

RESEARCH REPORT

Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram

KATHLEEN M. CARROLL, CHARLA NICH, SAMUEL A. BALL, ELINORE McCANCE & BRUCE J. ROUNSAVILLE

Division of Substance Abuse, Yale University School of Medicine, Connecticut, USA

Abstract

Aims. To evaluate disulfiram and three forms of manual guided psychotherapy for individuals with cocaine dependence and concurrent alcohol abuse or dependence. **Design.** Randomized controlled trial. **Setting.** Urban substance abuse treatment center. **Participants.** One hundred and twenty-two cocaine/alcohol abusers (27% female; 61% African-American or Hispanic). **Interventions.** One of five treatments delivered over 12 weeks: cognitive behavioral treatment (CBT) plus disulfiram; Twelve Step facilitation (TSF) plus disulfiram; clinical management (CM) plus disulfiram; CBT plus no medication; TSF plus no medication. **Measurements.** Duration of continuous abstinence from cocaine or alcohol; frequency and quantity of cocaine and alcohol use by week, verified by urine toxicology and breathalyzer screens. **Findings.** Disulfiram treatment was associated with significantly better retention in treatment, as well as longer duration of abstinence from alcohol and cocaine use. The two active psychotherapies (CBT and TSF) were associated with reduced cocaine use over time compared with supportive psychotherapy (CM). Cocaine and alcohol use were strongly related throughout treatment, particularly for subjects treated with disulfiram. **Conclusions.** For the large proportion of cocaine-dependent individuals who also abuse alcohol, disulfiram combined with outpatient psychotherapy may be a promising treatment strategy. This study underlines (a) the significance of alcohol use among treatment-seeking cocaine abusers, (b) the promise of the strategy of treating co-morbid disorders among drug-dependent individuals, and (c) the importance of combining psychotherapy and pharmacotherapy in the treatment of drug use disorders.

Introduction

Currently, there is no treatment that has been demonstrated to be broadly effective in general populations of cocaine-dependent individuals.^{1,2} While some behavioral therapies have been shown to be effective,^{3,4} and some pharmacotherapies have shown promise,^{1,5} there are currently no medications of established effectiveness for the treatment of cocaine dependence.

Treatment of a co-morbid disorder that is thought to play a role in the etiology or perpetuation of a principal disorder has been proposed as a promising strategy in the treatment of substance dependence disorders. Examples include antidepressant treatment in depressed alcohol-⁶ cocaine-⁷ and opioid-dependent populations,⁸ and anxiolytic treatment of alcoholics with anxiety disorders.⁹ However, pharmacological treat-

Correspondence to: Kathleen M. Carroll, PhD, Division of Substance Abuse 34 Park Street/SAC 208, New Haven, CT 06519, USA. Tel: +1(203) 789-7080 ext. 336.

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ment of a co-morbid substance dependence disorder has not been evaluated as a strategy to treat another, co-occurring substance use disorder.

Concurrent alcohol dependence is a significant problem among the majority of cocaine-dependent individuals in both community and clinical samples. Regier and colleagues¹⁰ reported that 85% of subjects in the Epidemiologic Catchment Area (ECA) study who met criteria for cocaine dependence also met criteria for alcohol abuse or dependence. In a sample of 298 treatment-seeking cocaine abusers, 62% had a life-time history of alcohol dependence.¹¹ Co-morbid alcohol-cocaine dependence has been associated with more severe dependence, poorer retention in treatment and poorer outcome with respect to either disorder alone.¹²⁻¹⁴

Several factors may support a strong relationship between alcohol and cocaine dependence. First, alcohol may be used by cocaine users to attenuate negative acute effects of cocaine or cocaine withdrawal symptoms.¹⁵ Secondly, once regular cocaine and alcohol use is established, it may be difficult to abstain from one substance without renouncing the other. In particular, alcohol may become a powerful conditioned cue for cocaine use through repeated pairings with cocaine. Similarly, alcohol's disinhibiting effects may impair users' judgement and control over cocaine use. Thirdly, Jatlow and colleagues¹⁶ have identified cocaethylene, a centrally active metabolite of cocaine and alcohol, which may enhance and extend cocaine euphoria.^{17,18} Potentiation of cocaine euphoria through alcohol use may increase cocaine users' vulnerability to secondary alcohol dependence.

In a pilot trial with 18 ambulatory cocaine-dependent individuals who also met criteria for alcohol abuse or dependence,¹⁹ we found that, compared with naltrexone, disulfiram treatment resulted in significantly fewer days of alcohol and cocaine use and longer sustained periods of abstinence from both alcohol and cocaine. The rationale for disulfiram was several-fold: first, reducing alcohol use through pharmacotherapy may reduce exposure to a powerful conditioned cue for cocaine use, as well as alcohol-related disinhibition and impairment of judgement that could lead to cocaine use; secondly, reduced alcohol use may reduce cocaethylene effects and thus perceived reduction of reinforcing aspects of cocaine;²⁰ thirdly, disulfiram may have a direct

effect on cocaine use by accentuating negative stimulant effects of cocaine.^{21,22} However, that pilot study,¹⁹ while consistent with other reports from uncontrolled studies,²³ suggesting the effectiveness of disulfiram among cocaine abusers, was limited by the small sample size and a pharmacological comparison group of unknown efficacy with this population (naltrexone).

Regarding the effectiveness of psychotherapy, our previous work with cocaine-dependent populations has suggested that cognitive-behavioral treatment may be more effective with more severely dependent cocaine users²⁴ and is associated with continued reductions of cocaine use after the treatment termination, compared with supportive clinical management.⁴ While cognitive-behavioral treatments have comparatively high levels of empirical support for substance use disorders,^{1,25} traditional, disease model treatments are much more broadly used in clinical settings, despite their weaker level of empirical support. One randomized trial of group therapies reported no significant main effects in a comparison of a traditional, Twelve-Step orientated treatment with respect to cognitive-behavioral relapse prevention for cocaine dependence,²⁶ but the lack of a control group complicated the interpretation of the magnitude of treatment effects.

