Published in final edited form as:

Drug Alcohol Depend. 2012 November 1; 126(1-2): 224–231. doi:10.1016/j.drugalcdep.2012.05.019.

Efficacy of disulfiram and Twelve Step Facilitation in cocaine-dependent individuals maintained on methadone: A randomized placebo-controlled trial

Kathleen M. Carroll¹, Charla Nich¹, Julia M. Shi^{1,2}, Dorothy Eagan¹, and Samuel A. Ball^{1,2}

¹Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, 151D, West Haven, CT 06516

²The APT Foundation, New Haven Connecticut, 1 Long Wharf, New Haven CT 06511

Abstract

Background—Cocaine use remains a major problem within methadone maintenance programs. Disulfiram's efficacy in reducing cocaine use has been demonstrated in several trials, but its relative efficacy among individuals who use versus abstain from alcohol remains unclear. Treatment approaches which seek to enhance substance users' involvement in self-help activities (Twelve Step Facilitation, TSF) have been associated with better outcomes among alcohol and cocaine users, but have rarely been evaluated among methadone-maintained cocaine-opioid users.

Methods—We conducted a randomized, placebo controlled, double blind (for medication condition), factorial (2×2) trial with 4 treatment conditions: Disulfiram plus TSF, disulfiram plus standard counseling only, placebo plus TSF, and placebo plus standard counseling in the context of a community-based methadone maintenance program. Participants (N=112) received either disulfiram (250 mg/d) or placebo in conjunction with daily methadone maintenance.

Results—Assignment to TSF was associated with less cocaine use throughout treatment and a higher number of cocaine-negative urines. While there were no significant main effects of disulfiram versus placebo, individuals without an alcohol use disorder demonstrated greater reductions in cocaine use over time when assigned to disulfiram.

Conclusions—TSF appears feasible in this methadone maintenance program and was associated with modest reductions in cocaine use, an often intractable problem in this setting. Support for the efficacy of disulfiram was weaker, as it appeared effective only for those without a current alcohol use disorder for this sample.

© 2012 Elsevier Ireland Ltd. All rights reserved.

Corresponding author: Kathleen M Carroll, Department of Psychiatry, Yale University School of Medicine, VA CT Healthcare Center (151D), West Haven, Connecticut 06516.

Clinical Trials.gov identifier: NCT00350870.

Contributors: Authors Carroll, Nich, Shi and Ball designed the study and wrote the protocol. Authors Eagan and Shi took primary responsibility for patient care and management. Authors Nich and Carroll undertook the statistical analysis, and authors Carroll, Nich & Eagan wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest: All authors have no conflicts to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Twelve step Facilitation; Disulfiram; Cocaine Dependence; Randomized clinical trial

1. Introduction

Concurrent cocaine use (Hubbard et al., 1997) remains a major problem within many methadone maintenance programs and is associated with poorer drug use outcomes (Hubbard et al., 1997) and a host of other medical and psychiatric problems (Bux et al., 1995; Grella et al., 1995; Peirce et al., 2006). While there is as yet no FDA-approved medication for cocaine dependence, disulfiram has shown promise (O'Brien, 2005; Vocci et al., 2005), both in outpatient trials (Carroll et al., 2004a; 1998b; Oslin et al., 2008) as well among cocaine users maintained on agonist therapies (George et al., 2000; Petrakis et al., 2000). The initial rationale for disulfiram was as a strategy to reduce alcohol use among cocaine users (Carroll et al., 1993b; Higgins et al., 1993), based on clinical observations of high rates of alcohol dependence among cocaine-dependent outpatients (Brady et al., 1995; Carroll et al., 1993a; Grant and Harford, 1990; Heil et al., 2001; McCance-Katz et al., 1995; McKay et al., 1999; Schmitz et al., 1997). Reduced alcohol use was hypothesized to reduce patients' exposure to this potent cue for cocaine use, lessen alcohol-related impairments in judgment and ability to resist craving and offers of drugs (Higgins et al., 1996), and reduce exposure to cocaethylene, a pharmacologically active metabolite of cocaine and alcohol when used concurrently (Jatlow et al., 1991; McCance-Katz et al., 1995). Data from existing disulfiram trials has suggested that disulfiram may be effective among cocaine users without a significant history of alcohol use (George et al., 2000; Petrakis et al., 2000) and in fact may be more effective among cocaine users who do not drink alcohol (Carroll et al., 2004a), underlining the possibility of a direct effect of disulfiram on cocaine use (Baker et al., 2007a; Schroeder et al., 2011).

The efficacy of most addiction pharmacotherapies is often constrained by limited compliance and failure to address the multiplicity of problems faced by those with substance use disorders. To address these issues, specific behavioral therapies, such as cognitive behavioral therapy (CBT; Carroll et al., 2004a) and contingency management (CM; Carroll et al., 2001; Poling et al., 2006) have been demonstrated to enhance the effects of addiction pharmacotherapies. Implementation of CBT and CM in clinical practice remains limited, however (Santa Ana et al., 2008), in part due to the complexity of training for CBT and limited acceptance among clinicians for CM. Conversely, approaches based on the Twelve Steps of Alcoholics Anonymous have been found to have broader support and wider implementation by the treatment community, but until recently had little empirical support from controlled clinical trials (Miller and Wilbourne, 2002; Tonigan et al., 1996b). Several recent rigorous randomized clinical trials have demonstrated efficacy, among both alcohol- and drug-dependent populations (Carroll et al., 1994; 1998b; 2000; Crits-Christoph et al., 1999; Humphreys, 2006; Project MATCH Research Group, 1998; Timko et al., 2006; Weiss et al., 2005), of well-defined, manualized treatments like Twelve-Step Facilitation (TSF; (Nowinski et al., 1992) that support meaningful involvement in self-help groups.

