# Gender Comparison in Referrals and Treatment Completion to Residential and Outpatient Alcohol Treatment



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#### ABSTRACT

**BACKGROUND:** Residential treatment for alcoholism is associated with high completion rates for clients, yet there appear to be gender disparities in patient referrals and treatment completion rates. We studied whether (A) gender is associated with differential patient placement to outpatient vs. residential treatment facilities and (B) completion rates differ by gender.

**METHODS:** In this cross-sectional study, we analyzed the admission and discharge data from 185 publicly funded substance abuse treatment facilities across Los Angeles County between 2005 and 2010.

**RESULTS:** Among the 33,745 studied cases, women were referred to residential treatment facilities less frequently than men (75% vs. 66%). The adjusted results derived from logistic regression models confirmed that females were more likely to be referred to outpatient treatment than to residential treatment facilities (odds ratio [OR]: 1.15, 95% confidence interval [CI]: 1.05–1.26). In addition, we observed that compared to White/Caucasian patients, all other races were associated with more referral to outpatient facilities (ie, less referral to residential facilities), indicating a racial disparity on the top of the observed gender disparity. However, there was no significant link between gender and treatment completion rates (OR: 0.93, 95% CI: 0.86–1.00).

**CONCLUSIONS:** Women seem to have treatment completion rates comparable to men, yet they are less likely to be referred to residential treatment facilities. Hence, there still remains a gender disparity in alcoholic patient referrals. Further studies should delineate which specific therapeutic aspects and programmatic components of women-focused treatments are essential to augment positive treatment outcomes.

KEYWORDS: gender, alcohol dependence, residential treatment, outpatient treatment, treatment completion

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# Introduction

Among patients with drug use disorders in general, and alcohol abuse in particular, gender is a key determinant in how their disorder is perceived by healthcare professionals, how they are referred for advanced care, and how they complete treatment.<sup>1-4</sup> With an increased recognition of the role of gender, gender differences, and gender inequality in health and social life, the past three decades have witnessed a paradigm shift from generic substance abuse treatment model to gender-responsive treatment model.<sup>5,6</sup> The crux of matter in this paradigm is to understand gender as the central construct that influences treatment initiation, processes, and outcome.<sup>7,8</sup> Following this line of reasoning, there appears to be gender differences in referrals to residential treatment for alcoholism with women receiving less referral despite the fact that women perceive their alcoholism more serious than men.  $^{1,9,10}$ 

Residential treatment may benefit vulnerable populations, including patients with severe psychiatric illness, low social functioning, few financial resources, and severe medical conditions.<sup>11</sup> Women with alcohol problems suffer from more psychiatric comorbidities, exhibit poorer social functioning, and have less economic resources; thus, they are at risk for poorer prognosis.<sup>12,13</sup> Women who are referred to residential treatments, once completing the treatment, are more likely to present with better outcomes such as remission from alcohol use and lower depression.<sup>14,15</sup> Yet, they are less referred to residential treatment facilities.<sup>1</sup>

Understanding the role of gender in treatment retention is important since treatment dropouts have a 6.5 times greater relative risk of relapse compared to those who stay in treatment.<sup>16,17</sup> In this study, we attempt to investigate if (A) gender is associated with disparities in patient placement to outpatient or residential treatment for alcohol abuse and (B) completion rates differ by gender. Our hypothesis is that women still face disparities in referrals to residential treatment facilities, while among those receiving treatment, women show comparable treatment completion rates.

## Methods

Study design and participants. We completed a crosssectional study using the admission and discharge data from 185 publicly funded substance abuse treatment facilities across Los Angeles County. Client placement was generally based on the severity of their addiction disorder, living situation, and availability of treatment space. Data were gathered via Los Angeles County Participants Reporting System (LACPRS), which is collected by the Substance Abuse Prevention and Control (SAPC) of the Los Angeles County Department of Public Health (DPH). The study population comprised adults (18 years or older) admitted and discharged in fiscal years 2005-2010 who reported alcohol as their primary drug of abuse and were not concurrently receiving methadone treatment. The patients were self-identified as White/Caucasian, African-American/ Black, Hispanic/Latino, or Asian/other. The data from detoxification programs were excluded. Our inclusion and exclusion criteria narrowed down our patient population to 33,745 adults (22,143 males and 11,602 females), from whom 23,381 and 10,364 were referred to outpatient and residential treatment facilities, respectively. Charles Drew University Institutional Review Board reviewed the protocol of this study and found it to be exempt from the requirement of formal IRB review.

