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## Gender Research in the National Institute on Drug Abuse National Treatment Clinical Trials Network: A Summary of Findings

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### Abstract

**Background**—The NIDA National Drug Abuse Treatment Clinical Trials Network (CTN) was established to foster translation of research into practice in substance abuse treatment settings. The CTN provides a unique opportunity to examine in multi-site, translational clinical trials, the outcomes of treatment interventions targeting vulnerable sub-groups of women; the comparative effectiveness of gender-specific protocols to reduce risk behaviors; and gender differences in clinical outcomes.

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**Objectives**—To review gender-related findings from published CTN clinical trials and related studies from January, 2000 through March, 2010.

**Methods**—CTN studies were selected for review if they focused on treatment outcomes or services for special populations of women with substance use disorders (SUDs) including those with trauma histories, pregnancy, co-occurring eating and other psychiatric disorders and HIV risk behaviors; or implemented gender-specific protocols.

**Results**—The CTN has randomized 11,500 participants (41% women) across 200 clinics in 24 randomized clinical trials in community settings, of which 4 have been gender-specific. This paper summarizes gender-related findings from CTN clinical trials and related studies, focusing on trauma histories, pregnancy, co-occurring eating and other psychiatric disorders, and HIV risk behaviors.

**Conclusions**—These published studies have expanded the evidence base regarding interventions for vulnerable groups of women with SUDs as well as gender-specific interventions to reduce HIV risk behaviors in substance using men and women. The results also underscore the complexity of accounting for gender in the design of clinical trials and analysis of results.

**Scientific Relevance**—To fully understand the relevance of gender-specific moderators and mediators of outcome, it is essential that future translational studies adopt more sophisticated approaches to understanding and measuring gender-relevant factors and plan sample sizes that are adequate to support more nuanced analytic methods.

## Keywords

substance use disorders; gender differences; substance use treatment; women substance abuse treatments; HIV risk behaviors; eating disorders; PTSD; co-occurring disorders; HIV prevention; pregnant women

## 1.0 Introduction

The National Institute of Drug Abuse's (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) [1, 2] was established in 1999 to foster the translation of research into practice by conducting rigorous, multi-site clinical trials of behavioral, pharmacological, and integrated behavioral and pharmacological interventions directly within community-based treatment programs [2, 3]. Currently, the CTN includes 16 network nodes, which is an organized partnership between researchers and approximately 240 affiliated community treatment programs.

The Gender Special Interest Group (GSIG) was established at the inception of the CTN because of known gender differences in the biological, psychological, and sociocultural factors associated with substance abuse initiation, progression, and treatment engagement [2]. The mission of the GSIG was to help expand gender research across CTN studies to (a) address inadequate representation of women in clinical trials of treatments for substance abuse [4–6], (b) support research designs with adequate power to detect gender differences, (c) reduce exclusion criteria that could differentially limit, by gender, the generalizability of results (e.g., co-occurring psychiatric disorders, psychotropic medications) [7], and (c) provide technical assistance with gender-specific assessments and analyses to evaluate differential treatment outcomes for men and women [7, 8]. The GSIG has played a particularly important role in the CTN because, while the NIH mandates inclusion of women in clinical trials and presentation of valid analyses of results by gender, most traditional randomized controlled trials (RCTs) of substance abuse treatments have not been designed in ways that enable researchers to address or assess gender differences in treatment outcomes [4–6]. Thus, in addition to contributing to design and analyses of CTN study

protocols, the GSIG works to synthesize gender-related findings and identify substance abuse research areas that could benefit from additional attention to gender-related outcomes. In order to provide guidance for future CTN protocols, members of the GSIG conducted a critical review of the literature published between 1975 and 2005, evaluating characteristics associated with treatment entry, retention, and outcomes in women with substance use disorders [9].

Given the relative lack of previous randomized clinical trials and gender-relevant studies of substance abuse treatment outcomes [9], the CTN provides a unique opportunity to examine in large, multi-site, translational clinical trials, the outcomes of treatment interventions targeting vulnerable sub-groups of women; the comparative effectiveness of gender-specific protocols to reduce risk behaviors; and gender differences in clinical outcomes. In addition, CTN researchers have used secondary data analysis across protocols, as well as national survey methods, to examine other treatment issues relevant to women with substance use disorders [10].

The purpose of this paper is to present results from CTN translational studies with gender-related findings, including those with gender-specific protocols for treatment seeking populations with substance use disorders. This paper will highlight new findings from these studies as well as lessons learned for future gender-specific research in substance abuse treatment outcomes.