If shown to complement or enhance medication effects, TSF would be an attractive model for clinical practice for several reasons: First, TSF and related approaches are widely accepted by the clinical community (Forman et al., 2001; Humphreys et al., 2004). Self-help programs are widely available at little or no cost (Humphreys, 2004) and can reduce treatment and other health care costs (Humphreys and Moos, 2001). Moreover, TSF may prolong the effects of treatment by fostering enduring connections with stable social networks that support abstinence (Humphreys, 2004; Humphreys et al., 2004). On the other

hand, several questions have been raised about the compatibility of TSF with combination with pharmacotherapies: Self-help groups have historically been seen as antithetical to addiction pharmacotherapies (Magura et al., 2002; Mark et al., 2003; Rychtarik et al., 2000; Swift et al., 1998) and particularly methadone maintenance (Carroll et al., 2004b; Forman et al., 2001). While self-help groups have generally become more accepting of pharmacologic approaches and TSF has even been used successfully as a 'platform' in multisite pharmacologic trials (Krystal et al., 2001), no previous trial has evaluated the feasibility or efficacy of TSF as a treatment for cocaine dependence in the context of methadone maintenance.

In this report, we present findings from a randomized placebo-controlled factorial trial evaluating disulfiram and TSF, implemented as add-ons to standard counseling, in a sample of methadone-maintained cocaine-dependent individuals. We hypothesized that disulfiram would be more effective than placebo in reducing cocaine use. As a secondary hypothesis, based on our previous research, we expected the effects of disulfiram to be most pronounced among individuals without a lifetime alcohol use diagnosis (Carroll et al., 2004a). Second, we hypothesized that TSF would be more effective than standard counseling alone in reducing cocaine use and in facilitating involvement in self-help groups. Third, we hypothesized a significant interaction in that the TSF/disulfiram combination would be more effective than placebo and standard counseling. In addition, although previous research suggests that disulfiram is safe in healthy adult cocaine users (Malcolm et al., 2008; Roache et al., 2011), we report on safety and adverse effects as disulfiram affects cocaine metabolism at some doses and routes of administration (Baker et al., 2007b; McCance-Katz et al., 1998; Suh et al., 2006).

2. Method

2.1. Participants

Participants were recruited from individuals stabilized on methadone maintenance treatment at the APT Foundation, a private non-profit outpatient substance abuse treatment center. Participants were self-referred or referred by clinician detection of positive urine tests for cocaine, which results in presentation of a range of treatment options, one of which was participation in the study. Methadone maintenance patients were included as participants if they met DSM-IV criteria for current cocaine dependence. Individuals were excluded if they (1) had current use of barbiturates or whose principal illicit drug used was not cocaine, (2) met lifetime DSM-IV criteria for a psychotic or bipolar disorder, or expressed significant current suicidal or homicidal ideation, or (3) had a current medical condition which would contraindicate disulfiram treatment (e.g., hepatic or cardiac issues, hypertension, pregnancy). Individuals who were physically dependent on alcohol were eligible for the protocol after they completed alcohol detoxification.

Participants were administered the Structured Clinical Interview for DSM-IV (SCID; (First et al., 1995) and a physical examination, including EKG, urinalysis and blood laboratory work at screening. As shown in Figure 1, 112 of the 169 individuals screened were determined to be eligible for the study, provided informed consent and were randomized. Primary reasons for ineligibility were (1) failure to complete pretreatment evaluation (n=24), (2) physical conditions that contraindicated disulfiram (n=20), (3) need for inpatient treatment, imminent incarceration or current administrative discharge from the methadone program (n=7), (4) benzodiazepene or uncontrolled opioid use (n=3), or (5) psychiatric instability (n=3). A computerized urn randomization (Stout et al., 1994) program used in several previous multicenter trials (Ball et al., 2007; Carroll et al., 2004a; 2009) was used to balance groups with respect to baseline severity of cocaine dependence, alcohol use, gender and race.

2.2. Treatments

All participants received standard methadone maintenance treatment which included daily methadone and weekly group counseling, with other services available as needed. Participants met with an independent clinical evaluator who assessed recent cocaine use and monitored other clinical symptoms. Adverse events and blood pressure were monitored weekly by the study nurse.

2.2.1 Disulfiram—Participants assigned to disulfiram treatment were prescribed 250 mg of disulfiram daily which was dissolved in their daily methadone dose to enhance compliance. Participants assigned to placebo received methadone formulated to appear identical to the disulfiram plus methadone combination. All participants were cautioned not to drink alcohol. Breath samples were collected prior to each daily methadone dose, which were held in cases where participants tested positive for alcohol. Of 8364 breath samples collected during the trial, only 10 (in 7 different participants, 3 of those assigned to disulfiram) indicated recent alcohol use.

2.2.2 Twelve-Step Facilitation (TSF)—The TSF manual (Baker, 1998) was adapted from that used in Project MATCH (Nowinski et al., 1992; Project MATCH Research Group, 1997). TSF is an individual therapy grounded in the concept of substance dependence as a spiritual and biopsychosocial disease. While not identical to Alcoholics Anonymous (AA), the content of TSF sessions is intended to be consistent with the Twelve Steps, with primary emphasis given to Steps 1 through 5, and with a disease model of addiction. A major goal of TSF is to foster active participation in self-help groups. TSF was delivered in weekly individual sessions over twelve weeks by two masters-level counselors who had extensive experience in TSF and who had served as the primary TSF trainer/supervisors for the Project MATCH Coordinating Center (Carroll et al., 1998a).

2.3 Assessments

Participants were assessed before treatment, weekly during treatment, at the 12-week treatment termination point, and at follow-up interviews conducted at three-month intervals through a year after treatment termination by an independent clinical evaluator. Primary outcome measures were frequency of self-reported cocaine use (operationalized for the ANOVAs as percent days of cocaine use and for the random regression analyses as the number of days per week the participant reported using cocaine) and results of urine toxicology screens (operationalized as the percent cocaine-positive urines submitted for the ANOVAs and as the likelihood of submitting a cocaine-positive urine sample each week for the random regression analyses). The Substance Abuse Calendar, similar to the Timeline Follow Back (Fals-Stewart et al., 2000; Hersh et al., 1999), was administered weekly during treatment to collect detailed day-by-day self-reports of cocaine use, alcohol use, and other drug use throughout the 84-day treatment period and at each follow-up interview through one year. The Alcoholics Anonymous Involvement Scale (Tonigan et al., 1996a) was used to evaluate frequency and level of participants involvement in self-help and AA activities

Self-reports of cocaine were verified through urine toxicology screens that were obtained three times weekly during treatment and at each follow-up interview. Of 2514 urine specimens collected during the 12 week treatment phase, 2228 (88.6%) were consistent with the participants' self-reports of recent cocaine use, 65 (2.6%) tested negative for cocaine although the participant reported recent cocaine use, and 221 (8.8%) were positive for cocaine in cases where the participant had denied use. This rate compares favorably with previous studies of cocaine-dependent and other substance using samples evaluating the accuracy of self-report data using the methods described here (Babor et al., 2000; Zanis et al., 1994). Because urine specimens were collected thrice weekly, carry-over of positive

urines tests was likely and may have resulted in conservative estimates of treatment effects (Chutuape et al., 2001; Preston et al., 1997).