In this report we present results from a randomized clinical trial evaluating five treatments for ambulatory cocaine-dependent individuals with comorbid alcohol abuse or dependence: (1) disulfiram in combination with cognitive-behavioral treatment (CBT), (2) disulfiram in combination with Twelve-Step facilitation (TSF), a disease-model approach, (3) disulfiram in combination with clinical management (CM), a psychotherapy control condition, (4) CBT alone and (5) TSF alone. We chose a no-medication over a placebo control condition because we hypothesized that disulfiram would exert effects primarily through patient expectations of the unpleasant disulfiram-ethanol reaction, and thus a placebo condition would not be an appropriate control for expectation effects.³⁰ We hypothesized that, first, disulfiram would be more effective than no medication in reducing alcohol and cocaine use. Secondly, CBT and TSF would be more effective in reducing both cocaine and alcohol use than the control condition, CM. Thirdly, reductions of alcohol use would be associated with reductions in cocaine use.

Methods

Subjects

Subjects were recruited from individuals seeking treatment at the Central Treatment Unit of the APT Foundation, a non-profit substance abuse treatment center affiliated with Yale University in New Haven, Connecticut, or from respondents to newspaper advertisements or public service announcements. Subjects were included who met DSM-III-R criteria for current cocaine dependence and for alcohol dependence or abuse. Individuals were excluded who (1) were currently physically dependent on opiates or barbiturates, or whose principal drug of dependence was not cocaine, (2) met life-time DSM-III-R criteria for a psychotic or bipolar disorder, or expressed significant suicidal or homicidal ideation, (3) had a current medical condition which would contraindicate use of disulfiram, (4) had been treated for substance use during the previous 2 months or who were currently involved in psychotherapy or pharmacotherapy for any other psychiatric disorder, or (5) had conditions of probation or parole requiring reports of drug use to officers of the court (and hence undercut the validity of self-reports of substance use).

Patients who cleared initial screening were administered sections of the Structured Clinical Interview for DSM-III-R (SCID)²⁷ to rule out major psychiatric disorder. Urinalyses and blood laboratory work were conducted for medical clearance. One hundred and twenty-two of the 187 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, medical, or psychiatric evaluation ($n = 25$), (2) insufficient current alcohol or cocaine use to meet abuse/dependence criteria ($n = 15$), (3) a medical condition that contraindicated disulfiram treatment ($n = 12$), (4) recent inpatient treatment ($n = 7$), (5) unwillingness to take disulfiram ($n = 2$), (6) inability to read or understand English ($n = 2$) and (6) psychiatric exclusion ($n = 2$).

Therapists

The 12 therapists (nine males, three females) who delivered study treatments were experienced in and committed to the type of treatment they delivered in the trial (four doctoral-level psychologists conducted CBT, two masters' level clini-

cians conducted TSF, and six psychiatrists conducted CM) and in treating substance users. Therapists averaged 7.9 years (SD 4.0) of experience and saw an average of 17.7 subjects in the trial. All therapists received training which included (1) a 2 day didactic seminar in which the treatment manual, study aims and procedures and videotaped case examples were reviewed, and (2) completion of at least one closely supervised training case. To promote adherence to manual guidelines, therapists in each condition met regularly with supervisors to discuss case material and review session videotapes.

To evaluate the potential influence of therapist effects²⁸ on findings reported herein, we conducted a one-way analysis of variance on continuous measures of treatment retention, cocaine use, alcohol use and disulfiram compliance. No significant effects for therapist were found for any of these variables, even using liberal (0.20) p values. This suggests that results presented below were not strongly influenced by the unique characteristics of the therapists participating in this trial and would generalize to other groups of therapists with similar backgrounds and training using the treatment manuals and methods presented here.

Treatments

Each of the study treatments was manual-guided and delivered to patients in weekly individual sessions offered over 12 weeks. Sessions were offered twice weekly for the first month and weekly thereafter. Subjects also met weekly with an independent clinical evaluator who collected urine specimens, assessed cocaine and alcohol use and monitored other clinical symptoms. To maintain a single blind, procedures found to be comparable in effectiveness to standard medication blinding procedures were used,²⁹ where the clinical evaluator saw patients in an office physically separated from the offices in which therapy was conducted and instructed patients not to disclose details of their therapist or treatment.

Disulfiram

Subjects assigned to disulfiram initiated medication with 250 mg of disulfiram, with a maximum dose of 500 mg/day and a modal dose of

261.5 mg. Dosage adjustments were made by a study psychiatrist in response to reported side effects and intensity of disulfiram reactions for subjects who reported drinking. The study nurse monitored disulfiram ingestion twice weekly for the first month of treatment and weekly thereafter. Medication compliance was monitored via a riboflavin compliance procedure used in previous large-scale studies.^{30,31} Overall, subjects reported taking the medication as prescribed 66.8% of treatment weeks. Riboflavin markers matched self-reported compliance for 88.2% of specimen, with only 7.6% of 327 urines tested negative for riboflavin when the patient reported taking medication. Medication compliance was not significantly different across psychotherapy conditions (CBT mean 63.3%, TSF mean 65.4%, CM mean 72.1%, $F = 0.75$, NS).

Cognitive-behavioral coping skills training (CBT)

The cognitive-behavioral treatment was based on Marlatt's³² relapse prevention model, adapted for use with cocaine users.³³ The goal of this treatment was abstinence from cocaine, alcohol and other substances through identification of high risk situations for substance use and the implementation of effective coping strategies. As described in the manual, skill training covered: (1) reducing exposure to cocaine and alcohol cues, (2) fostering resolution to stop both cocaine and alcohol use through exploring positive and negative consequences of continued use, (3) self-monitoring to identify high risk situations, (4) recognition of conditioned craving and development of strategies for coping with craving, (5) identification of seemingly irrelevant decisions which could culminate in high risk situations, (6) preparation for emergencies and coping with a relapse to substance use, and (7) identifying and confronting thoughts about alcohol and cocaine. Material discussed during sessions was supplemented with extra-session tasks intended to foster practice of coping skills.