## 2.0 Methods

From January 2000 through March 2010, the CTN launched 24 clinical trials [11] across approximately 200 treatment clinics, randomizing 11,500 participants including 4646 women (41%). Twenty of these trials have been completed, and 15 have published main outcome papers. Of these 15 trials, 4 studies were pharmacologic, 8 psychosocial/behavioral, 1 a combination of medication and counseling, and 2 targeted HIV/hepatitis C virus risk behavior [11]. In addition to these 24 trials, CTN investigators conducted 14 ancillary studies, 2 of which were gender-specific [12, 13], 5 cross-study secondary analyses, one of which was a secondary analysis examining gender differences in HIV risk behaviors [10], a national health services survey in collaboration with non-CTN investigators [14, 15], and a critical review of the literature on gender and substance abuse treatment [9]. Four of the 24 randomized clinical trials have been on gender-specific treatment protocols (3 focused on women and 1 on men) [16–19]. All CTN studies were approved by each local IRB for human research and all participants signed written informed consent prior to participating in the research. A detailed review of CTN procedures is beyond the scope of this paper but are summarized in the main outcome papers of each study as well as in several recent reviews of CTN studies [2, 11]. All CTN studies are described on the CTN Dissemination Library website (<http://ctndisseminationlibrary.org/>). Completed clinical trials and ancillary studies with published results were selected for review in this paper if they focused on (1) treatment outcomes or services for special populations of women with SUDs including pregnant women and women with co-occurring disorders (e.g., PTSD and eating disorders); or (2) gender differences in HIV risk behaviors and outcomes of gender-specific protocols for HIV risk reduction.

## 3.0 Results

Nine studies, including four CTN RCTs, two CTN sub-studies, a secondary analysis of CTN data, and two analyses of national survey data, were selected for review; their designs, sample sizes, and main findings are summarized in Table 1. Six of these studies address

special populations of women with SUDs, and three of these studies focus on gender differences in HIV risk behavior and gender-specific protocols for HIV risk reduction.

### 3.1 Interventions and studies targeting specific sub-groups of women with substance use disorders

The CTN conducted two clinical trials, two sub-studies, and two analyses of national survey data that examined treatment outcomes or treatment service availability for specific subgroups of substance abusing women including pregnant women, women with co-occurring PTSD, and women with co-occurring eating disorders.

**3.1.1. Interventions for pregnant women with substance use disorders—**The Motivational Enhancement Therapy for Pregnant Substance Users (MET-PS) trial (CTN-0013) evaluated the efficacy of MET-PS relative to treatment as usual (TAU) in increasing treatment utilization and decreasing substance use in pregnant substance users entering outpatient substance abuse treatment [16]. Two hundred participants, recruited from 4 treatment programs, were randomized to receive either 3 individual sessions of MET-PS or the first 3 individual sessions normally provided by the treatment program (e.g., treatment as usual or TAU).

One hundred and sixty two participants (81%) completed the 1-month active phase; average attendance was 62%. Intravenous use at baseline was reported by 10.2% of participants. Participants reported decreased substance use during the first month of treatment, with no differences between MET-PS and TAU participants. There were, however, greater decreases in self-reported substance use among minority participants who received MET-PS than in those who received TAU; this difference was marginally significant ( $Z=1.96$ ,  $p=0.0504$ ) in the entire sample and was significant in the evaluable sample ( $Z=2.24$ ,  $p=.0253$ ). Secondary analyses revealed that participants who reported a clear quit goal at baseline reduced their drug use more if they were assigned to the MET-PS condition, while those who did not endorse a clear quit goal had better outcomes if assigned to the TAU condition [20].

A post-hoc evaluation of the possible effect of financial incentives on visit attendance in non-methadone-maintained MET-PS participants ( $N=175$ ) compared attendance at monetarily reinforced research visits (\$25-30 retail scrip per visit) to attendance at non-incentivized treatment sessions [21]. Consecutive and overall weeks of attendance for incentive-reinforced research visits were significantly better than attendance at treatment sessions with no financial incentives. Greater attendance of research visits, compared to treatment visits, was associated with having fewer dependents, which might indicate that gift certificates were more reinforcing for those for whom the burden of attendance was less. No significant relationship was found between participant income and research versus treatment visit attendance. These results suggest that incentives might be effective in increasing attendance in difficult-to-retain populations, but more information is needed on the optimal magnitude of incentives and on the predictors of positive responses to incentives.

