavy drinking, were high. For example, more than half of the placebo group reported no heavy drinking across the entire treatment period. Since the % days responses contained many zeroes, log transformations failed to adequately reduce skewness. As a result, we focused on monthly abstinence as our primary measure, rather than days of use.

3.4.1 Cocaine Abstinence (Urine Drug Screens-UDS)—A full GEE model of the log-odds of missing and/or BE-positive urines showed no medication effects significant at the 5% level. All groups showed an increase in the odds of a missing and/or BE-positive urine across time, with the odds ratio increasing by a factor of 1.25 per week [$p = 0.001$; 95% CI = (1.09, 1.40)]. Patients who had provided BE-positive urines in the screening period had higher rates of missing and/or BE-positive urines during the treatment phase: OR = 5.21 [$p < 0.001$, 95% CI = (3.06, 8.88)].

3.4.2 Cocaine Abstinence (TLFB Self-report)—Of the 2,288 urine specimens expected to be collected during the treatment period, 1807 (78.9%) were actually collected. Of those collected, 1368 (75.7%) were consistent with self-report. Of the total collected urines, there were 358 (19.8%) urines that were positive for cocaine but patients denied cocaine use, and 81 (4.5%) urine specimens were found negative for cocaine, despite admission of cocaine use. Of the 481 missing urine specimens, 314 (65.2%) were self-reported by patients as positive for cocaine. These figures are comparable to previous studies using self-report data in cocaine dependent samples (Carroll et al., 2004; Hersh, Mulgrew, Van Kirk, & Kranzler, 1999; Zanis, McLellan, & Randall, 1994). This indicated that in this sample, self-reported cocaine use is relatively reliable.

A similar GEE model for self-reported cocaine use, with missing weeks regarded as use, showed a trend towards fewer patients using cocaine in the disulfiram groups [OR for use = 1.45, $p = 0.06$, 95% CI = (0.98, 2.16)]. However, the pattern of use across the four groups was about the same as in the UDS analyses. Patients who self-reported cocaine use in the screening period were significantly more likely to self-report cocaine use in the treatment phase ($p < 0.001$), but there were no significant time or medication effects.

3.4.3 Alcohol Abstinence (TLFB Self-report)—A similar GEE model for presence of any drinking showed linear and quadratic time trend interactions with the medication groups ($p = 0.02$ for the quadratic effect, and $p = 0.04$ for the linear effect). These interactions were due to the disulfiram only and naltrexone only groups showing faster initial rates of increase in drinking than the other two groups, followed by a leveling off later in the treatment phase. However, there were no significant medication group differences at any time point. A similar GEE model for presence of heavy drinking showed an overall increase in rates of alcohol use over time [OR = 1.13, $p = 0.02$, 95% CI = (1.02, 1.26)], but there were no significant effects for medication group.

3.4.4 Evaluation of Combined Abstinence from both Cocaine and Alcohol—A similar GEE model to what has just been described for evaluating separately cocaine and alcohol use during the trial was also performed for combined abstinence using a combination of UDS cocaine results and self-reported alcohol use. This analysis showed significantly more abstinence in patients taking disulfiram, OR = 1.64 [$p = 0.04$, 95% CI = (1.02, 2.65)], although abstinent days were not significantly different from the placebo group per se via post-hoc analyses. There were no significant time or naltrexone effects with the combined index of abstinence.

3.4.5 Pattern Mixture Models—We used a binary indicator of treatment completion as our pattern variable for these analyses, and included it as a main effect and interaction effect in the GEE models for the cocaine UDS, self-reported cocaine use, self-reported alcohol use, and

combined cocaine/alcohol use analyses. None of the interactions between the treatment factors and the pattern variable were significant (all p -values > 0.3), suggesting that the effects of the medications did not differ across completers and non-completers. When the interaction terms were removed, and the pattern variable retained as a main effect only, we observed that disulfiram was associated with significantly lower rates of use as indexed by the cocaine UDS ($p=0.02$), cocaine self-report ($p=0.04$), and combined alcohol-cocaine use outcome variable ($p=0.02$). While interpretation of these results is complicated by the fact that we are considering a post-randomization variable, they provide support for the disulfiram effect observed in the “missing = use” urine analyses reported above.

