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Gender differences in clinical outcomes for cocaine dependence: Randomized clinical trials of behavioral therapy and disulfiram☆

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Abstract

Background—Despite extensive research on gender differences in addiction, there are relatively few published reports comparing treatment outcomes for women versus men based on evidence-based treatments evaluated in randomized clinical trials.

Methods—An aggregate sample comprised of data from five randomized clinical trials of treatment for cocaine dependence (N = 434) was evaluated for gender differences in clinical outcomes. Secondary analyses compared gender differences in outcome by medication condition (disulfiram versus no medication) and across multiple behavioral treatment conditions.

Results—Women, compared with men, had poorer treatment outcomes on multiple measures of cocaine use during treatment and at post-treatment follow-up. These results appear to be primarily accounted for by disulfiram being less effective in women compared with men. There was no evidence of meaningful gender differences in outcome as a function of the behavioral therapies evaluated.

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Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2014.10.007

Conclusions—These findings suggest that women and men may benefit to similar degrees from some empirically validated behavioral treatments for addiction. Conversely, some addiction pharmacotherapies, such as disulfiram, may be associated with poorer outcomes among women relative to men and point to the need for careful assessment of pharmacological treatments in both sexes prior to widespread clinical implementation.

Keywords

Cocaine; Sex; Gender; Psychotherapy; CBT; Disulfiram

1. Introduction

Despite a growing appreciation of the importance of considering gender in clinical studies (Wetherington, 2007) and explicit National Institutes of Health (NIH) guidelines supporting this practice, a minority of published clinical trials test for gender-sensitive treatment effects (Marrocco and Stewart, 2001; Toneatto et al., 1992; Vidaver et al, 2000). Women have lower rates of substance use and dependence than men (SAMHSA, 2004) and represent a minority of those enrolled in substance use treatments (approximately 32% in the U.S.; Brady and Ashley, 2005). Thus, even well-controlled trials including both genders are likely more representative of men's treatment response or may have limited power to detect gender differences. Overgeneralization of results from studies in one gender can result in suboptimal treatment efficacy for the understudied gender (Nieuwenhoven and Klinge, 2010).

There are several compelling reasons for carefully considering gender differences in treatment outcome. First, gender differences are widely reported at substance abuse treatment-entry on characteristics associated with clinical outcomes. Treatment-seeking women tend to report more medical, social/family and psychological problems, are more likely to meet diagnostic criteria for depression, anxiety or post-traumatic stress disorder, but are less likely than treatment-seeking men to meet criteria for alcohol use disorders, antisocial personality disorder or attention deficit hyperactivity disorder; characteristics associated with cocaine use outcomes (Alterman et al., 2000; Brady and Ashley, 2005; Carroll et al., 1993; Crits-Christoph et al, 1999; Elman et al., 2002; Grella et al., 2003; Griffin et al., 1989; Hien et al., 2010; McCance-Katz et al., 1999; Najavits and Lester, 2008; Perez de Los Cobos et al., 2011). These gender differences are not unique to cocaine-dependent populations, but are also observed in groups dependent on other substances (Hernandez-Avila et al., 2004) as well as general population samples (SAMHSA, 2004). Demographic differences at treatment entry (e.g., women's greater likelihood of having children or being unemployed) impact treatment needs and accessibility and are cited as reasons for gender-specific treatment adaptations (Greenfield et al., 2007, 2011).

Second, clinical progression of cocaine dependence may differ by gender. Faster transition to problematic substance use in women than men (i.e., ‘telescoping’) was initially described for alcohol use disorders (e.g., Randall et al, 1999). In cocaine-dependent samples, women report fewer years or lower volumes of use but equivalent severity at treatment-entry compared with men (Griffin et al., 1989; Haas and Peters, 2000; Lozano et al., 2008;

McCance-Katz et al., 1999), but other studies have not found indications of 'telescoping' in cocaine samples (e.g., Hernandez-Avila et al., 2004).

Third, significant biological differences (e.g., sex-linked genetic differences, gonadal hormones) in addiction-relevant systems likely contribute to sex-sensitive responses to acute substance administration or withdrawal, which influence patterns of self-administration or transition to addiction (e.g., Becker and Hu, 2008; DeVito et al., 2013; Lynch, 2006; Lynch et al., 2002; Ramoa et al., 2013; Sinha et al., 2007; Sofuoglu et al., 1999). In as much as different treatments for addiction work through different mechanisms of action, biological sex differences may affect response to certain treatments more than others.

The literature on gender and cocaine treatment outcomes is limited and mixed. Several studies report no gender differences within cocaine dependent samples for behavioral treatments. In a randomized clinical trial (RCT) of cocaine-dependent inpatients (77M, 31F) receiving treatment as usual plus cocaine-specific coping-skills treatment or meditation-relation treatment, there were no gender or gender-by-treatment differences in cocaine use outcomes at one year follow-up (Rohsenow et al., 2000). Cocaine-dependent individuals (47M, 34F) randomized to a self-regulation of cocaine cue-response using biofeedback versus treatment as usual found no gender or gender-by-treatment interactions on cocaine use outcomes, despite higher cue reactivity and better regulation of cue-response with biofeedback in men than women (Sterling et al., 2004). An RCT (350M, 104F, 5 sites) comparing manual-guided psychotherapies (individual or group drug counseling, cognitive therapy, supportive expressive therapy) found no gender or gender-by-treatment effects on cocaine use outcomes, but men transitioned between use and abstinence states (or vice versa) more frequently (Gallop et al., 2007). Following inpatient treatment for cocaine use wherein within-treatment abstinence was ensured (64M, 37F), women were less likely than men to relapse to cocaine by 6-month follow-up (Weiss et al., 1997). However survey data from individuals who had undergone standard inpatient or outpatient treatment (i.e., not an RCT) (65M, 29F) found no gender differences in cocaine use outcomes at one year follow-up (McCance-Katz et al., 1999).

Several studies in mixed substance-using samples including substantial proportions of cocaine-dependent individuals receiving a mix of standard behavioral treatments also reported no gender differences in substance use outcomes. A survey of mixed substance users (552M, 201F, 52 sites) found no gender or gender-by-treatment-setting (residential versus outpatient) effects on cocaine use outcomes during treatment or follow-up but did not analyze by treatment type or primary substance of abuse (Stewart et al., 2003). A survey of cocaine or alcohol-dependent individuals (145M, 149F, 9 sites) found no gender or gender-by-treatment (managed care versus fee-for-service) effects on addiction severity in the first two weeks of treatment and gender did not predict drug use outcomes at follow-up (Alterman et al., 2000). In a mixed substance-using sample receiving methadone-maintenance plus counseling (343M, 205F, 6 sites), changes in frequency of cocaine use from baseline to 6 months post-treatment did not significantly differ (but were also not statistically equivalent) by gender (Mulvaney et al., 1999). In polysubstance users (72.7% primary cocaine), female gender was indirectly associated (via baseline resource needs) with greater likelihood of relapse during follow-up (Walton et al., 2003). Therefore, most survey

assessments (non-RCT) of mixed substance using groups receiving standard care have not reported finding gender differences.

