Drug and Alcohol Dependence 145 (2014) 156–167

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

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

Elise E. DeVito[a,*], Theresa A. Babuscio[b], Charla Nich[b], Samuel A. Ball[b,c], Kathleen M. Carroll[b]

[a] Department of Psychiatry, Yale University School of Medicine, 1 Church Street, Suite 701, New Haven, CT 06510, United States
[b] Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, 151D, West Haven, CT 06516, United States
[c] The APT Foundation, New Haven, CT 1 Long Wharf, New Haven, CT 06511, United States

ARTICLE INFO

Article history:
Received 4 April 2014
Received in revised form 11 October 2014
Accepted 12 October 2014
Available online 20 October 2014

Keywords:
Cocaine
Sex
Gender
Psychotherapy
CBT
Disulfiram

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.
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.

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

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

* Corresponding author. Tel.: +1 203 737 4882; fax: +1 203 737 3591.
E-mail address: elise.devito@yale.edu (E.E. DeVito).

http://dx.doi.org/10.1016/j.drugalcdep.2014.10.007
0376-8716/

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).