3.4.6 Periods of Abstinence—A non-parametric approach to evaluating combined abstinence from both cocaine and alcohol during the trial compared the four treatment groups on the number of patients who achieved 3 consecutive weeks of continuous abstinence from both cocaine and alcohol while in treatment. This measure has been shown to be predictive of long-term cocaine abstinence in previous trials. In this trial, the ability to achieve 3 consecutive weeks of abstinence while in treatment was found to be a significant predictor of higher rates of abstinence from alcohol and cocaine during the trial and at the 6-month follow up visit (64% of patients attended the 6-month follow-up visit). For example, patients with 3 consecutive weeks of abstinence, compared to patients without 3 consecutive weeks of abstinence, submitted significantly more BE-negative urine specimens during the trial (24/33 or 73% vs 9/33 or 27% BE-negative specimens, respectively; $t = -12.0$, $df=206$, $p < 0.001$), reported a significantly lower percentage of drinking days during the trial (3.0% vs 10.3% days drinking, respectively; $t = 4.7$, $df = 126$, $p < 0.001$), and at the 6-month follow-up visit, were more likely to submit a BE-negative urine specimen (60% vs 30%, respectively; $chi\ square = 13.4$, $df = 1$, $p < 0.001$), and self-report being abstinent from alcohol in the 30 days prior to their follow-up visit (17/43 (39.5%) vs 39/165 (23.6%), respectively; $chi\ square = 4.4$, $df = 1$, $p = 0.04$). Based on findings from previous trials, as well as data from this trial, the ability to achieve 3 weeks of continuous abstinence is a strong predictor of treatment response and long-term abstinence from both cocaine and alcohol.

Figure 1 shows the proportion of patients in each of the four treatment groups who achieved 3 consecutive weeks of abstinence from both cocaine and alcohol during the trial. Significantly more patients treated with the combination of disulfiram and naltrexone achieved 3 consecutive weeks of abstinence from both cocaine and alcohol compared to the other 3 medication groups (DISULF+NTX combination = 34.7%, NTX = 17.3%, DISULF = 17.0%, PLAC = 15.0%; $chi\ square = 7.8$, $df=3$, $p = .05$).

3.5 Adverse Events (AEs)

There were no participant deaths or serious medical conditions during the clinical trial. Adverse events or AEs ranged from mild to severe. The most frequently reported AEs were headache (64.4%), drowsiness (39.4%), anxiety/irritability (53.4%) and nausea (40.4%). Table 3 provides the prevalence of the most frequent AEs reported in this study (i.e., reported by 10% or more patients). Nausea and increased sexual desire were the only two events that differed across the groups. Differential reporting on these two events is predictable. With respect to nausea, the placebo group reported a lower frequency of nausea compared to the other three medication groups. With respect to increased sexual desire, the event is usually most salient in patients who become abstinent during treatment. Of note, the patient group with the highest frequency of reports of increased sexual desire was the group who were taking the combination of disulfiram and naltrexone. This also was the group who were most likely achieve 3 consecutive weeks of combined abstinence from both cocaine and alcohol while in treatment.

4. Discussion

Co-occurring cocaine and alcohol dependence is highly prevalent in the United States and is also very difficult to treat successfully. Adding pharmacotherapies that target one or both of these dependencies to an accepted counseling/psychosocial treatment for cocaine and alcohol dependence, i.e., CBT, was evaluated in this double blind, placebo-controlled study combining disulfiram and naltrexone as a treatment regimen for attaining abstinence in cocaine and/or alcohol use. Disulfiram and naltrexone have both been approved by the FDA for alcohol dependence, with disulfiram also being shown to reduce cocaine use in cocaine dependent patients (Carroll et al., 2004). Thus, this trial evaluated the use of 100mg/day naltrexone, or 250mg/day disulfiram, or their combination, or placebo, with twice weekly CBT for 11 weeks in patients with co-occurring cocaine and alcohol dependence.