A sub-study focused on a sample of women who had completed the MET-PS clinical trial in order to examine potential predictors of child abuse (CTN-0013-A-1). This study investigated associations between trauma, route of drug administration (intravenous [IV] use, 10.2% at baseline), and Child Abuse Potential (CAP) in pregnant substance abusers. Investigators used CAP as both a continuous and dichotomous measure, and used narrowly (i.e., PTSD) and broadly defined (i.e., anxious arousal, depression, and anger/irritability) trauma symptoms [13]. Participants were 44 ethnically diverse substance using pregnant women (61.4% Hispanic, 15.3 % Native American, and 15.3 % Caucasian women) who had completed the MET-PS clinical trial. Participants reported high child abuse potential (CAP), with 43% reaching the conservative CAP cutoff and the majority (56%) meeting the liberal

CAP cutoff [13]. Trauma symptoms-- narrowly and broadly defined--and intravenous (IV) drug use accounted for significant variance in CAP score: Women with greater trauma symptoms and IV users reported significantly greater CAP scores. To a lesser extent, trauma exposure also accounted for significant CAP variance. Although the relationships between trauma exposure, traumatic stress, and substance abuse have been documented empirically, little is known about the relevance of trauma variables to pregnant substance users' child abuse potential. In the only previous study that used trauma history to predict *mothers'* child abuse potential, Rinehart and colleagues (2005) [22] found it showed significant, but modest, correlations with child abuse potential. There is no literature addressing intravenous (IV) drug use as a predictor of child abuse potential in pregnant substance users. In fact, there are no extant studies that address the role of IV drug use in child abuse potential, beyond including it as one index of drug severity for cumulative environmental risk [23]. In this study of substance abusing *mothers*, Nair and colleagues (2003) [23] included IV use, as well as frequency of drug use overall, as an indicator of drug use severity. Drug use severity, incorporated into a cumulative environmental risk index, was predictive of child abuse potential [22, 23]. The results from the present study suggest that both trauma and IV use are significant predictors of CAP in this population.

**3.1.2. Interventions for women with co-occurring substance use and post-traumatic stress disorders**—The Women and Trauma study (WTS, CTN-0015) assessed the effectiveness of adding a trauma-focused group intervention to outpatient substance abuse treatment. WTS compared a 12-session version of Seeking Safety (SS) [24, 25], to an attention control women's health education intervention (WHE) [17]. Subjects were 353 women seeking treatment for SUDs who met criteria for posttraumatic stress disorder (PTSD) across 7 treatment programs. In addition to treatment as usual (TAU), participants received twice-weekly group interventions over a 6-week period.

Both the Seeking Safety and the WHE conditions were associated with large, clinically significant reductions in PTSD symptoms, with small interaction and trend effects favoring Seeking Safety, particularly in participants with greater treatment attendance [17]. While trauma symptoms were reduced in both interventions, abstinence rates and drug/alcohol days of use were not affected by either intervention. These main findings indicate that adding trauma-focused treatment to treatment as usual in substance abuse treatment programs reduced PTSD symptoms during active treatment and sustained these reductions over 1 year while not increasing substance use. Non-trauma oriented health groups, comprised of women with trauma histories, also reduced PTSD symptoms in substance using women [17].

A secondary analysis examined the temporal course of improvement in PTSD and substance use disorder symptoms [26]. A continuous Markov model was fit on four defined responder categories (non-responder, substance use responder, PTSD responder or global responder [improvement in both PTSD and substance use]) to investigate the temporal association between improvement in PTSD and substance use symptom severity during the study's treatment phase. A generalized linear model was applied to test this relationship over follow-up.

Results showed that non-responders, substance use responders and global responders tended to maintain original classifications, whereas PTSD responders were significantly more likely to transition to global responders over time, indicating that PTSD improvement that is maintained is associated with subsequent substance use improvement. Seeking Safety was significantly more effective in achieving substance use improvement compared to the WHE group, but only among those who were heavy substance users at baseline and had achieved significant PTSD reductions. Thus, PTSD severity reductions were more likely to be

associated with substance use improvement, with minimal evidence of substance use symptom reduction improving PTSD symptoms.

Relatively few women experienced adverse events related to the study (17%) and there was no difference in the number or severity of adverse events between women in the trauma group and WHE group [27]. These findings suggest that these interventions can be conducted without causing significant harm, such as increased PTSD symptoms, which is a common clinical concern when addressing trauma in the context of substance abuse treatment. In addition, trauma treatment had an effect on HIV risk behavior [28]. Of women who engaged in 12 or more unprotected sexual occasions (USO) per month at baseline, those in the Seeking Safety group had significantly fewer USOs at 12-month follow-up than the women in the WHE group. Trauma-focused treatment reduced USOs among women with high-risk sexual practices, even if sexual risk behaviors were not a primary focus of the treatment.