Twelve-Step facilitation (TSF)

This treatment³⁴ was adapted from that used in Project MATCH³⁵ and is grounded in the concept of substance dependence as a spiritual and medical disease. While this treatment is not Alcoholics Anonymous, its content is intended to be consistent with the Twelve Steps of Alco-

holics Anonymous (AA), with primary emphasis given to Steps 1–5, and with treatment programs that emphasize a disease model. Beyond abstinence from all psychoactive substances, a major goal of the treatment is to foster active participation in self-help groups. Patients are actively encouraged to attend AA or Cocaine Anonymous meetings, become involved in traditional fellowship activities, and maintain journals of their self-help group attendance and participation.

Clinical management (CM)

Clinical management was adapted for use with cocaine dependent individuals²⁴ from the guidelines developed by Fawcett and colleagues.³⁶ The provision of clinical management was intended (1) to provide non-specific, common factors of a psychotherapeutic relationship, including a supportive doctor-patient relationship, education, empathy and the instillation of hope, without providing active ingredients specific to CBT or TSF, (2) to provide medication management as well as opportunity to monitor patients' clinical status and treatment response, and (3) to provide a convincing therapeutic rationale and so foster greater retention in the protocol and compliance with medication. These features, although desirable in a psychotherapy control condition because they address many ethical and methodological concerns, may be powerfully therapeutic on their own and thus also act as much more stringent tests of active psychotherapies than would alternatives such as no-treatment or waiting list control conditions, which would provide neither non-specific elements nor a persuasive therapeutic rationale.

Treatment implementation

All training and main phase sessions were videotaped for supervision and process assessment. To evaluate discriminability of the three forms of psychotherapy, session videotapes were rated by blind evaluators using a modification of the NIMH Collaborative Study Psychotherapy Rating Scale³⁷ which assesses therapists' delivery of interventions characteristic of the three treatments evaluated here. Preliminary analyses of 742 sessions, with each session rated by raters who were blind to treatment condition, showed:

(1) CBT therapists were significantly more likely to engage in CBT interventions than TSF or CM therapists, (2) TSF therapists were significantly more likely to engage in TSF interventions than CBT or CM therapists, and (3) CM therapists were significantly more likely to engage in CM interventions than TSF or CBT therapists.

Other treatment process indicators suggested that psychotherapies were implemented as specified in the respective treatment manuals. For example, a critical component of the TSF treatment was promoting patients' involvement with self-help groups. Self-help involvement during treatment was significantly higher for patients assigned to TSF (13.8 days mean days of self-help group attendance) with respect to those assigned to CBT (1.1 days, $F = 11.8$, $p < 0.001$) or patients assigned to CM (5.4 days; $F = 5.2$, $p < 0.05$). Similarly, comparison of pre-treatment to post-treatment scores on an adaptation of the Situational Competency Test³⁸ for use with cocaine users indicated that subjects assigned to CBT had a significantly larger increase in proportion of responses suggesting acquisition of cognitive-behavioral coping skills (psychotherapy by time effect, $F = 4.76$, $p = 0.14$) than subjects assigned to TSF or CM.

Outcome assessment

Patients were assessed before treatment, weekly during treatment, and at termination by an independent clinical evaluator. Primary outcome measures were duration of periods of abstinence from cocaine, alcohol and both substances simultaneously, frequency of cocaine use (number of days per week the subject reported using cocaine while in treatment), quantity of cocaine use (grams per week), frequency of alcohol use (number of days subjects reported at least one standard drink per week), and quantity of alcohol use (number of standard drinks per week).

Patient self-reports of cocaine were verified through urine toxicology screens which were obtained at every visit. Of 683 urine specimens collected, 81.4% were consistent with patient self-report, 4.7% were negative for cocaine although the patient reported recent cocaine use, and 13.8% were positive for cocaine in cases where the patient had denied use. This rate is consistent with previous studies of outpatient

cocaine-dependent samples^{24,39} and suggests that self-reported substance use was, for the most part, valid in this study. In cases of discrepancy between self- and toxicology reports, the source of data which indicated cocaine use was used in outcome analyses. Self-reports of alcohol use were verified by breathalyzer, also conducted at every visit. Of 686 breathalyzer samples collected, 96.3% were negative for alcohol use, and only two patients ever had levels above 0.01.

Data analyses

The principal analyses for effects of study treatments were (1) χ^2 and survival analyses for dichotomous outcome variables, (2) analysis of variance for continuous summary variables, such as weeks in treatment and duration of abstinence and (3) random effects regression models^{40,41} for continuous outcome variables which were measured across time (cocaine and alcohol use by treatment week), using MIXREG software⁴² (random-intercepts model). The primary contrasts were: (1) medication (disulfiram versus no medication), (2) active psychotherapy versus psychotherapy control (CBT and TSF versus CM), (3) active psychotherapy type (CBT versus TSF) and (4) psychotherapy/pharmacotherapy interaction (interaction of medication and psychotherapy type (CBT versus TSF)). Because there was no control condition for the CM/disulfiram treatment, no interaction term for active psychotherapy versus control by medication was necessary.

Outcome analyses were conducted on the following samples: the 122 subjects randomized to treatment (intention to treat sample), the 117 subjects who initiated treatment (treatment exposed), and the 39 subjects who completed the full 12-week course of treatment and who were determined to be fully compliant with medication (compliant treatment completers). Unless otherwise noted, results are consistent across analysis samples, and only results from the treatment exposed analyses are presented here.