Using GEE analyses, in-trial reductions in cocaine and, independently, alcohol use occurred but were not significantly different on continuous outcome measures across the four study groups treated with either naltrexone or disulfiram or both or neither (placebo). Patients who had provided BE-positive urines in the screening period had higher rates of missing and/or BE-positive urines during treatment. In addition, patients who reported higher rates of heavy drinking in the pre-treatment period had higher rates of alcohol drinking during treatment. There was a finding that the patients from the two disulfiram groups tended to have greater combined abstinence from cocaine and alcohol during treatment.

Using a non-parametric approach, which has been associated with clinical significance, we found that significantly more patients treated with the combination of disulfiram and naltrexone achieved 3 consecutive weeks of continuous abstinence from both cocaine and alcohol while in treatment, compared to the other 3 treatment groups. The achievement of 3 consecutive weeks of abstinence from both cocaine and alcohol was also shown in this study to be a significant predictor of more abstinence during the trial and at a 6-month follow-up visit.

The apparent discrepancy in results between the GEE analyses and a non-parametric approach that targets 3 consecutive weeks of abstinence may indicate a difficulty in the sensitivity of traditional outcome measures to target levels of treatment response in the patient groups who traditionally include many patients who are treatment nonadherent. Essentially, the patients in this study demonstrated less than optimal medication adherence while in treatment (< 50% took 80% of their medications), and also the majority of patients went to fewer than 50% of their CBT sessions. Treatment nonadherence was comparable across the four study groups.

Taking fewer pills than prescribed for the full treatment period has also been consistently reported in alcohol dependent populations for both disulfiram (Fuller, Rieckmann, McCarty, Smith et al., 2005) and naltrexone (Pettinati et al., 2006; Volpicelli, Rhines, Rhines, Volpicelli et al., 1997). While typically disulfiram has had much higher nonadherence problems than naltrexone (De Witte et al., 2005; Fuller & Gordis, 2004; Suh et al., 2006), in this study, the medication adherence rates for patients taking 80% of their medications while in treatment were found to be similar for the two medications, although there was a nonsignificant difference that indicated patients overall ingested more naltrexone than disulfiram (medication exposure rates). Still, medication exposure to either medication was modest at best, suggesting that the majority of the patients took less than 80% of the targeted 11-week course of the expected medication regimen. Because patients with both cocaine and alcohol dependence tend to have high treatment nonadherence rates, it is possible that the high nonadherence and poor medication exposure rates were attributable to the patient population and not the medications selected.

Also, there were no serious adverse effects. General adverse effects were in the mild to moderate range and typical for these medications. No patient was discontinued or said they

would discontinue treatment because of a physical complaint that was reported as an adverse event.

Limitations to this study are that patients in this study agreed to participate in a research clinical trial and, therefore, may be different from clinical patients who are not asked to meet research eligibility criteria. In addition, the high levels of patient nonadherence to treatment regimens may have weakened the analysis to provide statistically confident results.

In summary, the lack of a consistent effect in the GEE outcome analyses using continuous outcome measures suggested that these treatments alone or in combination are unlikely to be robust enough to generalize an advantage to most patients who enter treatment with both cocaine and alcohol dependence. On the other hand, nonparametric analyses that were used in this trial suggested that some of the patients in this trial benefited from the combination of 250mg/day of disulfiram plus 100mg/day of naltrexone for 11 weeks in that increases in combined abstinence from cocaine and alcohol could be observed in over 30% of the patients who received both active medications. Patient adherence to medication regimens were generally poor, and nonadherence likely contributed to the inconsistency in results. Clinically, we would need to identify the patients whom we think will adhere to taking medications before initiating either or both of these medications. This study provides some modest evidence that treating co-occurring cocaine and alcohol dependence with a combination of disulfiram and naltrexone may be beneficial for some patients.