Another sub-study (CTN-0015-A-1) investigated the prevalence of eating disorder (ED) symptoms and their effect on treatment outcomes in a sample of participants enrolled in the WTS trial. Subjects were 122 of the 353 women who participated in the Women and Trauma Study (WTS). The Eating Disorder Examination-self report (EDE-Q), and measures of PTSD and SUD symptoms were administered at baseline, during treatment and at 4 follow-up points in four of the seven study sites [12]. This study found that the most common eating disorder (ED) behavior reported was binge eating, with almost one third (29%) reporting at least one episode of binge eating in the past month. Data were analyzed according to these findings, which indicated the presence of two subgroups of women in the sample: those who reported binge eating (Binge group;  $n = 35$ ) and those who did not report binge eating (No Binge group;  $n = 87$ ). Women in the Binge group endorsed significantly higher ED, PTSD and depression symptoms at baseline than those in the No Binge group. Though all participants showed significant reductions in PTSD symptoms and improvements in abstinence rates, the improvements for the Binge group were significantly lower. These findings suggest that a sub-group of women with co-occurring PTSD and SUDs who endorsed binge ED symptoms responded differently to SUD/PTSD group treatment [12]. The finding of lower abstinence rates in the binge eating group is consistent with previous reports that individuals with a range of psychiatric symptoms may use substances as a maladaptive way to manage these symptoms [29, 35]. Identification of eating disorder symptoms among treatment-seeking women with SUDs may be important for tailoring interventions and enhancing treatment outcomes.

### **3.1.3. Treatment services for co-occurring substance use and eating disorders**

—Given the potential clinical relevance of eating disorder symptoms among treatment-seeking women with SUDs, investigators examined data from the National Treatment Center Study (NTCS) [30,31] to enhance understanding of current treatment resources available to patients with co-occurring eating disorders who present for addiction treatment [14,15]. The first analysis focused on a nationally representative sample ( $n=351$ ) of publicly-funded programs that received more than 50% of their annual operating revenues from federal, state, or local grant sources [14]. Data were collected during on-site visits conducted between January 2005 and August 2006. This survey found that approximately half of publicly funded substance abuse treatment programs screen patients for eating disorders, but that patients are more likely to be assessed through informal clinical evaluations than with standardized diagnostic interviews. Less than one-third of publicly funded programs reported that they admit all eating disorder cases, while almost one-half of programs admitted cases of low severity. Fewer than 1 in 6 programs attempt to treat co-occurring eating disorders, and only 3% had formal referral agreements with other providers for eating disorder treatment. These authors concluded that while eating disorders can be

clinically relevant for substance abuse treatment outcomes, less than 50% of publicly funded programs screen for or provide eating disorder treatment or referral. This could lead to poorer outcomes for these patients [14].

By contrast, an analysis of 345 privately-funded addiction treatment programs [15], found that 75% of these programs reported screening for eating disorders. Only 21%, however, screened for eating disorders using a standardized instrument. Twenty percent of programs reported admitting patients with co-occurring eating disorders regardless of severity, and 67% reported admitting cases of low severity. Despite these higher rates among private addiction treatment programs, only 21% attempted to treat eating disorders. These two analyses demonstrate the need for enhanced screening, detection, and treatment of co-occurring eating disorders among those seeking treatment for substance use disorders.

### **3.2 Studies of gender-specific interventions for HIV risk reduction and gender differences in HIV risk behaviors among SUD treatment seekers**

Two studies (CTN-0018 and CTN-0019) examined gender-specific interventions for HIV risk reduction among substance abuse treatment seekers [18,19]. A secondary analysis of data from multiple treatment protocols evaluated gender differences in the prevalence and correlates of sexual and drug-related HIV risk behaviors (CTN-0039-S) [11].

#### **3.2.1 Human Immunodeficiency Virus (HIV) prevention interventions for men and women in substance abuse treatment**

—The CTN conducted two protocols to evaluate gender-specific interventions to reduce HIV/Autoimmune Deficiency Syndrome (AIDS) risk behaviors. These were ‘Real Men Are Safe’ for men (CTN-0018) [18], and ‘Safer Sex Skills Building’ for women (CTN-0019) [19]. Participants were 590 men in CTN-0018 across 14 sites [18], and 515 women in CTN-0019 across 12 sites [19]. The gender-specific interventions were 5 group sessions while the control interventions were a standardized single sessions meant to reflect treatment as usual.