**Study measures.** In order to clarify which patients successfully completed their treatments and which patients did not, we utilized the three discharge categories made available by the participating treatment facilities: (A) *completed discharge*, (B) *left before completion with satisfactory progress*, and (C) *left before completion with unsatisfactory progress*. "Completed discharge" was considered successful treatment completion, while the other two categories were not. Also, the types of treatment facilities were identified as outpatient versus residential.

We also extracted data regarding gender, race/ethnicity, age, highest level of education, economic resources including employment status, homelessness, and Medi-Cal beneficiary status. Moreover, we accessed and analyzed addiction characteristics at the time of admission, ie, reported prior treatment (yes/no), any additional drug use (marijuana, other, none), injection drug use (yes/no), number of days on which alcohol and/or other drugs were used over the past month, and age of first substance use. Patient's mental health was self-reported by answering the question "*Have you ever been diagnosed with a mental illness*?" (yes/no). The types of referral to treatment included self-referral, court/criminal justice, school/employer,

or other. Finally, legal supervision indicated whether the subject was on parole or probation.

Statistical analyses. In order to test if gender is associated with disparities in patient placement (in outpatient vs. residential facilities), we completed both univariate and multivariate logistic regression analyses, in which gender was the independent variable (exposure) and patient placement was the dependent variable (outcome). The multivariate logistic regression model was adjusted for the covariates listed under the above section. Our second hypothesis was tested by modeling the gender (exposure/independent variable) with treatment completion (outcome/dependent variable) in univariate and multivariate logistic regression models. The multivariate model was adjusted for similar covariates (listed above). In all regression models, continuous independent covariates were centered by subtracting their sample means to reduce the skewness and increase data granularity. An estimated odds ratio (OR) on a centered continuous covariate represented the change in the log odds of completion that would be expected from a unit increase over the covariate's sample mean. We have presented the odds ratios and their 95% confidence intervals (CIs). Statistical significance level was set at P < 0.05. For the data analyses, we used SAS (Release 9.1.3, 2002; SAS, Inc.).

# Results

**Sample characteristics.** Table 1 demonstrates the characteristics of our study population among males and females. Our results showed that females were referred to residential treatment facilities less frequently than males (75% vs. 66%). In addition, higher proportions of women used amphetamines (data not shown), were unemployed, were Medi-Cal beneficiaries, had mental illness, and were referred into treatment by "self-referral". On the other hand, higher percentages of men were homeless, abused alcohol and marijuana, were under legal supervision, and were referred by the court/criminal justice (Table 1).

Table 2 summarizes the results of our regression models investigating the relationship between gender (as well as other covariates) and patient placement, ie, outpatient vs. residential treatment facilities. The adjusted results showed that females were more likely to be referred to outpatient treatment than to residential treatment facilities (OR: 1.15, 95% CI: 1.05-1.26). In addition, we observed that compared to White/Caucasian patients, all other races were associated with more referral to outpatient facilities (ie, less referral to residential facilities), indicating a racial disparity on the top of the observed gender disparity (Table 2). Other significant determinants of patient placement included age, highest level of education, employment status, homelessness, Medi-Cal beneficiary status, history of prior treatment for drug abuse, other drug-related disorders, frequency of alcohol and drug use over the past month, and whether the patients were under legal supervision (Table 2).

Table 3 summarizes the results of our investigation whether gender, as well as other covariates, was associated with

 Table 1. Discharge status, treatment setting, and patient characteristics.