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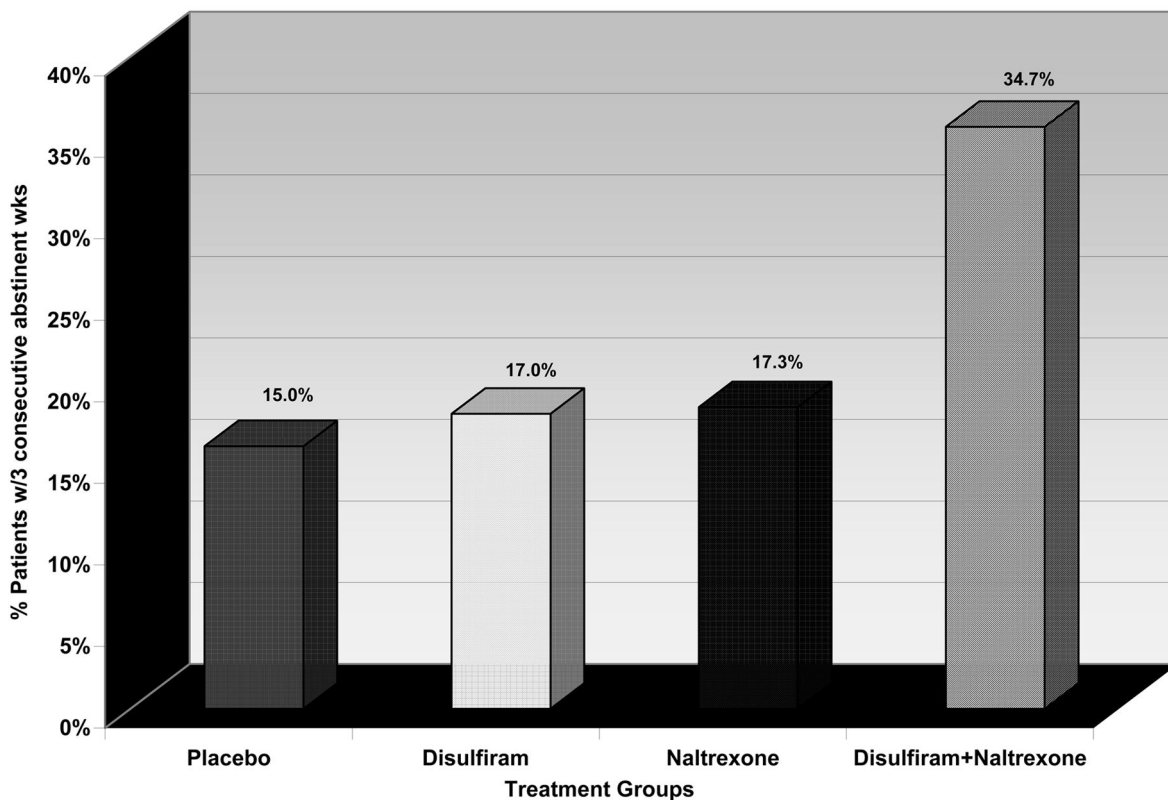


Figure 1. The percent of cocaine-alcohol dependent patients (via DSM-IV criteria) that achieved at least 3 consecutive weeks of abstinence from both cocaine and alcohol in an 11-week controlled clinical trial of four randomized groups, assigned to placebo, or 250mg/day of disulfiram, or 100mg/day of naltrexone, or the combination of these two medications at the dosages specified.

Table 1

Patient characteristics and pretreatment measures of drug use, mood, and anxiety, expressed as percents or means (w/standard deviations).