Results

Sample description

Of the 122 subjects randomized to treatment, 27% were female, 39% were white, 59% were single or divorced, and 43% were working full-

or part-time. Twenty-three per cent had some college education, 47% had a high school education only and 30% did not complete high school. The mean age of the sample was 30.8 years (SD 5.5). Mean cocaine use at baseline was 4.0 of cocaine per week (SD 5.1) and subjects reported using cocaine a mean of 14.1 days (SD 8.1) of the past 30 days. Mean alcohol use was reported at 11.6 standard drinks (SDU) per drinking occasion (SD 8.1) and subjects reported drinking a mean of 17.2 days of the past 30 days. Subjects reported an average of 7.5 years (SD 4.4) of cocaine dependence and 7.3 years of alcohol abuse (SD 6.2). Seventy-seven per cent reported predominantly freebase use of cocaine, 20% were intranasal users, and 3% were i.v. users. Fifty-three per cent had some previous exposure to treatment. All subjects met current DSM-III-R criteria for cocaine dependence, 85% for alcohol dependence and 15% met criteria for alcohol abuse. Regarding non-substance psychiatric disorders, 20% met criteria for a lifetime affective disorder, 8% met criteria for a life-time anxiety disorder, 53% met criteria for antisocial personality disorder and 51% for any other Axis II disorder. Analyses of variance and χ^2 tests revealed there was a statistically significant difference between psychotherapy groups for baseline frequency of alcohol use ($F = 4.92, p = 0.009$), and lower baseline cocaine use for subjects assigned to disulfiram versus no medication (2.9 versus 4.6 g/week, $F = 4.3, p < 0.05$), but no other statistically significant differences by treatment group for any other baseline variables (Table 1).

Attrition

Of the 122 subjects randomized, 117 (96%) initiated treatment. The mean number of sessions completed was 7.5 (SD 4.7). Eight subjects were removed from the protocol, one because of failure to comply with medication for 2 or more weeks, one because of medication side effects (a rash), four due to clinical deterioration and two received administrative discharges. The remainder of early terminators were due to dropouts. Subjects who remained in treatment the full 12 weeks/16 sessions ($n = 39$) did not differ from those who did not start treatment or dropped out ($n = 83$) in terms of gender, race, employment status, route of administration, presence of life-

time affective, anxiety or antisocial personality disorder, but those who met criteria for a non-ASP Axis II disorder were significantly more likely to complete treatment than those who did not (48.1% versus 23.1%, $\chi^2 = 7.6, p < 0.01$).

The CBT/disulfiram group had the highest rate of retention (mean 8.8 weeks), followed by CM/disulfiram (8.4 weeks), TSF/disulfiram (8.0), CBT/no medication (6.3) and TSF/no medication (5.3). By medication condition, subjects assigned to disulfiram treatment were retained significantly longer than those assigned to no medication (8.4 versus 5.8 weeks, $F = 8.7, p < 0.05$). No significant differences in retention by psychotherapy were found.

Outcome analyses

Duration of abstinence from cocaine and alcohol. As shown in Table 2, there was a significant effect for disulfiram on consecutive weeks of cocaine abstinence ($F = 7.67, p < 0.05$), consecutive weeks of alcohol abstinence ($F = 14.38, p < 0.001$) and weeks of consecutive abstinence from both cocaine and alcohol ($F = 9.49, p < 0.01$). Effect sizes (d) for disulfiram compared with no medication on duration of abstinence from cocaine, alcohol and both were, respectively, 0.42, 0.68 and 0.46. In addition, compared with the control condition (CM), the two active psychotherapies (CBT and TSF), were associated with significantly longer periods of abstinence from cocaine ($F = 3.80, p = 0.05$) and simultaneous abstinence from both cocaine and alcohol ($F = 4.02, p = 0.04$). Effect sizes for the active psychotherapies compared with CM on duration of abstinence were 0.16 for cocaine, 0.11 for alcohol and 0.18 for both cocaine and alcohol. Neither the comparison of the two active psychotherapies (CBT versus TSF) nor the medication/psychotherapy interaction were significant for these variables.

Rates of subjects who were abstinent from cocaine for 3 or more consecutive weeks during treatment, which has been found to be associated with better outcome at follow-up,⁴ were 58% (CBT/disulfiram), 52% (TSF/disulfiram), 30% (CM/disulfiram), 30% TSF/no medication) and 28% (CBT/no medication) (medication, $\chi^2 = 3.12, p = 0.07$). Rates of subjects who were abstinent from alcohol for 3 or more consecutive weeks were 60% (TSF/disulfiram), 54% (CBT/disulfiram), 48% (CM/disulfiram), 22% (TSF/