2.4 Data analyses

Random effect regression models (Bryk and Raudenbush, 1987) were used to evaluate change across time for alcohol and cocaine use frequency with three contrasts: TSF plus standard counseling (treatment as usual; TAU) versus TAU alone (TSF/placebo and TSF/DIS versus TAU/placebo and TAU/DIS), disulfiram (DIS) versus placebo (TSF/DIS and TAU/DIS versus TSF/placebo and TAU/placebo), and the interaction of TSF and DIS (TSF/DIS>TSF/placebo=TAU/DIS>TAU/placebo), with a piecewise model used for the follow-up data to evaluate change across treatment phases (treatment versus follow-up) (Singer and Willett, 2003). ANOVA models, with the same contrasts, were used to analyze variables that summarized outcomes across treatment (e.g., longest period of continuous abstinence during treatment, percent cocaine-free urine specimens).

In addition to the principal analyses that were conducted on the 112 participants randomized to treatment (intention to treat sample), supplemental analyses also evaluated treatment effects for the 107 participants who initiated treatment (treatment exposed sample) and the 81 participants who completed treatment. Unless otherwise noted, results were consistent across analysis samples, and only results from the intention to treat sample are presented below.

In cases where a randomized participant did not initiate ($n=5$) or dropped out of treatment ($n=26$), he or she was followed and interviewed at the 12-week termination point. Of the 31 participants who did not begin or who dropped out of treatment, 29 were successfully tracked and interviewed. Thus, complete self-report outcome data were available for 98% of the intention-to-treat sample at the 12-week post-treatment assessment point as well as 93% of the intention-to-treat sample at the 12-month follow-up interview (15 months post randomization).

3. Results

3.1 Participant characteristics

The mean age of the sample was 38.3 ($SD=7.5$) and 41% of the participants were female. Twenty-two percent identified themselves as African American, 14% as Latino or Hispanic American, and 64% as European American. Seventeen percent had not completed high school; 43% were high school graduates, and 34% had completed some college-level work. Most (65%) had never been married or were living alone, relatively few held a full time job (35%), and 45% were unemployed. On average, participants had been enrolled in the methadone program for 14.8 months ($SD=50.9$) at the time of the baseline assessment and their mean methadone dose was 87 mg ($SD=19.0$). The participants reported an average of 8 previous arrests and 20 months of incarceration during their lifetimes.

Regarding substance use and comorbid psychopathology, participants reported using cocaine an average of 15.4 days ($SD=8.9$) and alcohol an average of 4.6 days ($SD=7.7$) of the past 28 days. Thirty-seven percent met DSM-IV criteria for a current alcohol use disorder (62% lifetime); 35% met criteria for a lifetime diagnosis of a depressive disorder, and 17% met criteria for a lifetime anxiety disorder. There were no statistically significant differences by treatment condition on any of the variables reported above or in Table 1.

3.2 Retention and treatment compliance

There were no significant differences across conditions in numbers of TSF or standard counseling sessions completed or rates of completing the treatment protocol. Seventy-six percent of participants who initiated their study treatment completed the full 12-week course of treatment (DIS/TSF 67%, PLA/TSF 73%, PLA/TAU 81%, DIS/TAU 82%, $X^2=2.3$, $p=.51$). The mean weeks of treatment completed was 10.0 ($SD=3.8$), with no statistically significant differences across conditions. Participants who initiated treatment took their study medication on a mean of 94 % of treatment days, with no significant differences across conditions.

Participants assigned to TSF completed an average of 7 of the 12 TSF sessions offered, with no differences across medication condition ($F=.004$, $p=.95$). Participants assigned to TSF reported attending an average of 11.6 self-help meetings during treatment ($SD=17.0$); those not assigned to TSF reported attending 5.0 meetings ($SD=13.3$, $F(df\ 1,94)=4.95$, $p=.02$). By the end of treatment, 35 of the 53 TSF participants who initiated treatment attended at least one self help group (66%). Of these, 16 had attended at least one AA meeting, 27 had attended an NA meeting, and 1 participant reported attending Methadone Anonymous. In terms of activities indicating level of self-help involvement (Tonigan et al., 1996a; Weiss et al., 2000), by the end of treatment, 9 (12%) reported making a home group commitment, and 8 had acquired a sponsor by the end of treatment. Twenty percent of those assigned to TSF indicated they had revealed to another member of a self-help group that they were enrolled in a methadone maintenance program; none reported any negative consequences of revealing this status.

3.3 Adverse events

Given the possibility of disulfiram-associated hypertension among individuals using cocaine and/or alcohol, blood pressure was monitored for all participants at least once per week during the course of treatment. Participants assigned to disulfiram were more likely to have at least once instance of elevated blood pressure (greater than 130/90) during the trial compared to those assigned to placebo (26 from disulfiram, 14 from placebo). In each case, blood pressure normalized by the next assessment visit. Only one participant assigned to disulfiram had significantly elevated blood pressure which resulted in cessation of study medication as a precaution. There were no participant deaths during the protocol.

Other adverse events also tended to be reported more frequently for those assigned to disulfiram versus placebo. Frequencies of specific symptoms, combined across groups, that differed by medication condition (disulfiram versus placebo), are as follows: Drowsiness, 104 versus 67 reports ($X^2=8.2$, $p=.004$); fatigue, 111 versus 53 reports ($X^2=22.1$, $p<.001$); headache, 113 versus 47 reports ($X^2=29.6$, $p<.001$); diarrhea/constipation, 97 versus 45 reports ($X^2=20.1$, $p<.001$); skin rash, 69 versus 32 reports ($X^2=13.7$, $p<.001$); and aftertaste, 130 versus 56 reports ($X^2=32.9$, $p<.001$). There were no significant differences across groups in the frequency of reported nausea or vomiting (76 versus 61, $X^2=1.4$, $p=.24$), suggesting a number of participants did not test for a disulfiram reaction. At the end of treatment, 94 participants provided a guess as to which medication they were assigned. Of these, 72% guessed correctly (86% of those assigned to disulfiram, 67% for those assigned to placebo).