Although the interventions for ‘Real Men Are Safe’ and ‘Safer Sex Skills Building’ have many similarities, such as providing basic information about HIV, behaviors to prevent its transmission, and development of communication skills related to sexual situations, there were notable differences between the two. In ‘Real Men Are Safe’ there is a focus on the interplay between sex and drugs, recognizing partner needs and gender role expectations, the importance of accepting responsibility for one’s own behavior, and the use of assertive communication skills and “I” statements in safe sex negotiations. In ‘Safer Sex Skills Building,’ there is a focus on increasing self-efficacy, decision-making skills, negotiation and refusal skills, and skills for recognizing risk of partner abuse and preemptive safety planning for women having sexual relationships with substance-using men.

Both ‘Real Men Are Safe’ and ‘Safer Sex Skills Building’ were shown to be effective in reducing the number of USOs (vaginal or anal intercourse without a male or female condom) compared to a standardized HIV prevention educational intervention for both women and men, although the pattern of risk reduction differed by gender [18, 19]. Women randomized to the ‘Safer Sex Skill Building’ intervention and women in the control HIV intervention had a similar significant decrease in the number of USOs at the 3 month follow-up compared to baseline. For men, however, only those randomized to the ‘Real Men are Safe’ intervention significantly decreased their USOs at the 3-month follow-up. Both men and women who were randomized to ‘Real Men are Safe’ or ‘Safer Sex Skill Building,’ respectively, reported significantly greater reductions in the number of USOs at 6-month follow-up compared to participants in the control HIV educational interventions, suggesting a possible “sleeper effect” among women. In secondary analyses, the superiority of these gender-specific HIV prevention interventions was enhanced when session attendance was

added to the primary outcome regression models. Consistent with the emphasis on reducing sex under the influence, men assigned to the 'Real Men Are Safe' intervention were less likely than male controls to have engaged in sex under the influence of drugs or alcohol during their most recent sexual event prior to the 3 month follow-up assessment than men assigned to the control intervention [32].

**3.2.2 Gender differences in the prevalence and predictors of HIV risk behaviors**—This study examined gender differences in the prevalence and correlates of sexual and drug-related HIV risk behaviors in a large sample of treatment-enrolled individuals with substance use disorders participating in 5 separate multi-site trials of the NIDA CTN (CTN-0039-S) [11]. This study was a secondary analysis of common assessment data collected at entry for these 5 CTN studies (available at [www.ctndatashare.org](http://www.ctndatashare.org)). HIV risk behaviors were assessed using the HIV Risk Behavior Scale (HRBS) [33].

The sample of 1,429 individuals was 45% female, and women were more likely than men to report multiple partners (20% versus 13%), unprotected sex with regular partners (82% versus 75%), and a higher sex risk composite score overall (mean (SD) 6.1 (3.0) versus 5.8 (3.0)). In models predicting overall sex risk, greater alcohol and psychiatric severity was associated with higher sexual risk for women but not men. Greater alcohol severity was also associated with higher HIV drug risk behavior for women, but not men. These findings suggest that there is a context or culture in which HIV risk behaviors occur as well as individual differences in the presence of risk factors associated with engaging in HIV risk behaviors. Specifically, risk factors were differentially predictive of HIV risk behavior for women and men, highlighting the need for gender-specific risk reduction assessments and interventions [11].

## 4.0. Discussion

We have presented a summary of findings from the first decade of gender-related translational clinical trials in the CTN, including studies that focus on (1) specific subgroups of vulnerable women including pregnant women and those with co-occurring other psychiatric problems such as PTSD or eating disorders; and (2) gender differences and gender-specific interventions for HIV risk-reduction. Overall, there are a number of new and significant findings from these studies. For specific targeted sub-groups of vulnerable women with substance use disorders, CTN studies have found that (1) Motivational Enhancement Treatment for Pregnant substance abusers (MET-PS) may be especially beneficial to minority women; (2) Pregnant women with histories of trauma and intravenous drug use were at high risk of child abuse; (3) Adding trauma-focused group behavioral treatments to existing substance abuse treatment reduces PTSD symptoms in women with co-occurring substance use and post-traumatic stress disorder; (4) Treatment-seeking women with co-occurring substance use and PTSD reported binge eating as the most common eating disorder symptom, and the presence of these symptoms at baseline was associated with lower rates of abstinence at post-treatment follow-up compared to those without symptoms; and (5) In spite of the prevalence of co-occurring substance use and eating disorders among women [34, 35], not all substance abuse treatment programs screen for eating disorders, and only a minority of programs provide either assessment, referral, or, treatment of eating disorders.