Table 1. Pre-treatment characteristics of all subjects randomized (N = 122)*

Characteristic	Treatment group**					Total N = 122
	TSF n = 25	CBT n = 19	CM + disulfiram n = 27	TSF + disulfiram n = 25	CBT + disulfiram n = 26	
Demographic						
Female, % (n)	32 (8)	32 (6)	26 (7)	20 (5)	27 (7)	27 (33)
Race						
White	40 (10)	32 (6)	52 (14)	36 (9)	35 (9)	39 (48)
African-American	56 (14)	63 (12)	48 (13)	64 (16)	50 (13)	56 (68)
Hispanic	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)	3 (4)
Other	4 (1)	0 (0)	0 (0)	0 (0)	4 (1)	2 (2)
Married/cohabitating	42 (10)	32 (6)	52 (14)	36 (9)	42 (11)	41 (50)
Unemployed	76 (19)	53 (10)	33 (9)	65 (16)	62 (16)	57 (70)
Less than high school	40 (10)	32 (6)	30 (8)	24 (6)	27 (7)	30 (37)
Age	31.2 ± 4.8	30.0 ± 5.6	31.7 ± 5.4	30.9 ± 6.6	30.0 ± 5.1	30.0 ± 5.5
Baseline substance use						
Ave. weekly cocaine use/past month (g)	5.4 ± 8.6	5.6 ± 6.2	3.2 ± 3.0	3.3 ± 2.9	3.0 ± 2.4	4.0 ± 5.1
Days of cocaine use/past 30	12.7 ± 8.0	15.6 ± 6.5	16.2 ± 8.7	12.6 ± 8.9	13.7 ± 8.6	14.1 ± 8.3
Grams of cocaine per week/last 30 days	4.6 ± 6.6	5.0 ± 5.1	2.9 ± 2.6	3.1 ± 2.8	2.6 ± 2.1	3.6 ± 4.1
Average drinks per drinking day/past 30	10.2 ± 5.7	10.6 ± 8.0	11.4 ± 8.8	12.6 ± 10.0	13.0 ± 7.5	11.6 ± 8.2
Days of alcohol use/past 30	12.3 ± 8.0	18.5 ± 7.6	19.6 ± 8.0	16.3 ± 8.0	18.8 ± 7.7	17.2 ± 7.9
Years of cocaine use—life-time	7.5 ± 3.9	5.8 ± 3.1	8.9 ± 4.6	7.1 ± 5.1	7.4 ± 4.8	7.5 ± 4.4
Years of alcohol misuse—life-time	7.1 ± 6.3	7.3 ± 6.4	6.3 ± 5.0	8.1 ± 7.3	7.5 ± 5.9	7.3 ± 6.2
Primary route of administration						
Nasal	20 (5)	11 (2)	19 (5)	8 (2)	39 (10)	20 (24)
Smoking	72 (18)	84 (16)	82 (22)	88 (22)	62 (16)	77 (94)
Intravenous	8 (2)	5 (1)	0 (0)	4 (1)	0 (0)	3 (4)
Previous treatment for alcohol	36 (9)	32 (6)	19 (5)	48 (12)	23 (6)	31 (38)
Previous treatment for drugs	72 (18)	58 (11)	33 (9)	56 (14)	27 (7)	48 (59)
Life-time psychiatric disorders (from SCID interviews)						
Any affective disorder	24 (4)	33 (6)	17 (4)	17 (4)	13 (3)	20 (21)
Any anxiety disorder	24 (4)	6 (1)	0 (0)	4 (1)	8 (2)	8 (8)
Antisocial personality disorder	42 (5)	46 (5)	62 (8)	35 (6)	41 (7)	44 (31)
Any non-ASP personality disorder	35 (6)	50 (9)	42 (10)	58 (14)	63 (15)	51 (54)
Addiction Severity Index composite scores (range is 0–1, higher scores indicate higher severity)						
Medical	0.15 ± 0.26	0.19 ± 0.29	0.19 ± 0.28	0.13 ± 0.25	0.11 ± 0.25	0.15 ± 0.27
Employment	0.71 ± 0.28	0.67 ± 0.32	0.55 ± 0.32	0.70 ± 0.25	0.58 ± 0.27	0.64 ± 0.29
Legal	0.09 ± 0.18	0.09 ± 0.17	0.07 ± 0.12	0.14 ± 0.22	0.06 ± 0.17	0.09 ± 0.17
Family/social	0.21 ± 0.15	0.12 ± 0.15	0.20 ± 0.22	0.22 ± 0.24	0.15 ± 0.13	0.18 ± 0.18
Psychological	0.26 ± 0.17	0.16 ± 0.19	0.19 ± 0.20	0.22 ± 0.21	0.23 ± 0.24	0.21 ± 0.21
Alcohol	0.30 ± 0.19	0.40 ± 0.20	0.36 ± 0.14	0.39 ± 0.15	0.39 ± 0.16	0.37 ± 0.17
Cocaine	0.58 ± 0.24	0.58 ± 0.18	0.65 ± 0.22	0.59 ± 0.18	0.59 ± 0.17	0.60 ± 0.20
Other drugs	0.06 ± 0.06	0.07 ± 0.05	0.07 ± 0.07	0.05 ± 0.04	0.06 ± 0.07	0.06 ± 0.07

*Values are reported as mean ± SD or percentage (number). **TSF = Twelve-Step facilitation, CBT = cognitive behavioral therapy, CM = clinical management.

no medication) and 11% (CBT/no medication) (medication $\chi^2 = 14.96, p = 0.001$). Rates of subjects who were simultaneously abstinent from both alcohol and cocaine for 3 or more consecutive weeks were 48% (TSF/disulfiram), 46% (CBT/disulfiram), 22% (CM/disulfiram), 22% (TSF/no medication) and 6% (CBT/no medication) (medication $\chi^2 = 7.0, p = 0.008$). Survival curves representing the week in which 3 consecutive weeks of abstinence was initiated show similar effects and are presented in Fig. 1.

Results of analyses on urine toxicology screens also supported the effectiveness of disulfiram as well as the two active psychotherapies. Subjects treated with disulfiram had a significantly higher percentage of cocaine-free urines than subjects not on medication (52% versus 39%, $F = 6.88, p = 0.01, d = 0.30$). Subjects assigned to CBT or TSF also had significantly higher percentages of cocaine-negative urines compared with CM (50% versus 37%, $F = 8.93, p = 0.003, d = 0.34$).

Random regression analyses

The analyses presented above suggest greater effectiveness of disulfiram and the two active psychotherapies (CBT and TSF) in terms of rates of patients remaining in treatment and achieving significant periods of abstinence. However, such analyses, while pointing to clinically significant differences in cocaine and alcohol outcomes, are confounded by differences among the treatments in retention. To provide a fuller picture of how the treatments might be exerting their effects, random regression analyses were conducted for the continuous outcome variables (frequency and quantity of use, by week). The effect for time was significant for both cocaine and alcohol use, indicating a general reduction across treatment in use of both substances (cocaine frequency by time: $z = -8.43, p < 0.001$; alcohol frequency by time $z = -7.48, p < 0.001$). For the treatment-exposed sample, the active versus control psychotherapy by time effect was significant for quantity of cocaine use ($z = -1.92, p < 0.05$), and approached statistical significance for frequency of cocaine use over time ($z = -1.75, p = 0.08$), suggesting that subjects assigned to either CBT or TSF reduced their intensity of cocaine use more than subjects assigned to CM. For this sample, effects of active psychotherapy compared with CM by time were

significant for both quantity ($z = -2.06, p < 0.04$) and frequency of cocaine use ($z = -2.02, p = 0.04$). Neither the medication, active psychotherapy (CBT versus TSF) nor the medication-psychotherapy interaction effects were significant for cocaine quantity or frequency variables.

