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Sex differences in cocaine-dependent individuals' response to disulfiram treatment

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Abstract

The objective of this study is to evaluate differential response to disulfiram treatment of cocaine dependence by sex. Sex by treatment interactions from two pooled randomized clinical trials involving 191 cocaine-dependent subjects (36% female) were evaluated. Primary outcomes were days of abstinence and percentage of drug-free urine specimens. Significant sex by treatment interactions were found, where men treated with disulfiram had better outcomes than those who were not. Women had an intermediate outcome regardless of whether they received disulfiram. Sex differences in response to disulfiram treatment have important clinical and theoretical implications. Reasons for this apparent sex-based response are not clear, but possible mechanisms worthy of greater study include differences in alcohol use by sex as well as differences in dopamine-mediated responses to cocaine and disulfiram.

1. Introduction

Disulfiram has been used in the treatment of substance use disorders since its approval in 1948, first in alcohol-dependent populations, where it has shown varied levels of efficacy in randomized trials (Chick et al., 1992; Fuller et al., 1986; Ling, Weiss, Charuvastra, & O'Brien, 1983). More recently, studies evaluating the efficacy of disulfiram treatment in cocaine-dependent populations have suggested promising results (Carroll, Nich, Ball, McCance-Katz, & Rounsaville, 1998; George et al., 2000; Petrakis et al., 2000). If these early findings are replicated by other groups, it is likely, as with other treatments, that response will not be uniform and different subgroups of cocaine-dependent individuals will respond less (or more) favorably to disulfiram treatment of cocaine dependence. Sex effects associated with disulfiram treatment of cocaine abuse may be one such area, given evidence of sex effects in cocaine response (Wetherington & Roman, 1998). Moreover, sex effects remain a critical but understudied area in substance abuse treatment (Schuckit, 1985). For example, of the 1289 individuals treated in the five landmark studies evaluating the effectiveness of disulfiram treatment of alcohol use disorders (Chick et al., 1992; Fuller et al., 1986; Ling et al., 1983; Fuller & Roth, 1979), only 20 (1.5%) were women. No women were included in the three studies that were double blind and placebo controlled.

This report describes preliminary findings from a secondary analysis of two randomized controlled trials evaluating disulfiram as treatment for cocaine dependence—one took place in an outpatient setting (Carroll et al., 1998) and another in the context of methadone

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maintenance (Petrakis et al., 2000). We will address the issue of differential response to disulfiram treatment by sex.

2. Methods

2.1. Study 1

The first trial was a 12-week randomized clinical trial of 122 individuals who met *DSM-IV* criteria for cocaine dependence and alcohol abuse or dependence (Carroll et al., 1998). After the study protocol had been explained and informed consent was provided, subjects were randomly assigned to one of five treatment conditions: cognitive-behavioral therapy plus disulfiram, 12-step facilitation plus disulfiram, clinical management plus disulfiram, 12-step facilitation with no medication, or cognitive-behavioral therapy with no medication. All behavioral therapies were manual guided and delivered to patients in individual sessions; independent ratings of session tapes confirmed that treatments were discriminable and implemented in accordance with manual guidelines. Disulfiram was prescribed with an initial dose of 250 mg and taken in the presence of the study nurse twice weekly. Compliance was monitored with a riboflavin marker procedure that indicated adherence to disulfiram schedule.

2.2. Study 2

This study also involved individuals who met *DSM-IV* criteria for cocaine dependence (Petrakis et al., 2000) and took place in the context of a methadone maintenance program. After a full explanation of the study, subjects provided informed consent and were randomly assigned to methadone maintenance plus disulfiram or methadone maintenance plus placebo. The placebo was designed to resemble the disulfiram in color and consistency and both placebo and disulfiram were placed directly into the methadone to ensure compliance. Disulfiram was taken daily with an initial dose of 250 in the presence of clinic staff. All participants also received standard weekly group counseling sessions. Sixty-nine subjects were randomized to treatment and 67 began treatment.