3.4. Effects of study treatments on cocaine use

Simple ANOVA models evaluating the effects of treatment suggested that participants assigned to the TSF condition reported higher percentage of days abstinent from cocaine than those not assigned to TSF (mean 70.8 days vs. 57.5, $f(1,104)=9.5$, $p=.003$). Regarding outcomes based on urine specimens collected during treatment, participants assigned to TSF

submitted significantly more cocaine negative urine samples than those not assigned to TSF (mean 19.9 vs. 16.3, $t=2.0$, $p=.05$). Although significant differences for TSF were not seen for percent of urine specimens testing positive for cocaine for the full sample; when data from four statistical outliers were removed, results were significant and more closely paralleled those of the self reports. These analyses did not indicate any significant differences by medication condition or the interaction of TSF/DIS.

While the ANOVA model-based analyses just presented address cocaine use outcomes summarized over the course of treatment, they do not address rates of change over time. Thus, random effect regression models (Gibbons et al., 1993; Hedeker and Gibbons, 1996) were used to evaluate change in frequency of cocaine use over time. For these analyses, there was an overall effect for time, indicating decreased frequency of cocaine use over time for the sample as a whole ($t=104.17$, $p=.00$), with a trend for a TSF by time effect ($t=-1.74$, $p=.08$). There were no significant effects of disulfiram on cocaine use over time, nor were there significant interaction effects.

3.5 Effects of study treatments on alcohol use

Overall, participants were abstinent from alcohol an average of 94% ($SD=21.6$) of days in treatment. There were no significant differences in percent days abstinent by treatment condition. Random effect regression models evaluating change in frequency of alcohol use over time indicated decreased frequency of use for the sample as a whole ($t=-13.3$, $p<.05$). In addition, there was significant disulfiram by time effect ($t=2.01$, $p=.05$), indicating a greater reduction in alcohol use for those assigned to disulfiram. There were no significant effects of TSF assignment on alcohol use within the active phase of treatment, nor were there any significant interaction effects of the disulfiram-TSF combination.

3.6 Moderating effects of baseline alcohol use

Given our prior findings of disulfiram effects being stronger among cocaine users without significant alcohol use (Carroll et al., 2004a), these analyses were repeated evaluating individuals who did and did not meet DSM-IV criteria for a lifetime alcohol use disorder diagnosis. For those who did not meet criteria for a lifetime alcohol use disorder, ($n=70$), there was a significant time by medication effect ($t=4.26$, $p=.04$), indicating greater reductions in cocaine use across time for participants assigned to disulfiram versus placebo. For this sample, there was also a significant TSF by time effect ($t=6.9$, $p=.01$), as well as a trend for a disulfiram/TSF interaction ($t=2.7$, $p=.10$).

3.7. Follow-up outcomes

Results of piecewise random effect regression analyses (Singer and Willett, 2003) for cocaine use outcomes by treatment condition are presented in Figure 2. These analyses include terms for change within treatment (months 0–3), change post-treatment (months 4–15), and the interactions of these effects with the contrasts specified earlier (TSF versus no TSF, disulfiram versus placebo and the interaction of TSF and disulfiram with either treatment alone). These data indicated continued reductions in cocaine use across time for the group as a whole through the 12 months after treatment (main effect of time: $t=-3.26$, $p=.00$), but no significant time by treatment effects. Assignment to TSF was associated with higher rates of reported attendance at self-help groups through the follow-up, but attendance at TSF during treatment was not associated with reduced cocaine use during the follow-up.

4. Discussion

This trial of TSF, disulfiram, and their combination indicated the following: First, assignment to TSF was associated with reduced cocaine use via self-report. Second,

although the hypothesis that disulfiram would be associated with reduced cocaine use for the full sample was not supported, there was a significant disulfiram by time effect for the subsample of participants who did not meet criteria for a lifetime alcohol use disorder. Finally, data from the one year follow-up indicated stable effects overall, with no significant differences by group.

This trial is significant in that it was the first to demonstrate the feasibility and efficacy of TSF to reduce cocaine use in a methadone maintained sample and suggests this broadly accepted, readily disseminated treatment approach may be a viable option in agonist maintenance programs. Of the participants assigned to TSF, 66% attended at least one self-help meeting. Thus, TSF was reasonably well-accepted by methadone-maintained individuals in this sample and facilitated self-help group attendance as intended. Involvement in self-help group meetings was associated with better cocaine outcomes during treatment and more self-help involvement after treatment ended. Moreover, no individual assigned to TSF reported any instance of negative reactions by other self-help group members. While participants did not necessarily reveal that they were enrolled in a methadone maintenance program or a disulfiram trial, this nevertheless is consistent with observations that self-help group members may be more accepting than often perceived by individuals utilizing pharmacotherapies such as methadone maintenance. It should also be noted that TSF treatment was not strongly related with poorer levels of medication compliance during treatment. However, as study medication was mixed into daily methadone doses to facilitate compliance, compliance was excellent across conditions and use of alcohol appeared minimal. Finally, neither TSF nor disulfiram was associated with statistically significant effects through the end of the one-year follow-up. While enduring effects of pharmacotherapies are generally not anticipated after they are terminated, we did anticipate that TSF's effects, via encouraging strong ongoing relationships with self-help groups, would be more durable. While there was some evidence of continuing involvement in self-help through the follow-up period, this did not appear to have a strong continuing effect on cocaine use.

In this trial, assignment to disulfiram was not associated with reduced cocaine use within treatment for the sample as a whole, this finding is consistent with previous studies suggesting weaker effects for disulfiram treatment for cocaine dependence in the context of agonist maintenance than in outpatient drug-free settings (Oliveto et al., 2010). On the other hand, assignment to disulfiram was associated with greater reductions in cocaine use across time for the large subsample of those without a current alcohol use disorder similar to our previous work (Carroll et al., 2004a). This is consistent with a direct effect of disulfiram on cocaine use (Schroeder et al., 2010, Roache et al., 2011, Devoto et al 2012) independent of reductions in co-occurring alcohol use.