For the alcohol outcomes, the medication effect was significant for both quantity ($z = -1.98, p < 0.05$) and frequency ($z = -2.20, p < 0.05$) of alcohol use. No other psychotherapy effects (CBT/TSF versus CM; CBT versus TSF) nor the psychotherapy-medication interaction effects were significant for continuous alcohol outcomes. These analyses suggest that, over time, the active psychotherapies were more effective than the control psychotherapy in reducing cocaine use and that disulfiram treatment was more effective than no medication in reducing alcohol use.

Relationship between alcohol and cocaine use

Cocaine and alcohol use were strongly associated throughout treatment. Simple correlations of days of cocaine and days of alcohol use was 0.43 at pre-treatment, 0.45 at week 4, 0.40 at week 8 and 0.51 at week 12 (all significant at $p < 0.01$). As illustrated in Fig. 2, correlations between alcohol and cocaine use were higher for subjects assigned to disulfiram than those subjects not taking disulfiram.

Comment

This 12-week randomized clinical trial of disulfiram and three forms of manual-guided psychotherapy for individuals with cocaine dependence and alcohol abuse or dependence suggested the following: first, assignment to disulfiram was associated with significantly better retention in treatment as well as longer periods of consecutive abstinence from cocaine, alcohol, and cocaine and alcohol simultaneously, and fewer cocaine-positive urine toxicology screens. Secondly, the two active psychotherapies, cognitive-behavioral coping skills therapy and Twelve-Step facilitation, were more effective than clinical management, a psychotherapy control condition, in fostering longer periods of consecutive abstinence from cocaine, abstinence from both cocaine and alcohol simultaneously, as well as a higher percentage of cocaine-free

Table 2. Rates of consecutive abstinence by treatments, N = 117

	Treatment condition						Significance of effect		
	TSF n = 23	CBT n = 18	CM/Disulf n = 27	TSF/Disulf n = 25	CBT/Disulf n = 24	Medication F, p	Psychotherapy F, p	Interaction	
Maximum weeks of consecutive abstinence during treatment, mean (SD)									
Cocaine	2.22 (3.02)	1.83 (2.03)	2.59 (3.74)	3.76 (3.84)	4.54 (4.51)	7.67/0.007	3.80/0.05	NS	
Alcohol	2.13 (3.36)	1.27 (1.17)	3.85 (3.65)	4.92 (4.44)	4.62 (4.73)	14.38/0.000	1.12/0.29	NS	
Both	1.82 (2.75)	1.05 (0.93)	2.00 (3.27)	3.72 (3.85)	3.50 (4.23)	9.49/0.003	4.02/0.04	NS	
Number (%) of subjects achieving 3 or more weeks of consecutive abstinence during treatment									
Cocaine	7 (30.4%)	5 (21.7%)	8 (29.6%)	13 (52.0%)	14 (58.3%)	3.12/0.07	NS	NS	
Alcohol	5 (21.7)	2 (15.4)	13 (48.1)	15 (60.0)	13 (54.2)	14.96/0.000	NS	NS	
Both	5 (21.7)	1 (5.6)	6 (22.2)	12 (48.0)	11 (45.8)	7.02/0.008	NS	NS	

TSF = Twelve Step facilitation, CBT = cognitive behavioral therapies, CB = clinical management. Medication effect reflects disulfiram-no disulfiram contrast. Psychotherapy comparison reflects comparison of CBT and TSF (active psychotherapies) to CM. Interaction indicates CBT/TSF by disulfiram/no medication.