In contrast, several RCTs of pharmacotherapies for cocaine dependence reported poorer cocaine-outcomes for women. Within cocaine-dependent individuals (122M, 69F) randomized to standard treatments (psychotherapy; methadone maintenance) plus disulfiram or placebo, men receiving disulfiram had superior clinical outcomes compared to men on placebo, but no clinical benefit of disulfiram was observed within women (Nich et al., 2004). Similarly, RCTs of modafinil (157M, 53F; Dackis et al., 2012) and naltrexone plus CBT or medication management (116M, 48F; Pettinati et al., 2008 reported improved cocaine outcomes in men relative to placebo, but women tended towards worse outcomes on medication relative to placebo, even after accounting for depressive symptoms or alcohol use. Women's higher attrition rates were associated with more baseline psychiatric symptoms and more naltrexone-induced nausea (Pettinati et al., 2008; Suh et al., 2008)). Although a memantine trial reported no gender differences, this reflected no effects of medication versus placebo in either gender, and no gender difference in the effect of concurrent psychotherapy on cocaine outcomes (Bisaga et al., 2010). The one study reporting better cocaine use outcomes in women on standard treatment plus pharmacotherapy was a small trial (53M, 19F) that did not report gender-by-medication condition analyses (desipramine or lithium carbonate versus placebo), and gender differences only emerged in the follow-up period, not during the active medication trial period. Thus, it was not possible to determine whether women benefitted from the medications more than men (Kosten et al., 1993).

Therefore, a substantial majority of studies of behavioral treatments have found no gender differences in cocaine outcomes, while the fewer existing reports on pharmacotherapies tend to report poorer cocaine outcomes in women compared with men during the active medication phase. However, in the cocaine treatment outcome literature as a whole, gender analyses are often not reported. Frequent problems with this literature are that careful description of the treatment modalities administered and indicators of treatment dose/engagement are often not reported, analysis for differential gender effects across treatment condition are not always considered, sample sizes are varied and some of the available data on larger datasets are based on survey studies across clinics (which often include mixed and undefined treatment conditions) rather than RCTs.

Given the dearth of clinical trials of cocaine treatment that administer controlled treatment types and report on gender analyses overall or by treatment subtype, we evaluated gender differences in response to an evidence-based pharmacotherapy (disulfiram) and behavioral therapies (e.g., cognitive behavioral therapy, twelve-step facilitation) for cocaine dependence in an aggregate sample of five RCTs. Parallel methods and assessment batteries permitted evaluation of a comparatively large and heterogeneous sample. We assessed whether there were gender differences in clinical outcomes during treatment or follow-up, or gender-by-treatment interactions for evidence-based pharmacological and behavioral therapies. Based on the literature reviewed above, we hypothesized that women would show less therapeutic benefit from disulfiram than men (e.g., McCance-Katz et al., 1999; Nich et

al., 2004) but we did not predict significant gender differences in outcomes from behavioral therapies (e.g., Rohsenow et al., 2000; Sterling et al., 2004; Woody et al., 2003).

2. Method

2.1. Participants

Participants (*N* = 434; 291M, 143F) were outpatient treatment-seeking individuals who met DSM-IV criteria for cocaine dependence as their primary diagnosis and reported using cocaine in the prior month.

2.2. Procedures

The data represent a combined dataset from five RCTs of cocaine-dependent individuals receiving behavioral and/or pharmacological treatments, delivered in outpatient clinic settings. The combined dataset was compiled for and used in a previous set of analyses which focused on cocaine-dependence and involved analyses with one-year follow-up outcomes (Carroll et al., 2014).

The main study procedures and outcomes from the five RCTs are described in detail elsewhere (Carroll et al., 2008, 2009, 2004, 2014, 2000, 1998; Carroll et al., under review; see Table 1 for overview). For the RCTs, participants were assessed at pre-treatment, during treatment and at post-treatment follow-up appointments for up to one year. Common assessments included the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1990) to assess Axis I psychiatric co-morbidities and Antisocial Personality Disorder (ASPD); the Addiction Severity Index (ASI; McLellan et al., 1992), a structured interview measuring problem severity across a range of domains affected by substance use (see Supplemental Material for detailed description of ASI Composite Scores[1]); at least weekly urine toxicology screens throughout treatment; and self-reported recent substance use with the Timeline Follow-back method (Carroll et al., 2004; Robinson et al., 2012; Sobell and Sobell, 1992), which involves calendar-guided retrospective day-to-day reporting of substance use across a recent time point of interest (e.g., since prior visit).

2.3. Data analyses

We used analysis of variance (ANOVA), chi-square tests and logistic regression to compare men and women within the overall combined dataset on (I) baseline demographic and clinical measures; (II) clinical outcomes; (III) differential response to pharmacological or behavioral treatments; and (IV) analyses of gender differences in clinical outcomes were re-run including baseline variables that differed by gender as covariates. Primary clinical outcomes were those found to be most reliable, sensitive, and predictive of longer-term functioning in this sample (Carroll et al., 2014). Secondary analyses including study as a random effect did not significantly alter the results (data not shown).

To assess differential effects of disulfiram on clinical outcome by gender, the sample was grouped into those randomized to any treatment condition including disulfiram (without

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:…

regard to additional behavioral or psychological treatment conditions (N = 212)) versus randomized to no medication conditions (including placebo or no-medication conditions (N = 222)). Although these analyses assess within treatment and follow-up time points, disulfiram (or placebo) treatment was offered during the active treatment phase, and was not provided during follow-up.

To assess differential effects of behavioral treatment condition on clinical outcome by gender, individuals randomized to any disulfiram condition were excluded; hence these behavioral treatment analyses only included individuals assigned to placebo or no medication conditions. Individuals from one of the trials (Study E; Carroll et al., under review) were excluded for this analysis since CBT was included as a platform treatment in that study (to which CM and DSF were added), precluding evaluation of specific treatment by gender responses. Remaining individuals were coded as randomized to the following treatment conditions: CBT (N = 57), TSF (N = 48) or OTHER (including control and TAU conditions; N = 75).

3. Results

3.1. Baseline gender differences

Baseline variables by gender are presented in Table 2. Relative to men, women were less likely to have completed high school, paid for fewer days of work in the prior month, more likely to be on public assistance, and had lower ASI employment composite scores. Women were more likely to have a lifetime diagnosis of major depression, but less likely to have a lifetime diagnosis of an alcohol use disorder or antisocial personality disorder. Women reported fewer days of alcohol use in the month prior to treatment, but did not significantly differ from men in reported days of cocaine, cannabis, or cigarette use in that period. Although women showed a trend towards a later age of cocaine-use onset, women had more prior outpatient substance use treatments and higher ASI cocaine composite scores at baseline than men.