With regard to gender differences in HIV sexual risk behaviors and risk reduction, CTN studies have demonstrated that (1) treatment-enrolled women with substance use disorders were more likely than men to report a high frequency of HIV risk sexual behaviors; (2) alcohol and psychiatric severity increase this risk among women but not men; and (3) both



men and women who received gender-specific HIV risk prevention treatment reduced their HIV risk behaviors especially when three or more sessions were attended and when results were examined at the 6-month follow-up.

These study results are important in themselves in expanding the evidence base for gender-specific interventions targeted at vulnerable groups (e.g., pregnant women and women with co-occurring psychiatric disorders) as well as in providing additional evidence for gender differences in risky sexual behaviors and for the effectiveness of gender-specific interventions to reduce HIV sexual risk behaviors. The results also point out the complexity of accounting for gender in the design of clinical trials and in analyses of results. Federally funded clinical trials are required to provide a valid analysis of results by gender [36]. The studies highlighted in this paper provide evidence that analyzing substance abuse clinical trials data using gender as a dichotomous variable is not always the best approach to understanding the effectiveness of gender-specific interventions or gender differences in substance abuse risk behaviors or treatment outcomes.

Indeed, the translational studies highlighted here demonstrate that across protocols, women often present with other co-occurring psychiatric disorders and trauma histories that complicate both substance abuse treatment outcomes and pose additional psychosocial risks. For example, pregnant women who were enrolled in the MET-PS trial were at high risk for abusing their children, especially if they also had trauma histories. Similarly, a significant minority of women enrolled in a clinical trial adding an intervention to reduce trauma-related symptoms reported binge eating behaviors. Such behaviors were associated with smaller reductions in PTSD symptoms and substance use compared to women without binge eating.

There are a number of limitations in the present report. Although 16% of CTN protocols have been gender-specific and 41% of participants randomized have been women, it has been difficult to obtain adequate numbers of participants in mixed-gender protocols to conduct certain types of analyses (e.g., outcomes stratified by gender and race or ethnicity). In addition, diverse methods and assessments can make it difficult to otherwise analyze gender-relevant data across studies, even when common protocols are designed to foster such analyses. Conversely, the availability of a common battery of assessment instruments, implemented across studies, can provide an unusually large resource for conducting some types of analyses.

In spite of its limitations, the CTN provides a unique opportunity in substance abuse clinical treatment trials to examine gender differences in risk factors and vulnerability in real-world treatment settings. It has also provided important opportunities for examining moderators and mediators of outcomes that may vary by gender and require the potentially large and diverse samples that can be provided by the CTN to resolve gender-related questions. For example, it was only in the context of a large multi-site trial that it was possible to enroll an adequate number of pregnant women to conduct a clinical trial of a specific intervention versus TAU. Nevertheless, even the sample size attained in the CTN trial was sufficient only to provide preliminary evidence that the intervention may be most beneficial in minority women. Investigators have previously noted the dearth of research examining the interaction between gender and ethnicity in treatment process and clinical outcomes [9]. It is important to underscore the need for large sample sizes in T2 translation such as substance abuse clinical trials in order to answer fundamental questions of moderators and mediators of outcome that vary by gender [37].

While the opportunity to translate clinical trials in a large national network of community treatment programs has been a clearly recognized advantage of the CTN [1, 38], another less

recognized advantage is the establishment of collaborative relationships across the country among researchers and community treatment providers. Such collaborative networks have the opportunity to focus on specific issues, such as gender, that are relevant across the spectrum of treatment outcome trials. These collegial networks enhance the opportunity to design creative studies that maximize the impact of collected data. For example, the CTN's Gender Special Interest Group has brought together a national group of clinicians and clinical researchers who have been able to take advantage of opportunities to design research projects to investigate gender-specific treatment questions. The studies cited in this paper represent the effort of the GSIG to include the addition of a standard eating disorders measure to an ongoing trial to investigate the impact of these symptoms on outcome; the design of a secondary analysis of data across 5 trials to examine gender differences in HIV risk behaviors; and the inclusion of questions in a national survey of addiction treatment programs regarding screening, treatment, and referral of patients with eating disorder symptoms. Such studies amplify gender-specific results and can be obtained for a relatively small additional investment of resources when initiated by national networks of collaborators such as in the CTN.