Disulfiram also appeared comparatively safe and well tolerated in this sample. Consistent with previous systematic reviews (Malcolm et al., 2008) and laboratory evaluations of combined effects of disulfiram, cocaine, and alcohol in humans, there was some evidence of higher rates of elevated blood pressure among those assigned to disulfiram versus placebo. Blood pressures did not increase to dangerous levels however, and in only one case was disulfiram discontinued as a precaution. Rates of other symptoms and adverse events tended to be significantly higher among those assigned to disulfiram versus placebo; these, too, were comparatively mild, of brief duration, and did not lead to discontinuation of study medications or participant attrition. Thus, this trial adds to the growing literature pointing to the safety of disulfiram with this population, provided individuals are carefully screened for hypertension and other cardiac conditions and monitored closely while on disulfiram.

Limitations of the current study include lack of control for additional time and attention for those assigned to the TSF condition. We did not include an attention control as we wished to evaluate the effects of TSF specifically as an add-on to standard treatment in this context. This required additional time and effort from the participants (often an extra clinic visit), and hence many patients did not receive the intended 12 sessions of TSF. Similarly, we did not monitor weekly groups at the clinic and thus could not discern the extent to which some participants may have been exposed to TSF-like interventions as part of standard counseling.

Overall, this study indicates that adding TSF as a counseling enhancement has significant promise for what remains a significant problem among methadone maintained patients. Continued cocaine use often results in discharge from methadone programs, but program discharge also results in exposure to myriad health risks associated with resumed heroin addiction, particularly in combination with cocaine. Thus, referral to TSF groups may represent a highly preferred alternative to offer patients facing program discharge. TSF has the added advantage in that it is relatively easy to train most clinicians in this approach, counselors and programs tend to be receptive to TSF, and self-help meetings are widely available in most US communities.

Acknowledgments

Role of funding source: Support was provided by NIDA grants R01-DA10679 and P50-DA09241; NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. .

We gratefully acknowledge the contributions of Elizabeth Vollono, Joanne Corvino, MPH, Karen Hunkele, Stuart Baker, Arthur Woodard, and the staff of the APT Foundation's Central Medical Unit and the Legion, Park and Boulevard methadone maintenance programs.

References

- Babor TF, Steinberg K, Anton RF, Del Boca FK. Talk is cheap: measuring drinking outcomes in clinical trials. *J Stud Alcohol*. 2000; 61:55–63. [PubMed: 10627097]
- Baker JR, Jatlow P, McCance-Katz EF. Disulfiram effects on responses to intravenous cocaine administration. *Drug Alcohol Depend*. 2007a; 87:202–209. [PubMed: 16979847]
- Baker JR, Jatlow PM, McCance-Katz EF. Disulfiram effects on responses to intravenous cocaine administration. *Drug Alcohol Depend*. 2007b; 87:202–209. [PubMed: 16979847]
- Baker, SM. Twelve Step Facilitation Therapy for Drug Abuse and Dependence. Yale University PDC; New Haven: 1998.
- Ball SA, Martino S, Nich C, Frankforter TL, Van Horn D, Crits-Christoph P, Woody GE, Obert JL, Farentinos C, Carroll KM. Site matters: multisite randomized trial of motivational enhancement therapy in community drug abuse clinics. *J Consult Clin Psychol*. 2007; 75:556–567. [PubMed: 17663610]
- Brady KT, Sonne S, Randall CL, Adinoff B, Malcolm RJ. Features of cocaine dependence with concurrent alcohol dependence. *Drug Alcohol Depend*. 1995; 1995:69–71. [PubMed: 7587977]
- Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychol Bull*. 1987; 101:147–158.
- Bux DA, Lamb RJ, Iguchi MY. Cocaine use and HIV risk behavior in methadone maintenance patients. *Drug Alcohol Depend*. 1995; 37:29–35. [PubMed: 7882871]
- Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan D, Frankforter TL, Triffleman EG, Shi J, Rounsaville BJ. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. *Arch Gen Psychiatry*. 2001; 58:755–761. [PubMed: 11483141]
- Carroll KM, Connors GJ, Cooney NL, DiClemente CC, Donovan DM, Longabaugh RL, Kadden RM, Rounsaville BJ, Wirtz PW, Zweben A. Internal validity of Project MATCH treatments: discriminability and integrity. *J Consult Clinical Psychol*. 1998a; 66:290–303. [PubMed: 9583332]

- Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive-behavioral therapy in cocaine-dependent outpatients: a randomized placebo controlled trial. *Arch Gen Psychiatry*. 2004a; 64:264–272.
- Carroll KM, Kadden R, Donovan D, Zweben A, Rounsaville BJ. Implementing treatment and protecting the validity of the independent variable in treatment matching studies. *J Stud Alcohol Suppl*. 1994; 12:149–155. [PubMed: 7722991]
- Carroll KM, Martino S, Suarez-Morales L, Ball SA, Miller WR, Rosa C, Anez LM, Paris MP, Nich C, Frankforter TL, Matthews J, Szapocznik J. A multisite randomized effectiveness study of motivational enhancement therapy for Spanish-speaking substance abusers. *J Consult Clin Psychol*. 2009; 77:993–999. [PubMed: 19803579]
- Carroll KM, Nich C, Ball SA, McCance-Katz E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*. 1998b; 93:713–728. [PubMed: 9692270]
- Carroll KM, Nich C, Ball SA, McCance-Katz EF, Frankforter TF, Rounsaville BJ. One year follow-up of disulfiram and psychotherapy for cocaine-alcohol abusers: sustained effects of treatment. *Addiction*. 2000; 95:1335–1349. [PubMed: 11048353]
- Carroll KM, Rounsaville BJ, Bryant KJ. Alcoholism in treatment seeking cocaine abusers: clinical and prognostic significance. *J Stud Alcohol*. 1993a; 54:199–208. [PubMed: 8459714]
- Carroll KM, Rounsaville BJ, Kosten TR. Choosing a behavioral therapy platform for pharmacotherapy of substance users. *Drug Alcohol Depend*. 2004b; 75:123–134. [PubMed: 15276217]
- Carroll KM, Ziedonis D, O'Malley SS, McCance-Katz E, Gordon LT, Rounsaville BJ. Pharmacologic interventions for abusers of alcohol and cocaine: a pilot study of disulfiram versus naltrexone. *Am J Addict*. 1993b; 2:77–79.
- Chutuaue MA, Silverman K, Stitzer ML. Effects of urine testing frequency on outcome in a methadone take-home contingency program. *Drug Alcohol Depend*. 2001; 62:69–76. [PubMed: 11173169]
- Crits-Christoph P, Siqueland L, Blaine JD, Frank A, Luborsky L, Onken LS, Muenz L, Thase ME, Weiss RD, Gastfriend DR, Woody G, Barber JP, Butler S, Dale D, Salloum I, Bishop S, Najavits L, Lis J. Psychosocial treatments for cocaine dependence: results of the National Institute on Drug Abuse Collaborative Cocaine Study. *Arch Gen Psychiatry*. 1999; 56:495–502.
- Devoto P, Flore G, Saba P, Cadeddu R, Gessa GL. Disulfiram stimulates dopamine release from noradrenergic terminals and potentiates cocaine-induced dopamine release in the prefrontal cortex. *Psychopharmacol (Berl)*. in press.
- Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol*. 2000; 68:134–144. [PubMed: 10710848]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV, Patient Edition. American Psychiatric Press; Washington, D.C: 1995.
- Forman RF, Bovasso GB, Woody GE. Staff beliefs about addiction treatment. *J Subst Abuse Treat*. 2001; 21:1–9. [PubMed: 11516921]
- George TP, Chawarski MC, Pakes JA, Carroll KM, Kosten TR, Schottenfeld RS. Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol Psychiatry*. 2000; 47:1080–1086. [PubMed: 10862808]
- Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, Watkins JT. Some conceptual and statistical issues in analyses of longitudinal psychiatric data. *Arch Gen Psychiatry*. 1993; 50:739–750. [PubMed: 8357299]
- Grant BF, Harford TC. Concurrent and simultaneous use of alcohol and cocaine: results of a national survey. *Drug Alcohol Depend*. 1990; 25:97–104. [PubMed: 2323315]
- Grella CE, Anglin MD, Wugalter SE. Cocaine and crack use and HIV risk behaviors among high-risk methadone maintenance clients. *Drug Alcohol Depend*. 1995; 37:15–21. [PubMed: 7882869]
- Hedeker D, Gibbons RD. MIXREG: a computer program for mixed effect regression analysis with autocorrelated errors. *Comput Methods Programs*. 1996; 49:229–252.
- Heil SH, Badger GJ, Higgins ST. Alcohol dependence among cocaine dependent outpatients: demographics, drug use, treatment outcome and other characteristics. *J Stud Alcohol*. 2001; 62:14–22. [PubMed: 11271960]

- Hersh D, Mulgrew CL, Van Kirk J, Kranzler HR. The validity of self-reported cocaine use in two groups of cocaine abusers. *J Consult Clin Psychology*. 1999; 67:37–42.
- Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F. Disulfiram therapy in patients abusing cocaine and alcohol. *Am J Psychiatry*. 1993; 150:675–676. [PubMed: 8465895]
- Higgins ST, Roll JM, Bickel WK. Alcohol pretreatment increases preference for cocaine over monetary reinforcement. *Psychopharmacol (Berl)*. 1996; 123:1–8.
- Hubbard RL, Craddock SG, Flynn PM, Anderson J, Etheridge R. Overview of 1-year follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psych Addict Behav*. 1997; 11:261–278.
- Humphreys K. *Circles of Recovery: Self-help Organizations for Addictions*. Cambridge University Press; Cambridge, UK: 2004.
- Humphreys K. The trials of Alcoholics Anonymous. *Addiction*. 2006; 101:617–618. [PubMed: 16669879]
- Humphreys K, Moos RH. Can encouraging substance abuse inpatients to participate in self-help groups reduce the demand for outpatient aftercare? A quasi-experimental study. *Alcohol Clin Exp Res*. 2001; 25:711–716. [PubMed: 11371720]
- Humphreys K, Wing S, McCarty D, Chappel J, Gallant L, Haberle B, Horvath AT, Kaskutas LA, Kirk T, Kivlahan DR, Laudet A, McCrady BS, McLellan AT, Morgenstern J, Townsend M, Weiss RD. Self-help organizations for alcohol and drug problems: toward evidence-based practice and policy. *J Subst Abuse Treat*. 2004; 26:151–158. [PubMed: 15063905]
- Jatlow PM, Ellsworth JD, Bradberry CW, Winger G, Taylor R, Roth RK. Cocaethylene: a neuropharmacologically active metabolite associated with concurrent cocaine-ethanol ingestion. *Life Sci*. 1991; 48:1787–1794. [PubMed: 2020260]
- Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. for the Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. *New Eng J Med*. 2001; 345:1734–1739. [PubMed: 11742047]
- Magura S, Laudet AB, Mahmood D, Rosenblum A, Knight E. Adherence to medication regimens and participation in dual focus self-help groups. *Psych Serv*. 2002; 53:310–316.
- Malcolm R, Olive MF, Lechner W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. *Exp Op Drug Safety*. 2008; 7:459–472.
- Mark TL, Kranzler HR, Poole VH, Hagen CA, McLeod C, Crosse S. Barriers to the use of medications to treat alcoholism. *Am J Addict*. 2003; 12:281–294. [PubMed: 14504021]
- McCance-Katz EF, Kosten TR, Jatlow PM. Chronic disulfiram treatment effects on intranasal cocaine administration: initial results. *Biol Psychiatry*. 1998; 43:540–543. [PubMed: 9547934]
- McCance-Katz EF, Price LH, Kosten TR, Jatlow PM. Cocaethylene: pharmacology, physiology, and behavioral effects in humans. *J Pharmacol Exp Ther*. 1995; 274:215–223. [PubMed: 7616402]
- McKay JR, Alterman AI, Rutherford MJ, Cacciola JS, McLellan AT. The relationship of alcohol use to cocaine relapse in cocaine dependent patients in an aftercare study. *J Stud Alcohol*. 1999; 60:176–180. [PubMed: 10091955]
- Miller WR, Wilbourne PL. Mesa Grande: A methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction*. 2002; 97:265–277. [PubMed: 11964100]
- Nowinski, J.; Baker, S.; Carroll, KM. *Twelve-Step Facilitation Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence*. NIAAA; Rockville, MD: 1992.
- O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry*. 2005; 162:1423–1431. [PubMed: 16055763]
- Oliveto A, Poling J, Mancino MJ, Feldman Z, Cubells JF, Pruzinsky R, Gonsai K, Cargile C, Sofuoglu M, Chopra MP, Gonzalez-Haddad G, Carroll KM, Kosten TR. Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug Alcohol Depend*. 2010; 113:184–191. [PubMed: 20828943]
- Peirce JM, Petry NM, Stitzer ML, Blaine JD, Kellog S, Satterfield F, Schwartz M, Krasnansky J, Pencer E, Silva-Vazquez L, Kirby KC, Royer-Malvestuto C, Roll JM, Cohen A, Copersino ML, Kolodner K, Li R. for the Clinical Trials Network. Effects of lower-cost incentives on stimulant