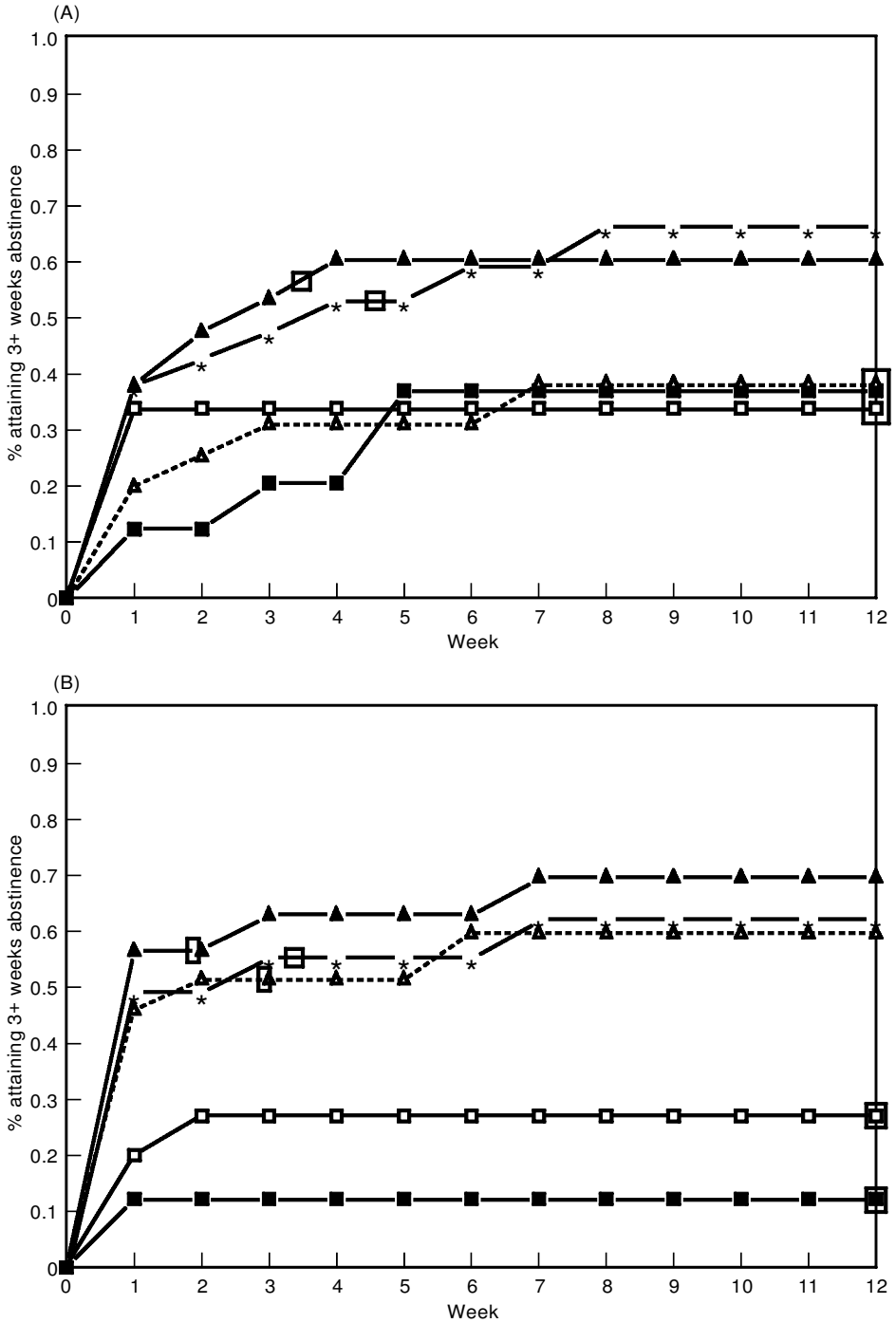


Figure 1. (A) Survival analysis: week of initiation of 3+ weeks of cocaine abstinence by treatment group, n = 117. (B) Survival analysis: week of initiation of 3+ weeks of alcohol abstinence by treatment group, n = 117. □, TSF; ■, CBT; △, CM + disulfuram; ▲, TSF + disulfuram; *, CBT + disulfuram. Boxes indicate points where median survival time occurs.

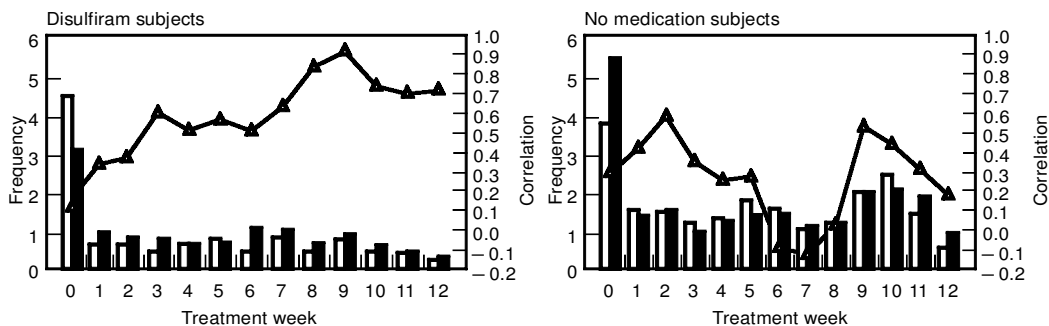


Figure 2. Average frequency of cocaine and alcohol use by week, with correlation between alcohol and cocaine use by medication condition. □, Alcohol; ■, cocaine; △, correlation.

with greater reductions in alcohol use across time while either CBT or TSF, compared with CM, were associated with significant reductions urine specimens. Thirdly, random regression models suggested that disulfiram treatment, compared with no medication, was associated in cocaine use across time, particularly for the subjects who received at least minimal exposure to treatment. Finally, use of cocaine and alcohol were strongly associated with each other during treatment, particularly for the subjects assigned to disulfiram.

Effectiveness of disulfiram

In this study, treatment with disulfiram, in the context of professional psychotherapy, appeared to have several clinically significant benefits, including significantly better retention in treatment, longer periods of abstinence from cocaine, alcohol and reduced frequency and intensity of alcohol use over time. The effect of disulfiram on alcohol was self-evident, in that subjects assigned to disulfiram treatment significantly reduced the number of days on which they drank and reduced their quantity of use per drinking occasion with respect to subjects in the no medication condition.

These findings contrast with some previous trials³⁰ which have failed to demonstrate effects for disulfiram on drinking outcomes compared with low-dose disulfiram or no medication, in large part because very few subjects were compliant with medication (20% in the Fuller³⁰ study). In contrast, in this study only two of the patients screened refused to participate in the study because of the disulfiram component, and sub-

jects' compliance with disulfiram was comparatively good. This may reflect, in part, that this group of patients tended to present with concerns about their cocaine use and minimized the severity of their alcohol use, even though their level of drinking at baseline was severe and comparable with levels seen in many recent clinical trials of alcohol dependence alone. Thus, compliance with disulfiram, which many patients thought would effect only their alcohol use, may have been less prone to compliance problems among individuals who considered cocaine, rather than alcohol, as their principal drug of abuse. This "back-door" compliance strategy may parallel recent experience with other pharmacotherapies for substance use. For example, compliance with naltrexone, an effective opioid antagonist, has been notoriously poor among opioid addicts;⁴³ whereas compliance with naltrexone among alcohol-dependent samples has been much more promising.^{44,45} It should also be noted that the effects for disulfiram seen here occurred in a comparatively short-term treatment and in the context of manual-guided, professional psychotherapy, delivered by experienced and closely supervised clinicians who closely monitored subjects' compliance with disulfiram and attempted to help them work through any problems with compliance.

It is also of note that disulfiram treatment was associated with clinically and statistically significant effects on measures of duration of cocaine abstinence and time to effect. How disulfiram treatment may have exerted these effects is less clear, as the random regression analyses did not indicate an effect of disulfiram on quantity or frequency of cocaine use over time, and thus do not strongly support a direct

effect of disulfiram on cocaine use. However, given the very close association between abstinence from alcohol and abstinence from cocaine in this sample, reduction of alcohol use through disulfiram treatment may have helped subjects to attain longer periods of abstinence from cocaine. The mechanisms for this effect may include reduced exposure to alcohol as a powerful conditioned cue for cocaine for many patients, better control of impulsivity through abstinence from alcohol, and reduction of cocaethylene-potentiated subjective effects on cocaine. However, a more direct effect of disulfiram on cocaine use, which was not tested in this study (as it would have required a placebo control condition, rather than a no medication control), is also possible, as disulfiram may make cocaine less reinforcing through heightening its negative subjective effects.²¹ It should also be noted that disulfiram was well tolerated by patients and appeared to be safe with this population, as adverse effects were very rarely seen.