Despite these advantages, the complexity of investigating the roles gender plays in substance abuse risk behaviors and treatment outcomes cannot be answered solely by increasing sample sizes such that there is sufficient power to analyze by sub-groups (e.g., race or ethnicity and gender status) or for moderators and mediators of outcome that may vary by gender. Rather, it behooves investigators of clinical trials to consider additional gender-related factors in protocol design, in both between- and within-gender analyses. For example, accumulating evidence shows that menstrual cycle phase can affect nicotine and stimulant dependence treatment outcomes among women [39–41]. Studies examining outcomes for these and other substance use disorders should consider collecting menstrual cycle data in the design to further assess outcomes by gender. The same would hold true for measures of abuse histories and psychiatric severity as potential gender-related moderators of outcome. In designing clinical trials that can examine gender-related outcomes, investigators might consider the following: (a) define gender-specific moderators of outcome at the outset; (b) examine characteristics of target samples for prevalence of these moderators; and (c) consider sample sizes that allow for analyses that take into account these moderators.

In addition to the national network of collaborators established through the CTN, the CTN has also created a rich database that is available for gender-specific secondary or meta-analyses (cf. Brooks and colleagues, [11]). Researchers can obtain public data sets at the data share site at <http://www.ctndatashare.gov>. Further gender-related analyses of this database could have important public health significance, and is consistent with the national emphasis on enhancing our knowledge about the adoption of evidence-based practices in community substance abuse treatment programs [42, 43].

Finally, the results reported in this paper underscore areas where additional research is needed. Women with PTSD in the Women and Trauma Study reported a high rate of disordered eating, and yet publicly-funded substance abuse treatment programs generally neither assess patients for eating disorder symptoms nor refer or deliver any treatment interventions for co-occurring eating disorders. Women are disproportionately affected by co-occurring eating and substance use disorders [44]. Nevertheless, there are currently no studies of delivering integrated treatments for these two disorders [9, 14], and development and evaluation of such treatments in a variety of relevant treatment service delivery settings seems warranted. In addition to the development and testing of effective treatments for specific subpopulations of women and men, randomized controlled trials testing the

effectiveness of mixed-gender versus gender-specific treatments and treatment programs is also warranted.

## 5.0 Future directions

The relevance of gender to substance abuse treatment outcomes is complex and multifactorial, requiring a sophisticated assessment of potential moderators and mediators of outcome that may be gender-specific. Ideally, researchers should measure predictors of treatment outcomes that vary by gender, with sample sizes adequate to complete assessments of the roles played by these factors. Future research could help us understand whether treatments tailored to meet the needs of certain populations of men and women with substance use disorders are more or less effective than standard treatments, and whether treatment delivered in single-gender formats (e.g., groups, residential programs, aftercare) are more or less effective than care delivered in mixed-gender settings. Vulnerable populations of women and men with co-occurring disorders may benefit from gender-specific treatments, and we recommend additional research to help design effective substance abuse treatment interventions for relevant subgroups, such as women with co-occurring substance use and other psychiatric disorders (e.g., eating disorders); women and men with PTSD; pregnant and parenting women; and women and men with behaviors that place them at risk for HIV.

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Table 1

Summary of CTN Studies Focusing on Gender Differences or Gender Specific Findings

Study	Design	Sample	Main Finding	Implications
<b>Women Subgroups: Pregnant Women</b>  CTN 0013: Pregnant Women (MET-PS) [ref. #16,20, 21]  CTN 0013-A-1: Trauma and IV use among Pregnant Women [ref. #13]	RCT to evaluate the efficacy of MET –PS (3 sessions) Vs. TAU)	200 pregnant women entering SUD treatment	<ul style="list-style-type: none"> <li>- Participants in both arms decreased substance use in first month</li> <li>- MET-PS may be beneficial to minority women</li> <li>- Women with clear quit goals at baseline reduced drug use more in the MET-PS arm</li> <li>- More weeks of attendance for incentive-reinforced research visits</li> </ul>	<ul style="list-style-type: none"> <li>- Expanding evidence based interventions targeted at pregnant women, including culturally-based treatment approaches</li> <li>- Baseline motivation moderated outcomes</li> <li>- Incentives might be effective in increasing treatment attendance</li> </ul>
	Survey of a sample of women who completed the MET-PS study	44 pregnant women with SUD	<ul style="list-style-type: none"> <li>- Women reported high child abuse potential (CAP)</li> <li>- Women with trauma and high IV drug use history reported greater CAP</li> </ul>	<ul style="list-style-type: none"> <li>- Trauma and IV drug status are significant predictors of CAP</li> <li>- Need for preventative interventions targeted toward CAP</li> </ul>
	RCT to assess SS treatment vs. WHE for women with SUD and PTSD	353 women with PTSD and SUD	<ul style="list-style-type: none"> <li>- Both SS and WHE associated with reductions of PTSD symptoms with a trend favoring SS group</li> <li>- There was no difference between interventions in reduction of drug use outcomes -Few Adverse Events</li> <li>- For women with high HIV risk behavior, group in SS had fewer USOs</li> </ul>	<ul style="list-style-type: none"> <li>- Adding trauma-focused treatments to treatment programs is feasible, and reduces PTSD symptoms without increasing substance use.</li> <li>- Interventions are safe, without increasing PTSD symptoms,</li> <li>- Trauma-focused treatment reduced USOs among women with high risk sexual practices</li> </ul>
<b>Women Subgroups: Co-Occurring Disorders</b>  CTN-0015-A-1: Women with PTSD and Eating Disorders [ref. #12]	Addition of EDE-Q to baseline assessment in sub-sample of women enrolled in the WTS study	122 women with PTSD and SUD	<ul style="list-style-type: none"> <li>- Most common (29%) eating disorder behavior was binge eating</li> <li>- Women in binge eating group endorsed higher ED, PTSD and depression symptoms at baseline</li> <li>- Women with PTSD, SUDs and binge eating behavior had significantly less improvement in SUD/PTSD symptoms</li> </ul>	<ul style="list-style-type: none"> <li>- Need to identify ED symptoms among treatment seeking women with SUD/PTSD to tailor treatment</li> </ul>
	National Survey of publicly funded addiction treatment programs	351 treatment programs	<ul style="list-style-type: none"> <li>- Approximately 50% of programs screen for ED</li> </ul>	<ul style="list-style-type: none"> <li>- Individuals with co-occurring disorders ED and SUD do not appear to receive structured</li> </ul>