- abstinence in methadone maintenance treatment: a National Drug Abuse Treatment Clinical Trials Network study. *Arch Gen Psychiatry*. 2006; 63:201–208. [PubMed: 16461864]
- Petrakis IL, Carroll KM, Gordon LT, Nich C, McCance-Katz E, Rounsaville BJ. Disulfiram treatment for cocaine dependence in methadone maintained opioid addicts. *Addiction*. 2000; 95:219–228. [PubMed: 10723850]
- Pettinati HM, Kampman KM, Lynch KG, Xie H, Dackis C, Rabinowitz AR, O'Brien CP. A double-blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addict Behav*. 2008; 33:651–667. [PubMed: 18079068]
- Poling J, Oliveto A, Petry NM, Sofuoflu M, Gonsai K, Gonzalez G, Martell B, Kosten TR. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry*. 2006; 63:219–228. [PubMed: 16461866]
- Preston KL, Silverman K, Schuster CR, Cone EJ. Assessment of cocaine use with quantitative urinalysis and estimation of new uses. *Addiction*. 1997; 92:717–727. [PubMed: 9246799]
- Project MATCH Research Group. Matching alcohol treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol*. 1997; 58:7–29. [PubMed: 8979210]
- Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcohol Clin Exp Res*. 1998; 22:1300–1311. [PubMed: 9756046]
- Roache JD, Kahn R, Newton TF, Wallace CL, Murff WL, De La Garza R 2nd, Rivera O, Anderson A, Mojsiak J, Elkashef A. A double-blind, placebo-controlled assessment of the safety of potential interactions between intravenous cocaine, ethanol, and oral disulfiram. *Drug Alcohol Depend*. 2011; 119:37–45. [PubMed: 21696894]
- Rychtarik RG, Connors GJ, Derman KH, Stasiewicz PR. Alcoholics Anonymous and the use of medications to prevent relapse: an anonymous survey of member attitudes. *J Stud Alcohol*. 2000; 61:134–138. [PubMed: 10627107]
- Santa Ana E, Martino S, Ball SA, Nich C, Carroll KM. What is usual about 'treatment as usual': audiotaped ratings of standard treatment in the Clinical Trials Network. *J Subst Abuse Treat*. 2008; 35:369–379. [PubMed: 18337053]
- Schmitz JM, Bordnick PS, Kearney ML, Fuller SM, Breckenridge JK. Treatment outcome of cocaine-alcohol dependent outpatients. *Drug Alcohol Depend*. 1997; 25:55–61. [PubMed: 9279498]
- Schroeder JP, Cooper DA, Schank JR, Lyle MA, Gaval-Cruz M, Ogbonmwan YE, Pozdeyev N, Freeman KG, Iuvone PM, Edwards GL, Holmes PV, Weinshenker D. Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine beta-hydroxylase. *Neuropsychopharm*. 2010; 35:2440–2449.
- Schroeder JP, Cooper DA, Schank JR, Lyle MA, Gaval-Cruz M, Ogbonmwan YE, Pozdeyev N, Freeman KG, Iuvone PM, Edwards GL, Holmes PV, Weinshenker D. Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine beta-hydroxylase. *Neuropsychopharm*. 2011; 35:2440–2449.
- Singer, JD.; Willett, JB. *Applying Longitudinal Data Analysis: Modeling Change and Event Occurrence*. Oxford University Press; New York: 2003.
- Stout RL, Wirtz PW, Carbonari JP, DelBoca FK. Ensuring balanced distribution of prognostic factors in treatment outcome research. *J Stud Alcohol Suppl*. 1994; 12:70–75. [PubMed: 7723001]
- Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. *J Clin Psychopharmacol*. 2006; 26:290–302. [PubMed: 16702894]
- Swift RM, Duncan D, Nirenberg TD, Femino J. Alcoholic patients' experience and attitudes on pharmacotherapy for alcoholism. *J Addict Dis*. 1998; 17:35–47. [PubMed: 9789158]
- Timko C, DeBenedetti A, Billow R. Intensive referral to 12-Step groups and 6-month substance use disorder outcomes. *Addiction*. 2006; 101:678–688. [PubMed: 16669901]
- Tonigan JS, Connors GJ, Miller WR. Alcoholics Anonymous Involvement (AAI) Scale: reliability and norms. *Psychol Addict Behav*. 1996a; 10:75–80.
- Tonigan JS, Toscova R, Miller WR. Meta-analysis of the literature on Alcoholics Anonymous: sample and study characteristics that moderate findings. *J Stud Alcohol*. 1996b; 57:65–72. [PubMed: 8747503]

- Vocci FJ, Acri J, Elkashef A. Medication development for addictive disorders: the state of the science. *Am J Psychiatry*. 2005; 162:1432–1440. [PubMed: 16055764]
- Weiss RD, Griffin ML, Gallop R, Onken LS, Gastfriend DR, Daley D, Crits-Christoph P, Bishop S, Barber JP. Self-help group attendance and participation among cocaine dependent patients. *Drug Alcohol Depend*. 2000; 60:169–177. [PubMed: 10940544]
- Weiss RD, Griffin ML, Gallop RJ, Najavits LM, Frank A, Crits-Christoph P, Thase ME, Blaine JD, Gastfriend DR, Daley DC, Luborsky L. The effect of 12-step self-help group attendance and participation on drug use outcomes among cocaine-dependent patients. *Drug Alcohol Depend*. 2005; 77:177–184. [PubMed: 15664719]
- Zanis DA, McLellan AT, Randall M. Can you trust patient self-reports of drug use during treatment? *Drug Alcohol Depend*. 1994; 35:127–132. [PubMed: 8055734]

Figure 1. CONSORT diagram
Flow of Participants through protocol

Figure 2.