3.2. Gender differences in clinical outcomes

Table 3 presents overall within-treatment and follow-up outcomes by gender. Men and women did not significantly differ on indicators of treatment dose and compliance (days in treatment, number of urines submitted). However, women had poorer substance use outcomes (see Fig. 1). Women reported more days of cocaine use, were less likely to report 3 or more weeks of consecutive abstinence, and submitted a higher percentage of cocaine-positive urines than men during active treatment. Women, compared to men, also reported more days of psychological trouble in the month prior to their final within-treatment ASI assessment. During the post-treatment follow-up period, women reported more days of cocaine use within the first follow-up month, but there were no significant gender differences by 6 or 12 month follow-ups.

3.3. Differential effects of gender-by-treatment condition

Analyses evaluating outcomes by medication condition and gender are presented in Table 4. Although there was an effect of medication condition on days in treatment (with participants

receiving disulfiram showing better treatment retention), there were no gender or gender-by-medication group interactions on treatment compliance measures (days in treatment, number of urines submitted). Gender-by-medication group interactions on percent days self-reported abstinence during treatment reflected a diminished benefit from disulfiram for women relative to men during treatment (see Fig. 2). This difference did not persist through follow-up, when medications were no longer administered. Other non-significant trends in treatment outcome indicators suggested men benefitted from disulfiram more than women.

Data for behavioral treatment condition-by-gender analyses for clinical outcome variables are presented in Table 5. Within the sample not receiving disulfiram, there were no overall gender differences in treatment outcomes and no gender-by-behavioral treatment condition effects on any measure of treatment compliance or outcome.

3.4. Covarying for baseline gender differences

The pattern of results held when analyses of gender on clinical outcomes or gender-by-treatment type were re-run including the following baseline variables as covariates: ASI alcohol and employment composite scores, number of previous outpatient treatments, and lifetime diagnoses of alcohol use disorder, major depression, and antisocial personality disorder, as determined by the SCID.

4. Discussion

4.1. Summary

Data from this aggregate sample drawn from five RCTs evaluating different forms of treatment for cocaine dependence found the following: First, in terms of baseline differences, women and men differed in rates of co-morbid psychiatric disorders, socioeconomic status and alcohol use, but not on baseline indicators of cocaine use frequency, duration, or route of administration. Second, women had poorer treatment outcomes than men across a range of clinical indicators, including measures of cocaine use during treatment and early follow-up. Third, analyses by treatment condition found support for poorer treatment outcomes for women than men amongst patients receiving disulfiram, but did not identify gender differences in outcomes amongst patients receiving behavioral treatment without disulfiram. Finally, the findings remained consistent when baseline gender differences were included as covariates.

The gender differences in pre-treatment clinical characteristics were consistent with patterns previously reported in the literature, supporting the clinical representativeness of this sample. Women had lower rates of lifetime alcohol use disorders and ASPD, higher rates of lifetime major depression, and unemployment than men, replicating findings in other clinical SUD samples (Griffin et al., 1989; Hernandez-Avila et al., 2004; White et al., 1996), and general population samples (SAMHSA, 2004). Baseline cocaine use indices were generally consistent with ‘telescoping’. Women trended towards later age of first use yet had more prior substance use treatments. While the genders did not differ in days of cocaine use in the month prior to treatment, women reported higher ASI cocaine composite scores, indicating greater severity of cocaine-associated problems. Patterns similarly consistent with cocaine

'telescoping' have been reported in other samples (Griffin et al, 1989; Haas and Peters, 2000; Lozano et al., 2008; McCance-Katz et al., 1999).

To assess whether baseline gender differences contributed to differential treatment outcomes we re-ran analyses including these baseline variables as covariates. The same overall pattern of results remained, suggesting our findings are not explained by gender differences at treatment entry, but by treatment response. Our findings are consistent with previous reports that baseline gender differences do not fully account for gender differences in treatment outcomes (e.g., Dackis et al, 2012; Pettinati et al, 2008).

In this aggregate sample, women's poorer cocaine use outcomes following treatment appeared to be driven more by their poorer response to disulfiram treatment, rather than by differential response to behavioral therapies. It is noteworthy that the gender differences in outcomes were less pronounced over the follow-up period (when medications were no longer administered), compared to the within-treatment period. These findings replicate and extend previous findings from our group in a smaller yet partially overlapping sample showing disulfiram to be less effective in women than men for the treatment of cocaine dependence (Nich et al., 2004). Additionally, these findings are consistent other trials of pharmacotherapies for cocaine dependence showing poorer outcomes in women (Dackis et al., 2012; Pettinati et al., 2008). None of these trials were specifically designed to assess gender differences so these findings should be interpreted with caution. However, the pattern across trials should encourage careful assessment of pharmacological treatments in both sexes prior to widespread clinical implementation.

Women may experience more frequent adverse reactions to pharmacotherapies (Domecq et al., 1980), which may contribute to diminished efficacy (e.g., non-compliance, drop-out). However, in our sample there were no medication-by-gender interactions on treatment-engagement measures (days in treatment, number of urines submitted) and individuals randomized to disulfiram remained in treatment for longer. So, early treatment drop-out does not explain gender effects in this sample.

It is not clear whether poorer outcomes in women on disulfiram are specific to its efficacy in treating cocaine dependence or also extends to other applications. Although no pharmacotherapies are approved for treatment of cocaine dependence, disulfiram is an approved pharmacotherapy for alcohol use disorders. The landmark studies testing disulfiram's efficacy in treating alcohol use disorders were predominantly in men (e.g., Fuller et al., 1986; Fuller and Roth, 1979; Ling et al., 1983) or included few women and did not report results by gender (e.g., 120M, 20F; Chick et al., 1992). Female gender predicted poorer 6-month post-treatment outcomes in an alcohol dependence treatment study (176M, 33F) wherein 82% of patients were prescribed disulfiram during the treatment period alongside other treatments (Aguiar et al., 2012). However, treatments were not randomly assigned, and neither the breakdown of numbers of men and women receiving disulfiram nor gender-by-treatment analyses were included. Therefore, it is unclear whether women's poorer outcomes were disulfiram-dependent. Given the relative dearth of data testing the efficacy of disulfiram in women for addictive behaviors, this topic deserves more direct assessment.

Several potential mechanisms of action of disulfiram as a treatment for cocaine dependence have been proposed. Disulfiram is thought to reduce alcohol use largely due to its effects on alcohol metabolism that result in an aversive reaction to alcohol (e.g., nausea; Kitson, 1977). Due to the high rates of co-morbid alcohol use disorders in cocaine dependent populations and frequency of concurrent alcohol and cocaine consumption (e.g., Carroll et al.,1993), disulfiram was proposed as a treatment for cocaine dependence partly on the logic that its reduction of alcohol consumption would mediate its effects on cocaine use (e.g., Higgins et al., 1993). In our sample, women reported less alcohol use and alcohol-related problems and lower rates of lifetime alcohol use disorders at pre-treatment compared to men. However, covarying for baseline alcohol variables did not significantly change the pattern of findings. Furthermore, self-reported alcohol use during treatment was very low in both the medication and placebo groups in the disulfiram trials, perhaps due to participants being strongly advised to avoid alcohol use since the study medication could interact negatively with alcohol. In addition, within women in this sample there was no significant lifetime alcohol use disorder diagnosis by medication condition effects on within-treatment or follow-up cocaine use outcomes (data not shown), further suggesting that lower rates of alcohol use disorders in the women were unlikely to be accounting for disulfiram's diminished efficacy in women relative to men. Previous studies have found disulfiram to reduce cocaine use even in individuals who do not concurrently abuse alcohol (Carroll et al., 2004; George et al., 2000; Petrakis et al., 2000). As such, gender differences in alcohol use are unlikely to fully explain differential responses to disulfiram.