INDEPENDENT VARIABLES	MALE (n = 22,143)	FEMALE (n = 11,602)
Treatment setting		
Outpatients	66.25%	75.08%
Residential	33.75%	24.92%
Discharge status		
Completed treatment	45.45%	41.47%
Demographics		
Race/ethnicity		
White/Caucasian	36.09%	37.44%
Black/African-American	23.85%	28.32%
Hispanic/Latino	31.38%	25.70%
Asian/Other	8.68%	8.53%
Age in years (Mean $\pm$ SD)	$40.90 \pm 12.41$	$40.08 \pm 12.52$
Highest level of education in years (Mean $\pm\text{SD})$	$11.50\pm3.05$	11.58 ± 3.03
Economic resources		
Employment <sup>b</sup>	81.19%	87.55%
Unemployed/not in labor market employed	18.81%	12.45%
Homelessness	24.51%	18.87%
Medi-Cal beneficiary status	34.20%	50.24%
Addiction characteristics		
Ever received prior treatment	39.06%	36.11%
Additional drug problems Marijuana	18.38%	13.09%
Other drugs	29.97%	29.97%
No other drug	51.65%	56.94%
Injection drug use	27.52%	35.66%
Days drinking over past month (Mean $\pm$ SD)	$12.63 \pm 12.21$	11.74 ± 12.15
Days secondary drug use over past month (Mean $\pm$ SD)	$5.86 \pm 9.73$	$5.53 \pm 9.75$
Age of first substance abuse in years (Mean $\pm\text{SD})$	$15.97\pm5.11$	17.15 ± 6.11
Mental health		
History of mental illness	27.52%	35.66%
Legal supervision status		
Under legal supervision	32.93%	19.76%
Principle source of referral		
Self-referral	43.71%	47.17%
Court/criminal justice	31.36%	22.81%
School/employer	1.69%	1.57%
Other	23.25%	28.45%

higher rates of treatment completion. Our results indicated a trend toward lower treatment completion among females; however, this trend was not statistically significant (OR: 0.93, 95% CI: 0.86–1.00). Our results also showed that those referred to residential treatment facilities were 2.5 times more likely to complete the treatment. Patients who were employed were also 3.35 times more likely to complete treatment. Conversely, homelessness, other drug problems, frequency of drinking and drug use, and history of mental illness were all associated with lower rates of treatment completion (ie, lower treatment compliance).

#### Discussion

Association of gender with patient placement. We found that women in Los Angeles County who needed treatment for alcohol were more likely to be referred to outpatient treatment rather than residential. This finding was in line with the reports from two decades ago.<sup>18</sup> We did not have access to further data regarding how the treatment facilities addressed patients' impairments or to what extent they provided gendersensitive services, eg, childcare.<sup>19</sup> It can be argued that patient placement should follow the criteria put forth by the American Society of Addiction Medicine (ASAM), in which gender is not a determinant of patient placement. The ASAM criteria comprise six dimensions based on which each patient is assigned a score that guides patient placement.<sup>20</sup> However, the State of California (including Los Angeles County) does not require compliance with the ASAM standard patient placement criteria, which leaves room for gender disparity at treatment assignment.<sup>20</sup>

Women undergoing substance abuse treatment should overcome many barriers including difficulty in attending regular services, lack of financial resources and social support, childcare responsibilities, and daily stressors, as well as other comorbidities including mental disorders, all of which complicate the course of treatment referral, treatment utilization, and outcomes.<sup>3,21-23</sup> In addition, previous studies of national data on admission to treatment facilities have shown that women's and men's pathways to treatment referral and utilization have interconnections with the types of primary substance use, sources of payment for treatment, and sources of referral.<sup>18</sup> Women, for example, are more likely to abuse cocaine, amphetamines, or heroin/other opioids, whereas men are more likely to abuse alcohol and marijuana.<sup>18</sup> Also, a greater portion of men are referred to treatment by court, whereas women are more often referred by child welfare or mental health service agencies.<sup>18</sup> Moreover, women rely more on public insurance to pay for their treatment due to the lack of economic resources and unemployment.<sup>18</sup> Additionally, women view substance abuse more negatively and attach more stigma to those who seek treatment,18 effecting their treatment seek behaviors.