2.2.1. Assessment and data analysis—In both studies, urine samples were collected weekly for urine toxicology screens and were found to be highly consistent with subjects' self-reports. The two 12-week outpatient trials shared several design features such as random assignment to treatment, identical sets and schedules of outcome assessments, and identical doses of disulfiram. In addition, in both studies, there was a significant effect of disulfiram on cocaine outcomes and in neither study was there a significant main effect for sex on outcome. Although there was a trend for men responding better to disulfiram than women in both studies, there was not enough power to evaluate this in either study alone. Therefore, data from the two studies were pooled to maximize power. The primary outcome measures for both studies were frequency of cocaine use (days used/past 28) and percentage of cocaine-free urine specimens. Sex differences at baseline and percentage of cocaine-free urine samples were analyzed using ANOVA and repeated-measures outcomes were analyzed using random effect regression modeling.

3. Results

As shown in Table 1, neither study had many significant differences between men and women in terms of demographic characteristics or baseline drug use. Across both studies, women were more likely to be unemployed than men. On average, men initiated alcohol use 1 year earlier than women in both studies and had been drinking alcohol regularly for a longer period of time. In addition, the men in Study 2 were more likely to have a lifetime diagnosis of alcohol dependence.

With data from the two studies combined, random effect regression analyses showed a significant reduction in cocaine use frequency over time for the sample as a whole (z = 16.72, P < .05) in addition to a significant medication by time effect (z = 3.09, P < .05), suggesting that subjects assigned to disulfiram made greater reductions in their use of cocaine over time than those not assigned to disulfiram. There was also a significant sex by disulfiram by time interaction (z = 2.15, P < .05), suggesting that men assigned to disulfiram had better outcomes than men not assigned to disulfiram, whereas the subgroup of women had comparable outcomes whether assigned to disulfiram or not. In practical terms, men assigned to disulfiram had significantly better outcomes than those who were not [percentage of cocaine-negative urine specimens 49% vs. 30%, F(1,120) = 7.31, P < .05], whereas there was no difference in the same outcomes for women assigned to versus not assigned to disulfiram [38% vs. 39%, F(1,67) = 0.02, P=.89]. These findings held when covarying for several other baseline characteristics, including level of alcohol use and severity of cocaine use.

Although this sex by treatment interaction was not statistically significant when analyzed within each study, a similar pattern was seen when outcomes were compared within each group; that is, in both studies, the subgroup of men assigned to disulfiram had significantly better outcomes, whereas no significant disulfiram effects were seen among the subgroup of women.

4. Discussion

This secondary analysis of two randomized clinical trials of disulfiram treatment for cocaine dependence suggested that men who were assigned to disulfiram treatment had better outcomes than those who were not, whereas there were no significant outcome effects for disulfiram among women. Disulfiram is the only medication that has been found to be efficacious for cocaine dependence in three randomized clinical trials with no negative studies to date. These findings are limited by their exploratory nature but are intriguing as they highlight both the possible sex effects in response to an emerging treatment approach for cocaine dependence and the underrepresentation of women in previous trials evaluating disulfiram in substance-abusing populations (Miller & Wilbourne, 2002).

The mechanisms for this apparent sex interaction are as yet unclear, but possibilities include (1) more chronic and intense alcohol use among men; that is, if disulfiram exerts its effect on cocaine use through discouragement of drinking and hence patient exposure to cocaethylene (McCance-Katz, Price, Kosten, & Jatlow, 1995), cocaine-dependent individuals who are heavier drinkers may have improved response to disulfiram treatment. However, in this sample, baseline differences in alcohol use by sex were comparatively infrequent and alcohol use within treatment was very rare in Study 2. (2) Disulfiram is an inhibitor of dopamine-β-hydroxylase (DBH; Faiman, 1979; Haley, 1979; Wright & Moore, 1990). Inhibitors of this enzyme are known to alter central ratios of dopamine to norepinephrine (Stanley et al., 1997). Hypothetically, such an effect could increase negative stimulant (anxiety and restlessness) responses to cocaine in disulfiram-treated patients. Laboratory studies in which disulfiram-treated cocaine abusers were challenged with a dose of intranasal cocaine revealed a moderate increase in anxiety (McCance-Katz, Kosten, & Jatlow, 1998a). Men and women may experience these negative effects differently. In a recent study of repeated administration of cocaine, alcohol, or combination, women reported significantly greater ratings for the visual analog “feel good” when cocaine alone was administered, a finding that approached significance for alcohol alone as well (McCance-Katz, Kosten, & Jatlow, 1998b). Moreover, recent evidence suggests that estradiol administration increases DBH in rodents (Serova, Rivkin, Nakashima, & Sabban, 2002). If