Disulfiram has also been proposed to influence cocaine use by other mechanisms (for review, Gaval-Cruz and Weinshenker, 2009). For example, disulfiram affects cocaine metabolism, possibly shifting the rewarding or aversive properties of acute cocaine. Disulfiram has been proposed to normalize dopaminergic tone in hypodopaminergic cocaine dependent individuals. Disulfiram may also interference with cocaine's addictive properties, through its action on dopamine or indirect impact on noradrenaline or glutamate systems. Therefore, sex differences in cocaine's acute rewarding or aversive properties (e.g., Lynch, 2006; Sofuoglu et al., 1999); striatal dopaminergic function (e.g., Laakso et al., 2002); or effects of dopamine-manipulations on addiction-relevant cognitive effects (de Wit et al., 2012; Robinson et al., 2010) are all candidate mechanisms through which disulfiram may have sex-sensitive effects on cocaine use.

In contrast, these analyses provided little support for gender differences in primary clinical outcomes with behavioral treatments. Within the sample that received behavioral treatment without disulfiram, no significant gender or gender-by-treatment type effects were observed on cocaine outcomes. These findings are consistent with the bulk of prior research in behavioral treatments reviewed above, and extend these findings to different behavioral treatments (e.g., CBT), which have not been formally assessed in this manner in cocaine-dependent samples. One possible reason why behavioral treatments may have less gender-sensitive effects than pharmacological treatments could be that behavioral therapies' mechanisms of action may be broader and more varied than those of pharmacotherapies. For example, if a given medication predominantly works by diminishing the rewarding properties of acute cocaine administration (e.g., ‘high’), that medication will be most effective in individuals whose drug-taking is primarily driven by that ‘high’ and may be

ineffective in individuals whose cocaine use is primarily driven by other factors (e.g., to alleviate a negative mood state). In contrast, psychotherapies such as CBT incorporate a range of behavioral and cognitive strategies and skills (Carroll, 1998) which may be more broadly applicable and adaptable to individuals' drug use patterns and motivations. Additionally, in most cases, behavioral therapies are intended to be targeted to the patient's greatest need, which may allow them to effectively address gender differences at treatment entry, even when gender-specific approaches are not being deliberately employed.

4.2. Strengths and limitations

This study has several strengths. The five studies included in the aggregate sample were all RCTs with participants randomized to well-defined evidence-based treatments versus control conditions. Measures of treatment engagement were collected and substance use outcomes were available for the treatment and follow-up periods. The sample size was large relative to most other clinical trials investigating gender differences. Use of data from separate trials spanning decades and several clinical settings may increase the generalizability of the findings. We analyzed a range of well-validated and widely-used cocaine and other life (as measured by ASI) outcomes.

Despite substantial strengths, there are some noteworthy limitations. The studies were not primarily designed to assess gender differences and included a range of treatment types. We had less power to detect behavioral treatment differences than medication treatment differences, due to comparison across three behavioral treatment conditions and smaller sample size after excluding medicated individuals and one group of participants (Study E). Behavioral therapy analyses focused on CBT, TSF and a range of control conditions (typically ‘treatment as usual’). Since the original studies were not designed to directly compare these three conditions, additional study-related variance (e.g., treatment setting, therapists, total treatment time) were not controlled across these conditions. As such, these findings do not rule out the possibility of gender differences in certain clinical outcomes from these or other behavioral therapies and the analyses comparing behavioral treatments should be considered preliminary. Structured, well-validated assessment measures (e.g., urine toxicology) were used to minimize bias, but societal expectations of gender roles and related reporting biases could still have influenced outcomes; particularly with the ASI composite scores which include participants' subjective assessment of severity and need for treatment. Since this was a secondary analysis of existing data, some variables of interest for gender differences were unfortunately unavailable (e.g., sexual, emotional or physical abuse history, post-traumatic stress disorder or Axis II personality disorders other than ASPD). Furthermore, factors related to gender roles (e.g., child-rearing or child-custody concerns, substance use of the current partner) could not be assessed with this secondary analysis, but should be examined in further studies. Finally, different aspects of treatment engagement, treatment satisfaction, quality of life or other life functioning metrics may be important to assess further in the context of evidence for gender differences in motivations for treatment and life consequences from substance dependence.

4.3. Conclusions

These findings reinforce the importance of considering gender-sensitive effects of novel or established treatments for substance use disorders. While behavioral treatments appear to be efficacious for men and women, disulfiram appears less effective for treating cocaine dependence in women than in men. Gender difference analyses in treatment outcome research should be more consistently integrated with ongoing research into the mechanisms of actions for behavioral or pharmacological therapies, given the literature suggesting gender differences in mechanisms contributing to the development and maintenance of addictive behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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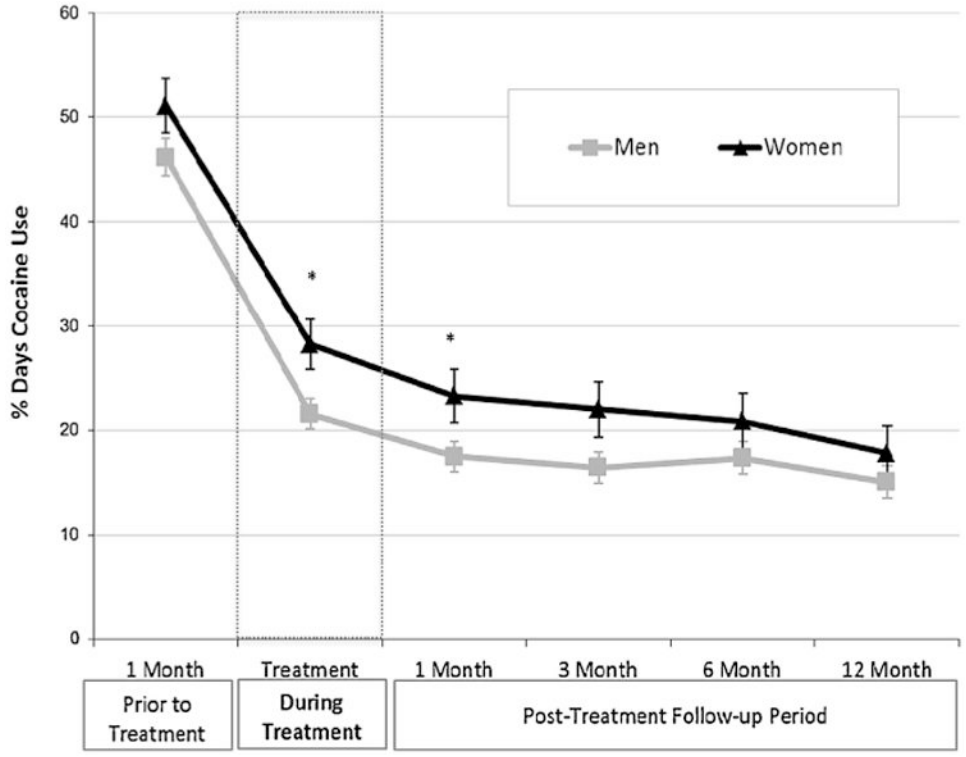

Fig. 1.