Similar to women, minority patients (African-American, Hispanic, and Asian), older patients, those with less education, those under Medi-Cal coverage, and those referred by the court or criminal justice were more likely to be referred to outpatient treatment, whereas prior treatment for alcohol addiction, injection drug use being under legal supervision,



 Table 2. Logistic regression models predicting patient placement in outpatient vs. residential treatment facilities (n = 33,589).

INDEPENDENT VARIABLES	REFERENCE	
	UNADJUSTED OR 95% CI	ADJUSTED MODEL OR 95% C
Demographics		
Gender		
Male	1.53 (1.45–1.62) <sup>‡</sup>	1.15 (1.05–1.26)†
Female	-	_
Race/ethnicity		
White/Caucasian	1.75 (1.64–1.86) <sup>‡</sup>	1.60 (1.43–1.78)*
Black/African-American	2.26 (2.12–2.41) <sup>‡</sup>	2.12 (1.89–2.37)*
Hispanic/Latino	1.44 (1.31–1.58) <sup>‡</sup>	1.22 (1.04–1.43)*
Asian/Other	_	_
Age in years <sup>a</sup>	1.01 (1.01–1.01)*	1.02 (1.01–1.02) <sup>‡</sup>
Highest level of education (in years) <sup>a</sup>	0.91 (0.90-0.92)*	0.96 (0.94-0.97)*
Economic resources		
Employment	0.47 (0.44-0.50)	3.61 (3.20-4.08)*
Unemployed/not in labor market employed	-	_
Homelessness		
Yes	0.08 (0.08-0.09)*	0.11 (0.10-0.12)*
No		_
Medi-Cal beneficiary		
Yes	6.01 (5.65-6.39)*	4.73 (4.27–5.23)*
No	_	_
Addiction characteristics		
Ever received prior treatment		
Yes	0.44 (0.42-0.46)*	0.70 (0.64-0.76)*
No	-	_
Additional drug problems Marijuana		
Other drugs	0.94 (0.87–1.01)	1.63 (1.43–1.87) <sup>‡</sup>
No other drug	0.48 (0.46–0.51)*	0.91 (0.81–1.03)
Injection drug use		
Yes	0.39 (0.33-0.46)*	0.87 (0.68–1.10)
No	-	_
Days drinking over past month <sup>a</sup>	0.96 (0.96-0.97)*	0.98 (0.97–0.98)*
Days secondary drug use over past month <sup>a</sup>	0.95 (0.94–0.95)*	0.96 (0.96–0.97)*
Age of first substance abuse in years <sup>a</sup>	1.05 (1.05–1.06)*	1.02 (1.01–1.03)*
Mental health		
Mental illness		
Yes	1.48 (1.40–1.56)*	1.03 (0.93–1.13)
No	-	_
Legal supervision status		
Under legal supervision		
Yes	0.62 (0.59-0.66)*	0.66 (0.60-0.73)*
No	-	_
Principle source of referral		
Self-referral	1.64 (1.54–1.74)*	3.00 (2.68–3.35)*
Court/criminal justice	12.78 (8.72–18.74)*	8.40 (4.63–15.23)*
School/employer	4.12 (3.84–4.43)*	5.44 (4.83–6.13)*
School/employer	-	-
Other	_	_
Pseudo R <sup>2</sup>	0.01 <sup>b</sup>	0.52
$\chi^2$	230.42 <sup>‡b</sup>	4313.39 <sup>‡</sup>
Log likelihood	17321.07 <sup>b</sup>	- 6980.70

Notes: P < 0.05. P < 0.01. P < 0.001. P < 0.001. aCentered continuous variable. Model fit statistic for gender only.