Study	Design	Sample	Main Finding	Implications
Programs (mixed gender) [ref. #14]			<ul style="list-style-type: none"> <li>&lt;1 in 6 programs attempt to treat ED</li> <li>3% have formal referrals for ED treatment</li> </ul>	<ul style="list-style-type: none"> <li>assessments or treatment for ED in addiction treatment programs</li> <li>Need for education and implementation of standard assessments and either treatment or referral for ED in addiction treatment</li> </ul>
Treatment for ED in National Survey of Addiction Treatment Programs (mixed gender) [ref. #15]	National Survey of <b>privately</b> funded addiction treatment programs	345 treatment programs	<ul style="list-style-type: none"> <li>Approximately 74% of programs screen for ED, but few programs use standardized assessments.</li> <li>Although most programs admit ED, only 20% programs attempt to treat ED on site.</li> <li>11% have formal referrals for ED treatment.</li> </ul>	<ul style="list-style-type: none"> <li>Individuals with co-occurring ED and SUD are likely to be screened for an ED but not with structured assessments.</li> <li>Although programs admit ED patients, specialized treatment for ED is lacking.</li> <li>There is a need for education of addiction treatment professionals in assessment, referral and treatment of eating disorders.</li> </ul>
CTN-0039-S: Gender Differences and HIV Risk Behaviors [ref. #11]	Secondary analysis of 5 trials to examine gender differences in HIV risk behaviors	1,429 individuals across 5 trials (45% female)	<ul style="list-style-type: none"> <li>Women reported more multiple partners, unprotected sex with regular partners and a higher sex risk composite score overall</li> <li>Greater alcohol and psychiatric co-morbidity was associated with higher sexual risk for women</li> </ul>	<ul style="list-style-type: none"> <li>Risk factors were differentially predictive of HIV risk behavior for women and men, highlighting the need for gender-specific risk reduction assessments and interventions</li> </ul>
	CTN-0018: HIV Prevention for Men [ref. #18] CTN-0019: HIV Prevention for Women [ref. #19]	590 men 515 women	<ul style="list-style-type: none"> <li>Greater reduction in the number of unprotected sexual occasions (USO) at 3 &amp; 6 mo. compared to standard HIV prevention education.</li> <li>Greater reduction in number of USOs at 6 months; effect enhanced for both protocols when &gt;2 sessions were attended.</li> </ul>	<ul style="list-style-type: none"> <li>Results shows some similarities and notable differences among genders</li> <li>Results are consistent with the need to have gender specific HIV prevention interventions and interventions of more intensity than a single education session</li> </ul>

CAP: Child Abuse Potential

ED: Eating Disorders

MET-PS: Motivational Enhancement Therapy for Pregnant Women with Substance Abuse Disorders

PA: Physical Abuse

PTSD: Post-traumatic Stress Disorder

RCT: Randomized Clinical Trial

SA: Sexual Abuse

SS: Seeking Safety

SUD: Substance Use Disorder



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USO: Unprotected Sexual Occasions  
WHE: Women Health Education  
WTS: Women and Trauma Study