Gender differences in cocaine use across time-points. Data presented as means with standard error of the mean error bars. * Indicates significant gender difference ($p < 0.05$).

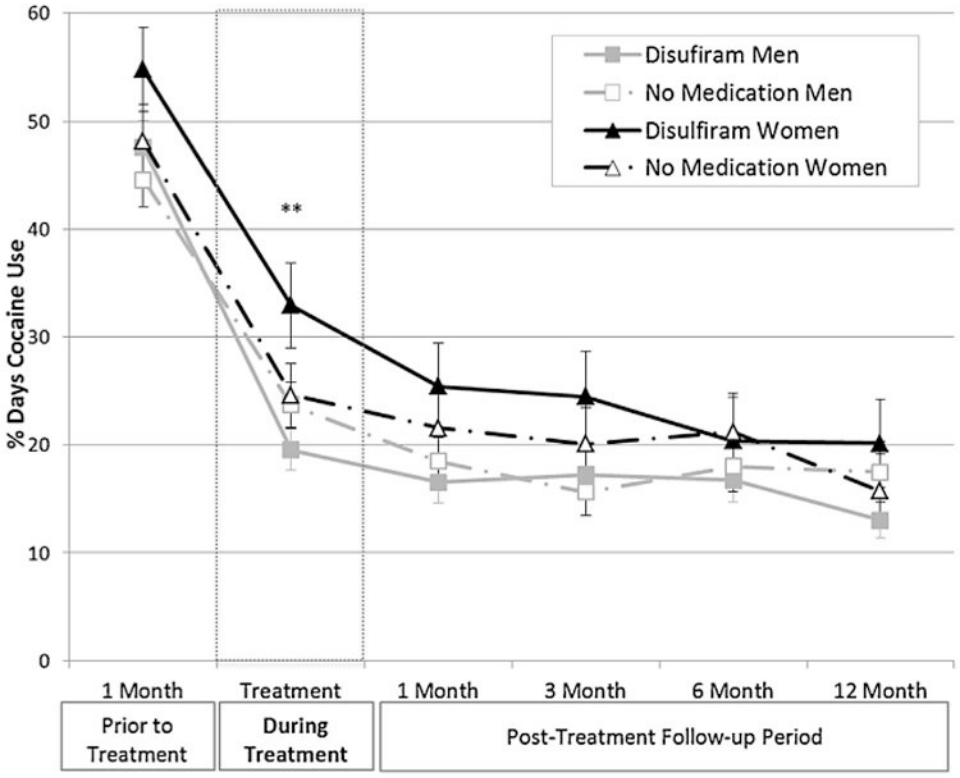

Fig. 2.

Gender by Medication group effects on cocaine use across time-points. Data presented as means with standard error of the mean error bars. ** Indicates significant gender by medication interaction ($p < 0.05$).

Table 1

Summary of the five randomized clinical trials comprising the aggregate sample.

Study characteristics	Study A	Study B	Study C	Study D	Study E
Patient sample	Cocaine dependent with co-morbid alcohol dependence	Cocaine dependent	Cocaine dependent stabilized on methdaone maintenance	Cocaine dependent	Cocaine dependent
N; female *N*(%)	91; 26 (28.6)	108; 27 (25.0)	112; 46 (41.1)	38; 18 (47.4)	85; 26 (30.6)
Treatment duration	12 weeks	12 weeks	12 weeks	8 weeks	12 weeks
Urine screen frequency during treatment	1 week	1 week	3 week	2 week	3 week
Follow-up duration	12 months	12 months	12 months	6 months	12 months
Treatment cells[1]	CBT + DSF	CBT + DSF	TSF + DSF	CBT4CBT + TAU	CBT + CM + DSF
	ClinM + DSF	IPT + DSF	TAU + DSF	TAU	CBT + DSF
	CBT + No Meds	CBT + PLAC	TSF + PLAC		CBT + CM + PLAC
	TSF + No Meds	IPT + PLAC	TAU + PLAC		CBT + PLAC
Primary outcome or follow-up cCitations	Carroll et al. (2000), Carroll et al. (1998)	Carroll et al. (2004)	Carroll et al. (2012b)	Carroll et al. (2008, 2009)	Carroll et al. (under review)

[1]CBT = clinician-delivered Cognitive Behavioral Therapy following the manualized guidelines for CBT for substance use disorders (Carroll, 1998); DSF = disulfiram (250mg/day); ClinM = clinical management (Carroll et al., 1998; O'Malley and Carroll, 1996); IPT = interpersonal therapy adapted for drug abuse (Rounsaville et al., 1985); PLAC = placebo capsule; TSF = twelve step facilitation (Baker, 1998); CBT4CBT = computer-delivered Cognitive Behavioral Therapy; TAU = treatment as usual in a community outpatient setting, including access to individual and group therapy sessions and urine screens; CM = prize-based contingency management (Carroll et al., 2012a; Petry et al., 2000).

Table 2

Demographics and substance use severity at pre-treatment baseline.