Days of cocaine use per month over time, within treatment (months 1–3) and through follow-up (months 3–15). Effects are estimates from random regression analyses.

Table 1

Baseline demographic, psychiatric, and substance use characteristics by treatment group, N=112

Variable	DIS/TSF (29)	DIS/NO TSF (30)	PLA/TSF (27)	PLA/NO TSF (26)	TOTAL (112)	F or X ²	p-value
Number (percent) female	9 (31.0)	11 (36.7)	15 (55.6)	11 (42.3)	46 (41.1)	3.80	0.28
Race, number (%)							
Caucasian	18 (62.1)	20 (66.7)	18 (66.7)	16 (61.5)	72 (64.3)	.720	0.99
African-American	7 (24.1)	7 (23.3)	5 (18.5)	6 (23.1)	25 (22.3)		
Hispanic	4 (13.8)	3 (10.0)	4 (14.8)	4 (15.4)	15 (13.4)		
Number (%) Completed High School	24 (82.8)	24 (80)	23 (85.2)	22 (84.6)	93 (83)	.332	0.95
Number (%) Never Married/Living Alone	18 (62.1)	21 (70)	18 (66.7)	16 (61.5)	73 (65.2)	.609	0.89
Number (%) Unemployed	10 (34.5)	15 (50)	13 (48.1)	13 (50)	51 (45.5)	1.95	0.58
Number (%) Alcohol use disorder - Lifetime	18 (62.1)	23 (76.7)	16 (59.3)	13 (50)	70 (62.5)	4.43	0.22
Number (%) affective disorder - Lifetime	10 (34.5)	15 (50)	7 (25.9)	7 (26.9)	39 (34.8)	4.70	0.20
Number (%) anxiety disorder	1 (3.4)	9 (30)	5 (18.5)	4 (15.4)	19 (17)	7.47	0.06
Age, mean + SD	38.9 + 7.2	37.4 + 7.3	37.6 + 7.4	39.4 + 8.6	38.3 + 7.5	.457	0.71
Months in current methadone program	13.3 + 10.2	11.1 + 13.5	21.5 + 21.6	13.9 + 22.8	14.8 + 17.8	1.84	0.15
Days of alcohol use, 28 prior to baseline, mean + SD	4.8 + 8.4	6.03 + 9.0	2.5 + 4.3	4.8 + 7.8	4.6 + 7.7	1.02	0.39
Days of opioid use, past 28	2.1 + 3.8	1.7 + 2.6	1.8 + 5.3	2.4 + 4.9	2.0 + 4.2	0.15	0.93
Days cocaine use, past 28	14.5 + 9.5	16.7 + 8.5	14.0 + 9.3	16.1 + 8.2	15.4 + 8.9	0.58	0.63
Years of regular alcohol use, mean + SD	8.6 + 8.9	7.8 + 9.4	5.9 + 7.6	5.5 + 8.2	7.0 + 8.6	0.83	0.48
Years of regular opioid use	6.8 + 5.4	8.9 + 7.6	5.6 + 5.5	9.3 + 9.4	7.6 + 7.2	1.65	0.18
Years of regular cocaine use	4.3 + 3.7	5.8 + 6.3	4.1 + 3.9	4.8 + 5.1	4.8 + 4.9	0.71	0.55
Number of previous treatment episodes for substance use, mean + SD)	9.5 + 7.7	9.8 + 9.4	7.8 + 8.4	13.4 + 17.7	10.1 + 11.3	1.12	0.35
Total number of months incarcerated, lifetime (mean + SD)	16.6 + 24.5	26.6 + 45.1	14.3 + 21.9	23.9 + 35.1	20.5 + 33.2	.87	0.46

Note. DIS=disulfiram 250 mg/day. TSF=Weekly individual manual guided Twelve Step Facilitation Treatment. PLA=Placebo

Table 2

Cocaine and alcohol use by treatment condition

Variable	DIS/TSF		DIS/NO TSF		PLA/TSF		PLA/NO TSF		TOTAL		TSF		DIS		TSF by DIS	
	Mean	sd	Mean	sd	mean	sd	mean	sd	mean	sd	F	p	F	p	F	p
Days retained in treatment	63.2	31.5	72.1	25.9	67.1	29.7	76.6	17.11	69.6	26.9	3	108	3.27	.07	0.68	.40
Percent of 84 day span abstinent																
Cocaine	68.3	22.9	60.3	22.7	73.4	23.1	54.3	22.3	63.9	23.6	3	105	9.49	.00	0.01	.92
Alcohol	96.1	19.2	98.2	3.7	99.4	1.1	99.6	0.65	98.3	9.7	3	105	0.38	.54	1.57	.21
% cocaine-positive urine specimens	74.9	25.9	78.7	24.8	71.8	32.1	81.0	23.5	76.7	26.5	3	101	1.57	.21	0.01	.95
% cocaine positive urine specimens, Outliers removed	74.9	25.9	84.2	14.7	71.8	32.1	86.1	15.9	76.7	26.5	3	97	6.5	.01	0.02	.90
% completing treatment and abstinent at end of treatment	29.6		39.3		26.9		26.9		30.8		1		.56	.45	.83	.26

Note. DIS=disulfiram 250 mg/day. TSF=Weekly individual manual guided Twelve Step Facilitation Treatment. PLA=Placebo Contrast 1 = main effect, for TSF vs no TSF main effect. Contrast 2= DIS versus placebo main effect. TSF by DIS refers to interaction of TSF and DIS combination versus either treatment alone.