estrogen stimulates DBH activity in humans, and disulfiram inhibits DBH, the disulfiram effect could possibly be attenuated in women.

Although exploratory, these findings suggest two things: (1) first-line treatments assumed to have been deemed useful for a particular disorder may not have been evaluated on a representative sample and (2) future clinical trials must assess differential response by sex, bearing in mind that the lack of statistical power may mask clinically meaningful trends.

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Table 1

Baseline demographic and substance use variables by sex, both studies

	Study 1						Study 2					
	Men (n = 89)		Women (n = 33)		χ^2 or F	p-value	Men (n = 33)		Women (n = 36)		χ^2 or F	p-value
	Mean/#	SD/%	Mean/#	SD/%			Mean/#	SD/%	Mean/#	SD/%		
Age	30.47	5.59	31.64	5.21	1.08	.30	35.45	5.71	35.06	5.70	0.08	.77
Years of education [no. (%)]												
Some college up	20	23	8	24			12	36	19	53		
High school graduate/GED	40	45	17	52			13	39	8	22		
Less than high school	29	33	8	24	0.81	.37	8	24	9	25	2.70	.26
Ethnicity [no. (%)]												
African American	46	52	22	67			1	3	14	39		
White	39	44	9	27			29	88	22	61		
Hispanic	4	5	0	0	2.72	.10	2	6	0	0	14.04	.00
Single or divorced	73	82	31	94	2.72	.10	25	76	27	75	0.04	.95
Unemployed	45	51	25	76	6.25	.01	21	64	33	92	7.95	.004
Cocaine (g/week)	3.75	4.04	2.87	4.26	0.87	.35	1.99	2.91	2.67	4.76	0.50	.48
Days of cocaine use/past 30	13.73	8.2	15.18	8.55	0.74	.39	18.71	9.75	18.11	10.01	0.06	.81
Age at first cocaine use	20.27	5.70	22.03	5.25	2.39	.12	20.53	5.26	21.64	5.39	0.70	.40
Years of regular cocaine use	8.04	4.56	5.87	5.83	5.88	.02	10.33	8.93	7.37	6.37	2.48	.12
Number of times previously treated for drugs	1.40	3.19	.97	1.69	0.55	.46	4.13	3.40	3.46	2.31	0.90	.35
Days of drinking/past 30	17.76	7.98	16.12	8.81	0.96	.33	5.10	8.34	3.31	6.89	0.93	.34
Drinks per drinking day	11.53	8.19	11.42	7.87	0.004	.95	2.28	4.64	1.53	4.07	0.51	.48
Age first alcohol use	13.08	3.31	14.61	4.34	4.31	.04	14.45	2.53	16.06	3.87	3.89	.05
Years of regular alcohol use	8.08	6.53	5.03	4.19	6.22	.01	9.58	8.77	3.94	6.41	9.19	.003
Meet criteria for DSM lifetime [no. (%)]												
Alcohol dependence	66	86	25	83	0.10	.95	18	67	10	22	4.75	.03
Affective disorder	20	26	11	37	1.20	.27	2	7	6	22	2.51	.11
Anxiety disorder	5	6.5	3	10	0.38	.54	1	4	1	4	0.00	.98
Beck Depression Inventory, 13 items	11.57	6.42	12.09	6.16	0.16	.69	8.94	7.59	8.69	7.02	0.02	.89

Data are means and S.D. unless otherwise stated.