	Men		Women		Total		Gender Difference Statistics[2]		
	Mean + SD or *N*(%)[1]	N	Mean + SD or *N*(%)[1]	N	Mean + SD or *N*(%)[1]	N	For X^2	df	*p*-Value
Demographics									
Age (Mean + SD)	36.2 + 8.1	291	37 + 7.6	143	36.5 + 8	434	ns	ns	ns
Race/ethnicity (*N* (%))									
Caucasian	159 (54.6)	291	65 (45.5)	143	224 (51.6)	434	ns	ns	ns
African-American	103 (35.4)		66 (46.2)		169 (38.9)				
Hispanic	24 (8.2)		10 (7)		34 (7.8)				
Other	5 (1.7)		2 (1.4)		7 (1.6)				
Never married/living alone (*N* (%))	209 (71.8)	291	98 (68.5)	143	307 (70.7)	434	ns	ns	ns
Education and employment									
Completed high school (*N* (%))	236 (81.1)	291	104 (72.7)	143	340 (78.3)	434	**4.0**	**1**	**0.05**
Unemployed (*N* (%))	139 (47.8)	291	65 (45.5)	143	204 (47)	434	ns	ns	ns
Number of days paid for working in past 30 (Mean + SD)	12.2 + 9.7	290	6.6 + 9.2	143	10.4 + 9.9	433	**33.2**	**1431**	**<0.001**
On public assistance (*N*(%))	67 (23.1)	290	76 (53.1)	143	143 (33)	433	**39.1**	**1**	**<0.001**
Criminal Justic System Contact									
Referred by criminal justice system (*N*(%))	43 (14.9)	289	24 (16.8)	143	67 (15.5)	432	ns	ns	ns
Lifetime number of arrests (Mean + SD)	5.9 + 8.4	289	5 + 8.3	143	5.6 + 8.3	432	ns	ns	ns
Lifetime psychiatric diagnoses[3] (*N* (%))									
Alcohol use disorder	204 (79.1)	258	92 (69.2)	133	296 (75.7)	391	**4.7**	**1**	**0.03**
Major depression	38 (15.1)	279	32 (24.1)	141	70 (18.2)	420	**4.7**	**1**	**0.03**
Anxiety disorder	50 (19.4)	285	37 (27.8)	141	87 (22.3)	426	*3.6*	*1*	*0.057*
Antisocial personality disorder	74 (30.2)	245	20 (16.3)	123	94 (25.5)	368	**8.4**	**1**	**0.004**
Primary route of cocaine use (*N* (%))									
Smoke	214 (73.8)	290	114 (79.7)	143	328 (75.8)	433	ns	ns	ns
Snort	62 (21.4)		22 (15.4)		84 (19.4)				
Intravenous	14 (4.8)		6 (4.2)		20 (4.6)				
Oral	0		1 (0.7)		1 (0.2)				

	Men		Women		Total		Gender Difference Statistics[2]		
	Mean + SD or *N*(%)[1]	N	Mean + SD or *N*(%)[1]	N	Mean + SD or *N*(%)[1]	N	For X^2	df	*p*-Value
Days of use in 28 days prior to treatment (Mean + SD)									
Cocaine	12.9 + 8.4	290	14.3 + 8.7	143	13.4 + 8.5	433	ns	ns	ns
Alcohol	10.1 + 10	290	6.9 + 8.5	143	9 + 9.6	433	**10.6**	**1431**	**0.001**
Marijuana	2.8 + 6.8	225	2.7 + 6.5	117	2.8 +6.7	342	ns	ns	ns
Cigarette	21.6 + 10.4	79	24 + 9.2	44	22.4 + 10	123	ns	ns	ns
Substance use duration and treatment history (Mean + SD)									
Age at first cocaine use	21 +6.3	291	22.2 + 6.8	143	21.4 + 6.5	434	*3.2*	*1432*	*0.07*
Years of regular cocaine use	9.3 + 7.3	289	8.9 + 6.8	143	9.2 + 7.1	432	ns	ns	ns
Number outpatient substance use treatments	1.8 + 3.1	226	2.6 + 3.4	117	2.1 +3.2	343	**5.2**	**1341**	**0.02**
Number inpatient substance use treatments	2.5 + 4.8	226	3.3 + 6.2	117	2.8 +5.3	343	ns	ns	ns
Pre-treatment ASI composite scores[4] (Mean + SD)									
Cocaine	0.64 + 0.20	289	0.69 + 0.21	143	0.65 +0.21	432	**6.5**	**1430**	**0.011**
Alcohol	0.21 +0.22	289	0.14 + 0.18	143	0.19 + 0.21	432	**12.2**	**1430**	**0.001**
Psychological	0.17 + 0.19	289	0.21 +0.21	143	0.19 + 0.20	432	*3.7*	*1430*	*0.06*
Employment	0.56 + 0.29	290	0.71 +0.29	143	0.61 +0.30	433	**25.6**	**1431**	**<0.001**
Family	0.18 + 0.18	288	0.21 +0.21	143	0.19 + 0.19	431	ns	ns	ns
Other drug	0.05 + 0.06	288	0.06 + 0.09	143	0.06 + 0.07	431	ns	ns	ns
Medical	0.13 + 0.25	290	0.17 + 0.28	143	0.14 + 0.26	433	ns	ns	ns
Legal	0.09 + 0.17	289	0.10 + 0.18	143	0.09 + 0.17	432	ns	ns	ns

[1] Results are reported as Mean + SD for continuous variables and as *N* (%) for categorical or dichotomous variables.

[2] ns = statistically non-significant ($p > 0.1$); df = degrees of freedom; *F* statistics are reported for continuous variables and X^2 statistics for categorical or dichotomous variables.

[3] Psychiatric diagnoses were based on DSM-IV criteria and determined by the Structured Clinical Interview for DSM-IV (SCID). Participants were screened for Axis I disorders and only those endorsed by at least one patient are listed in the table. However, antisocial personality disorder (ASPD) was the only Axis II disorder for which systematic data is available in this sample.

[4] ASI = Addiction Severity Index; Pre-Treatment ASI composite scores reflect the month prior to the pre-treatment assessment with higher scores.

Table 3

Substance Use and Related Outcomes During Treatment and Follow-up.