Variable N	DISULF 53	NTX 52	DISULF+NTX 49	PLAC 54
Mean age	42.1 (7.2)	41.3 (6.8)	40.3 (5.6)	41.2 (7.5)
% Male	67.9%	75.0%	67.3%	70.4%
% African American	88.7%	86.5%	87.8%	92.6%
Mean years of education	12.2 (2.6)	12.2 (1.9)	12.7 (1.7)	12.1 (1.6)
Mean proportion of days employed in past 30	0.34 (0.3)	0.33 (0.3)	0.32 (0.3)	0.27 (0.3)
% smoked route of cocaine use	81.5%	73.6%	78.8%	81.4%
Mean years cocaine use	12.8 (6.3)	13.8 (6.2)	11.7 (6.8)	14.4 (7.9)
Mean years alcohol problem use	22.0 (7.9)	22.6 (8.2)	20.9 (7.7)	20.7 (9.2)
% days cocaine use in past 30	45.5% (.25)	48.8% (.24)	45.9% (.28)	43.0% (.25)
\$ spent for cocaine in past 30	\$1153.5 (1680.6)	\$1048.3 (1114.8)	\$1081.6 (1401.8)	\$1149.1 (1173.9)
% days alcohol use in past 30	55.3% (.28)	56.8% (.25)	54.1% (.28)	57.0% (.25)
% days heavy alcohol use in past 30	49.4% (.25)	47.0% (.24)	49.1% (.29)	49.7% (.25)
Mean drinks/drinking day in past 30	13.3 (10.9)	12.7 (7.0)	17.4 (19.0)	14.3 (8.5)
Number of prior D&A treatments	4.4 (8.3)	3.2 (3.6)	2.9 (2.8)	3.8 (7.6)
Hamilton Anxiety Rating Scale	7.8 (7.6)	6.4 (6.4)	9.6 (6.6)	7.7 (6.7)
Hamilton Depression Rating Scale	11.2 (10.8)	8.9 (8.7)	12.6 (8.9)	9.4 (7.0)

DISULF = disulfiram; NTX = naltrexone; PLAC = placebo; D&A = Drug and Alcohol

Table 2

In-trial continuous outcomes for cocaine and alcohol use, expressed as median percentages or medians (w/95% confidence intervals).

N	DISULF 53	NTX 52	DISULF+NTX 49	PLAC 54
<i>In-Trial Outcomes</i>				
% days cocaine use	5.2% [2.6, 11.1]	7.8% [2.9, 11.7]	4.3% [1.3, 6.5]	5.2% [2.6, 11.7]
% BE-negative urines (missing ignored)	45.5% [27.3, 63.6]	28.6% [9.1, 54.5]	54.5% [40, 81.8]	23.6% [0, 66.7]
% BE-negative urines (missing BE-positive)	18.2% [9.1, 27.3]	9.1% [0, 18.2]	9.1% [0, 36.4]	4.6% [0, 18.2]
\$ spent for cocaine	\$195 [50, 300]	\$107.5 [50, 260]	\$47.5 [20, 200]	\$88.5 [45, 170]
% days alcohol use	2.6% [1.3, 7.8]	3.4% [1.3, 9.1]	2.6% [1.3, 7.1]	2.6% [0, 6.5]
% days heavy alcohol use	0.6% [0, 2.6]	0.6% [0, 3.9]	1.3% [0, 3.9]	0% [0, 1.3]
<i>End-of-Tx Scale Scores</i>				
Hamilton Anxiety Rating Scale	2.0 [1.0, 4.0]	3.0 [0.0, 6.0]	5.0 [2.0, 7.0]	3.5 [2.0, 8.0]
Hamilton Depression Rating Scale	3.0 [1.0, 5.0]	5.0 [3.0, 7.0]	5.0 [2.0, 10.0]	3.5 [2.0, 7.0]

DISULF = disulfiram; NTX = naltrexone; PLAC = placebo; BE = benzoylecgonine

Table 3

Patient percentages reporting frequent adverse events during treatment (frequent adverse events are those reported in 10% or more of patients).

Adverse event	DISULF N=53	NTX N=52	DISULF +NTX N=49	PLAC N=54
Headache	68%	63%	73%	54%
Drowsiness	42%	40%	49%	28%
Anxiety/irritability	55%	46%	61%	52%
Nausea	42%	38%	57%	26%
Upper respiratory tract infection	45%	38%	43%	50%
Decreased sexual desire	32%	29%	33%	28%
Increased sexual desire	11%	19%	33%	28%
Vomiting	17%	23%	29%	19%
Skin rash	15%	8%	10%	9%
Difficulty achieving orgasm	17%	13%	14%	9%
Toothache	15%	21%	10%	11%
Diarrhea	13%	8%	8%	12%

DISULF = disulfiram; NTX = naltrexone; PLAC = placebo

* $p = 0.05$;

** $p = 0.01$