Effectiveness of psychotherapy

Random regression analyses also suggested the effectiveness of CBT or TSF compared with CM on cocaine use. The main effect of the active psychotherapies over a psychotherapy control condition underlines the important role that well-defined, competently delivered psychosocial interventions play in the treatment of cocaine dependence. Because CM provided a control for general, non-specific aspects of psychotherapy (including a supportive doctor-patient relationship), it should be noted that this study provided a rigorous test of the unique elements of CBT and TSF above and beyond simple support and attention.

Furthermore, the finding that the active psychotherapies were more effective than CM in reducing cocaine use over time contrasts findings from our previous clinical trial, which found that CBT was not more effective than CM overall.²⁴ However, in that previous study CBT was found to be more effective than CM for the subgroup of subjects who were more severely dependent on cocaine. Because concurrent cocaine-alcohol dependence has been associated with higher severity of cocaine use and poorer prognosis with respect to cocaine dependence alone,¹¹⁻¹⁴ subjects in this study appeared to be similar to the more severely dependent subsample from our

previous study. Thus, findings from these two studies may suggest that more severe groups of cocaine-dependent individuals differentially benefit more from the comparatively intensive active ingredients of TSF or CBT, in contrast to the supportive but less directive CM, which also made fewer demands on patients to carry out assignments outside of sessions.

Findings from this study did not point to significant differences between the two active psychotherapies, TSF and CBT, in either cocaine or alcohol outcomes. This suggests that, despite clear differences in theoretical basis of the treatments,⁴⁶ specific interventions used by the therapists (as detected by independent raters blind to subjects' treatment assignment), as well as evidence that subjects demonstrated specific behavioral changes consistent with the theoretical mechanisms of action of their study treatments (changes in coping skills in CBT, more AA involvement in TSF), use of either of these treatments is likely to benefit individuals similar to those treated here. These findings are thus consistent with previous research with cocaine-dependent samples,²⁶ as well as the bulk of psychotherapy efficacy research with substance users,^{35,47,48} which have failed to demonstrate the overall superiority of any one form of "active" psychotherapy over others.

Limitations

This study included many important design features intended to adequately systematize and protect the integrity of both pharmacological and psychotherapeutic components of treatment. These features included specification of all aspects of pharmacological and psychotherapeutic treatment in manuals, monitoring disulfiram compliance through riboflavin screens, monitoring delivery of psychotherapy through adherence/competence ratings based on session videotapes, delivery of treatment by experienced therapists committed to the type of treatment they conducted, training and ongoing supervision of therapists, use of appropriate control groups for each form of treatment, adequate duration of treatment to allow emergence of effects of both forms of treatment and analyses based on the full intention-to-treat sample.

This study also had several limitations. First, this study used a no-medication rather than a placebo-control condition for disulfiram. Selec-

tion of an appropriate control condition for disulfiram, which is thought to work primarily through patients' expectations of the ethanol-disulfiram reaction (and was rarely tested by patients), is complicated.³⁰ However, because (1) the Fuller study failed to find differences between outcome for no-medication versus low-dose/placebo control for disulfiram, and (2) our rationale for use of disulfiram with this population was for an indirect effect of disulfiram on cocaine through reducing subjects concomitant alcohol abuse, use of a no-medication control condition was most appropriate at this stage of evaluation. Nevertheless, the no-medication condition could not control for patient expectations for medications nor direct effects of disulfiram on cocaine use. We are currently conducting a placebo-controlled study to evaluate a more direct effect of disulfiram on cocaine use in a methadone-maintained sample. Secondly, the level of attrition was significantly higher for subjects not assigned to disulfiram. Thus, while differential attrition makes it difficult to disentangle effects of disulfiram on retention versus duration of abstinence, high rates of attrition are characteristic of cocaine users,^{1,2} as well as substance abusers in general. Moreover, it should be noted that retention is a clinically significant outcome, as the treatments that are most effective for substance use disorders have been those which promote better retention in treatment, such as behavioral incentives for cocaine-dependent individuals³ and methadone for opioid addicts.⁴⁹ Finally, statistical power to detect psychotherapy by medication interactions was limited by the small sample size for some contrasts.

Summary and implications

Findings from this study have several implications for treatment and research in drug abuse. First, these data suggest the promise of the strategy of treating co-morbid disorders associated with the development or perpetuation of drug dependence. Moreover, given that the majority of cocaine-dependent individuals also abuse alcohol,^{10,11} the disulfiram treatment strategy may have broad applicability in the treatment of cocaine abuse. Future research should address the effectiveness of disulfiram on cocaine dependence *without* co-morbid alcohol abuse, as direct effects of disulfiram on cocaine use are also possible, as disulfiram may alter some reinforc-

ing effects of cocaine, resulting in a less pleasant high.^{21,22} Two studies evaluating disulfiram's effect on cocaine use are ongoing in our clinics.

Secondly, while the "back-door" compliance technique used here was promising, the effectiveness of any pharmacological approach, including disulfiram, is constrained by the willingness of patients to take it. As effective strategies used in clinical and research settings to enhance treatment compliance are inherently psychosocial, not attending to compliance issues by failing to provide a well-specified psychosocial intervention, will undermine compliance with disulfiram and any other medication.⁵⁰

Finally, as demonstrated here as well as many times before,^{44,48,51} the most promising strategies for the treatment of disorders as complex and challenging as drug dependence involve combination of pharmacotherapy and psychotherapy. Both pharmacotherapies and behavioral treatments have weaknesses when used alone, but these two very different forms of treatment have several strengths when used in combination.

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