Ciinical Indicators	Men		Women		Total		Gender Difference Statistics[2]		
	Mean + SD or N (%)[1]	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	*F* or Wald	df	*p*-Value
A. Clinical outcomes during treatment period									
Treatment compliance measures									
Number of days inactive treatment (Mean + SD)	54 + 32.7	291	52.4+32.3	143	53.5 + 32.6	434	ns	ns	ns
Number of urine samples submitted after day 1 of active treatment (Mean + SD)	13.1 +10.8	259	14.2 + 11.4	130	13.5 + 11	389	m	ns	ns
Cocaine Abstinence During Treatment									
Proportion days cocaine use during active treatment (self-report) (Mean + SD)	0.22 + 0.23	261	0.28 +0.28	133	0.24 + 0.25	394	**6.4**	**1392**	**0.01**
Proportion cocaine-positive urine samples during active treatment (Mean + SD)	0.56 + 0.39	253	0.67 +0.36	m	m	378	**7.7**	**1376**	**0.006**
Completed treatment and abstinence in last week of treatment (N(%))	91 (33.2)	291	37(28)	143	128(31.5)	434	ns	ns	ns
Duration of Abstinence During Treatment									
Achieved >3 weeks of consecutive cocaine abstinence (N(%))	131 (45.0)	291	49(34.3)	143	180(41.5)	434	**4.6**	**1**	**0.03**
Longest duration abstinence during actual treatment (days) (Mean + SD)	23.9 + 24.4	269	19.9 + 23.8	134	22.6 + 24.2	403	ns	ns	ns
Days of self-reported trouble within-treatment across ASI domains (Mean + SD)[3]									
Days of cocaine-related trouble (Mean + SD)	7.3 + 9.7	265	9.2 + 10.8	132	7.9 + 10.1	397	*3.1*	*1395*	*0.080*
Days of alcohol-related trouble (Mean + SD)	1.1 +4.1	265	0.55 + 2.7	132	0.90 + 3.7	397	ns	ns	ns
Days of psychological-related trouble (Mean + SD)	5.7 + 9.2	266	8 + 10.6	132	6.5 + 9.7	398	**4.7**	**1396**	**0.03**
Days of employment-related trouble (Mean + SD)	4.3 + 8.6	267	3.9 + 8.8	132	4.2 + 8.6	399	ns	ns	ns
Days of family-related trouble (Mean + SD)	1.2 + 4.6	267	1.7 +5.5	132	1.4 + 4.9	399	ns	ns	ns
Days of other drug-related trouble (Mean + SD)	1.1 +4.5	265	1.4 + 5.2	132	1.2 + 4.8	397	ns	ns	ns
Days of medical-related trouble (Mean + SD)	1.1 +4.3	268	1.8 +5.8	132	1.4 + 4.8	400	ns	ns	ns
Days of social-related trouble (Mean + SD)	0.7 + 3.2	267	1.2 + 4.4	132	0.9 + 63.7	399	ns	ns	ns
B. Clinical outcomes during follow-Up period									
Self-reported cocaine use during follow-up									
Days cocaine use in follow-up month l (Mean + SD)	4.9 + 6.9	286	6.5 + 8.5	143	5.4 + 7.5	429	**4.4**	**1427**	**0.04**
Days cocaine use in follow-up month 3 (Mean + SD)	4.6 + 7.1	284	6.2 + 8.9	142	5.1 + 7.7	426	*3.8*	*1424*	*0.05*
Days cocaine use in follow-up month 6 (Mean + SD)	4.9 + 7.1	272	5.8 + 8.8	139	5.2 + 7.7	411	ns	ns	ns
Days cocaine use in follow-up month l2 (Mean + SD)	4.2 + 6.7	237	5 + 8.1	118	4.4 + 7.2	355	ns	ns	ns

Ciinical Indicators	Men		Women		Total		Gender Difference Statistics[2]		
	Mean + SD or N (%)[1]	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	*F* or Wald	df	*p*-Value
Achieved total abstinence during 12 month follow-up period (*N* (%))	35(12.2)	286	19(13.3)	143	54(12.6)	429	ns	ns	ns

[1] Results are reported as Mean + SD for continuous variables and as *N* (%) for dichotomous variables.

[2] ns = statistically non-significant ($p > 0.1$); df = degrees of freedom; *F* statistics are reported for continuous variables and Wald statistics for dichotomous variables.

[3] ASI = Addiction Severity Index; 'Days of self-reported trouble within-treatment' variables reflect the month prior to the end of treatment, or prior to their final ASI administration in situations when participants did not complete the full treatment period.

Table 4

Medication condition effects on substance use and related outcomes during treatment and follow-up.

	Placebo or no medication						Disulfiram						Statistics		
	Men		Women		Total		Men		Women		Total		Gender	Medication	Gender × jmedication
	Mean + SD or *N*(%)[1]	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	Mean + SD or *N*(%)	*N*	*F* (or Wald),p	*F* (or Wald),p	*F* (or Wald),p
A. Clinical outcomes during treatment period															
Treatment compliance measures															
Number of days in active treatment (Mean + SD)	48.6+31.8	141	49.3 + 32.2	81	48.9 + 31.9	222	59.1 +32.9	150	56.5 + 32.3	62	58.3 +32.6	212	ns	**7.1, 0.01**	ns
Number of urine samples submitted after day 1 of active treatment (Mean + SD)	12.5 +9.9	129	13.5 + 11.7	76	12.9 + 10.6	205	14.5 + 10.7	135	15.2 + 10.7	57	14.7 + 10.6	192	ns	ns	ns
Cocaine abstinence during treatment															
Proportion days cocaine use during active treatment (self-report) (Mean + SD)	0.24 + 0.24	127	0.25 + 0.25	75	0.24 + 0.25	202	0.20 + 0.22	134	0.33 + 0.30	58	0.24 + 0.25	192	**7.3, 0.01**	ns	**5.6, 0.02**
Proportion cocaine-positive urine samples during active treatment (Mean + SD)	0.58 +0.39	123	0.65 + 0.37	69	0.61 +0.38	192	0.53 + 0.39	130	0.71 +0.35	56	0.58 +0.39	186	**7.9, 0.005**	ns	ns
Completed treatment and abstinence in last week of treatment (*N*(%))	33 (25.2)	131	21 (29.2)	72	54 (26.6)	203	58 (40.6)	143	16 (26.7)	60	74 (36.5)	203	ns	**5.5, 0.02**	ns
Duration of abstinence during treatment															
Achieved >3 weeks of consecutive cocaine abstinence (*N*(%))	59 (41.8)	141	28 (34.6)	81	87 (39.2)	222	72 (48.0)	150	21 (33.9)	62	93 (43.9)	212	ns	ns	ns
Longest duration abstinence during actual treatment (days) (Mean + SD)	20.2 + 21.8	132	18.8 + 22.3	76	19.7 + 21.9	208	27.5 + 26.2	137	21.4 + 25.7	58	25.7 + 26.2	195	ns	*3.8, 0.05*	ns
B. Clinical outcomes during follow-up period															
Self-reported cocaine use during follow-up															
Days cocaine use in follow-up month 1 (Mean + SD)	5.2 + 7.2	139	6 + 8.4	81	5.5 + 7.7	220	4.6 + 6.6	147	7.1 + 8.7	62	5.4 + 7.4	209	**4.7, 0.03**	ns	ns
Days cocaine use in follow-up month 3 (Mean + SD)	4.4 + 6.9	138	5.6 + 8.5	80	4.8 + 7.6	218	4.8 + 7.3	146	6.8 + 9.3	62	5.4 + 8	208	**4.2, 0.04**	ns	ns
Days cocaine use in follow-up month 6 (Mean + SD)	5 + 7.8	133	5.9 + 8.9	78	5.4 + 8.2	211	4.7 + 6.5	139	5.7 + 8.7	61	5 + 7.3	200	ns	ns	ns
Days cocaine use in follow-up month 12 (Mean + SD)	4.9 + 8.1	107	4.4 + 7.7	62	4.7 + 8	169	3.6 + 5.3	130	5.6 + 8.5	56	4.2 + 6.4	186	ns	ns	ns
Achieved total abstinence during 12 month follow-up period (*N* (%))	18 (12.9)	139	13 (16.0)	81	31 (14.1)	220	17 (11.6)	147	6 (9.7)	62	23 (11.0)	209	ns	ns	ns

[1] Results are reported as Mean + SD for continuous variables and as *N* (%) for dichotomous variables.

[2] ns = statistically non-significant ($p > 0.1$); F statistics are reported for continuous variables and Wald statistics for dichotomous variables.

Table 5

Behavioral treatment condition effects on substance use and related outcomes during treatment and follow-up.

	Other treatments (Not CBT or TSF)				Cognitive Behavioral Therapy (CBT)								Twelve step facilitation (TSF)						Overall behavioral treatment sample						Statistics[3]		
	Men		Women		All Other Treatments		Men		Wom0en		All CBT		Men		Women		All TSF		Men		Women		All		Gender	Treatment	Genderx Treatment
	Mean + SD or N(%)[2]	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean+ +SD or N(%)	N	Mean+SD or N(%)	N	F (or wald), p	F (or wald), p	F (or Wald), p
A. Clinical Outcomes During Treatment Period																											
Treatment Compliance Measures																											
Number of days in active treatment (Mean + SD)	59.4 + 29.3	46	46 53.1 +28.4	29	57.0 + 29.0	75	47.7 + 29.7	39	38.7 + 29.1	18	44.9 + 29.6	57	51.6+ +34.6	25	55.4 + 34.6	23	53.4 + 34.3	48	53.5 + 30.9	110	50.2+31.1	70	52.2+30.9	180	ns	*2.7, .07*	ns
Number of urine samples submitted after day 1 of active treatment (Mean + SD)	14.6 + 9.7	43	43 13.6+10.4	28	14.2 + 9.9	71	8.2 + 5.1	37	6.6 + 5.3	17	7.7 + 5.2	54	14.5 + 13.7	23	14.7 + 13.2	23	14.6+ 13.3	46	12.3 + 9.9	103	12.2 + 10.9	68	12.3 + 10.3	171	ns	8.0, <001	ns
Cocaine Abstinence During Treatment																											
Proportion days cocaine use during active treatment (self-report) (Mean + SD)	0.3 +0.3	44	44 0.3+0.2	28	0.3 +0.3	72	0.2 + 0.2	37	0.2 + 0.2	18	0.2 + 0.2	55	0.2 + 0.1	20	0.3 +0.3	21	0.2 + 0.2	41	0.2 + 0.2	101	0.3 + 0.3	67	0.2 + 0.3	168	ns	4.1, .02	ns
Proportion cocaine-positive urine samples during active treatment (Mean + SD)	0.6 + 0.4	43	43 0.7 + 0.3	28	0.7 + 0.4	71	0.4 + 0.4	34	0.6 + 0.4	16	0.5 + 0.4	50	0.7 + 0.3	20	0.7 + 0.3	17	0.7 + 0.3	37	0.6 + 0.4	97	0.7 + 0.3	61	0.6 + 0.4	158	ns	5.1, .007	ns
Completed treatment and abstinence in last week of treatment (N(%))	14 (35.0)	40	40 8 (34.8)	23	22 (34.9)	63	12 (33.3)	36	3 (20.0)	18	15 (29.4)	51	5 (20.8)	24	6 (26.1)	23	11(23.4)	47	31 (31.0)	100	17 (27.9)	61	48 (29.8)	161			
Duration of Abstinence During Treatment																											
Achieved >3 weeks of consecutive cocaine abstinence (N(%))	13 (28.3)	46	46 4(13.8)	29	17 (22.7)	75	17 (43.6)	39	6 (33.3)	18	23 (40.4)	57	8 (32.0)	25	8 (34.8)	23	16 (33.3)	48	38 (34.5)	110	18 (25.7)	70	56 (31.1)	180	ns	ns	ns
Longest duration abstinence during actual treatment (days) (Mean + SD)	18.8 + 20.7	44	44 14.5 +19.8	28	17.1 +20.3	72	26.4 + 23.9	37	16.9 + 17.5	18	23.3 + 22.5	55	22.3 + 20.7	20	22.3 + 23.6	19	22.3 + 21.9	39	22.3 + 22.0	101	17.5 + 20.4	65	20.4 + 21.4	166	ns	ns	ns
B. Clinical Outcomes																											

	Other treatments (Not CBT or TSF)				Cognitive Behavioral Therapy (CBT)								Twelve step facilitation (TSF)								Overall behavioral treatment sample						Statistics[3]		
	Men		Women		All Other Treatments		Men		Wom0en		All CBT		Men		Women		All TSF				Men		Women		All		Gender	Treatment	Genderx Treatment
	Mean + SD or N(%)[2]	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N	Mean + SD or N(%)	N			Mean + SD or N(%)	N	Mean+ +SD or N(%)	N	Mean+SD or N(%)	N	F (or wald), p	F (or wald), p	F (or Wald), p
During Follow-Up Period																													
Self-reported Cocaine Use During Follow-Up																													
Days cocaine use in follow-up month 1 (Mean + SD)	6.1 +7.4	45	45 4.5 + 6.9	29	5.5 + 7.2	74	5.3 +8.2	39	8.8 + 9.7	18	6.4 + 8.8	57	3.8 + 5.2	24	8.3 +9.7	23	6.0 + 8.0	47			5.3 +7.3	108	6.9 + 8.8	70	5.9 + 7.9	178	3.0, *.09*	ns	*2.7, .07*
Days cocaine use in follow-up month 3 (Mean + SD)	6.2 + 8.8	45	45 4.2 + 6.8	28	5.4 + 8.1	73	3.8 + 5.3	38	7.7 + 8.8	18	5.1 +6.8	56	4.7 + 6.9	24	6.9 + 10.0	23	5.8 + 8.6	47			5.0 + 7.3	107	6.0 + 8.5	69	5.4 + 7.8	176	ns	ns	ns
Days cocaine use in follow-up month 6 (Mean + SD)	6.5 + 8.6	44	44 5.7 + 7.8	26	6.2 + 8.3	70	4.7 + 6.5	36	9.0 + 11.7	18	6.1 +8.7	54	5.1 +8.5	23	5.3 +8.0	23	5.2 + 8.2	46			5.6 + 7.9	103	6.4 + 9.1	67	5.9 + 8.3	170	ns	ns	ns
Days cocaine use in follow-up month 12 (Mean + SD)	4.4 + 6.9	34	34 5.1+7.5	18	4.6 + 7.0	52	7.6 + 10.2	24	7.6 + 11.6	10	7.6 + 10.4	34	4.5 + 8.5	19	4.2 + 7.4	23	4.4 + 7.8	42			5.4 + 8.4	77	5.2 + 8.3	51	5.3 + 8.3	128	ns	ns	ns
Achieved total abstinence during 12 month follow-up period (N(%))	3 (6.7)	45	45 6(20.7)	29	9 (12.2)	74	7 (17.9)	39	3 (16.7)	18	10 (17.5)	57	1 (4.2)	24	1 (4.3)	23	2 (4.3)	47			11 (10.2)	108	10 (14.3)	70	21 (11.7)	178	ns	ns	ns

Data from individuals receiving disulfiram and all individuals from study E have been excluded from the table above. Study E was excluded because it involved CBT as a platform treatment on which other treatments were added, so it was not possible to classify the treatment conditions accurately in that case. ‘Results are reported as Mean + SD for continuous variables and as N(%) for dichotomous variables. ns = statistically non-significant (p > .1); F statistics are reported for continuous variables and Wald statistics for dichotomous variables.