**Table 3.** Logistic regression models predicting treatment completion (n = 33,589).

INDEPENDENT VARIABLES	REFERENCE		
	UNADJUSTED OR 95% CI	ADJUSTED MODEL OR 95% C	
Demographics			
Gender			
Male	0.85 (0.81–0.89)*	0.93 (0.86–1.00)	
Female	_	_	
Race/ethnicity			
White/Caucasian	0.55 (0.52–0.58) <sup>‡</sup>	0.79 (0.73–0.86)‡	
Black/African-American	0.67 (0.63–0.70)*	0.90 (0.82–0.98)†	
Hispanic/Latino	0.75 (0.69–0.81) <sup>‡</sup>	0.92 (0.81–1.04)	
Asian/Other	-	_	
Age in years <sup>a</sup>	1.01 (1.01–1.01)*	1.02 (1.01–1.02)*	
Highest level of education (in years) <sup>a</sup>	1.05 (1.04–1.05) <sup>‡</sup>	1.00 (0.99–1.01)	
Treatment setting			
Outpatient residential	1.96 (1.86–2.06) <sup>‡</sup>	2.54 (2.32–2.77)*	
Economic resources			
Employment	2.28 (2.15–2.42)*	3.15 (2.87–3.44)*	
Unemployed/not in labor market employed	_	_	
Homelessness			
Yes	1.12 (1.06–1.18) <sup>‡</sup>	0.91 (0.83–0.99)*	
No	_	_	
Medi-Cal beneficiary			
Yes	0.49 (0.47–0.52)*	1.00 (0.92–1.09)	
No	_	_	
Addiction characteristics			
Ever received prior treatment			
Yes	1.01 (0.97–1.06)	1.03 (0.96–1.09)	
No	_	_	
Additional drug problems Marijuana			
Other drugs	0.63 (0.59–0.67)*	0.88 (0.80-0.97)*	
No other drug	0.79 (0.75–0.83) <sup>‡</sup>	0.76 (0.69–0.83)*	
Injection drug use			
Yes	0.95 (0.81–1.11)	0.90 (0.74–1.10)	
No	_	_	
Days drinking over past month <sup>a</sup>	1.03 (1.02–1.03) <sup>‡</sup>	0.99 (0.98-0.99)*	
Days secondary drug use over past month <sup>a</sup>	1.01 (1.01–1.02) <sup>‡</sup>	1.00 (0.99–1.00)	
Age of first substance abuse in years <sup>a</sup>	1.01 (1.00–1.01)†	1.00 (0.99–1.01)	
Mental health			
Mental illness			
Yes	0.69 (0.66-0.73)*	0.89 (0.82–0.96)*	
No	_	_	
Legal supervision status			
Under legal supervision			
Yes	0.95 (0.91–1.00)*	1.01 (0.93–1.10)	
No			
Principle source of referral			
•			
Self-referral	0.92 (0.88–0.97)†	1.17 (1.07–1.28)*	
Court/criminal justice	0.67 (0.56–0.80)‡	1.27 (0.99–1.64)	
School/employer	0.59 (0.56-0.63)‡	0.95 (0.87–1.03)	
Other	_	_	
Pseudo R <sup>2</sup>	0.02 <sup>b</sup>	0.11	
χ <sup>2</sup>	649.80 <sup>‡b</sup>	1283.09*	
λ	073.00 <sup>-</sup>	1200.03	

 $\textbf{Notes: } ^{*}\textit{P} < 0.05. ~ ^{\dagger}\textit{P} < 0.01. ~ ^{\dagger}\textit{P} < 0.001. ~ ^{\circ}\textit{C} entered continuous variable. ~ ^{b}\textit{Model fit statistic for treatment setting only.}$ 

and homelessness increased the odds of being referred to residential treatment. Minority individuals are more likely to stigmatize and report embarrassed receiving alcohol abuse treatment,<sup>24,25</sup> and they may demand referring to outpatient settings to lift some of the attached stigma. With the same token, issues related to language barrier and other cultural barriers may be in play. Less educated individuals are also reported to stigmatize alcohol abuse treatment more often,<sup>25</sup> which can help explain the lower rates of residential treatment among them. With respect to older patients, research indicates that they usually suffer from a higher baseline severity of addiction and stay in residential treatment for a shorter duration of time, regardless of readiness to change.<sup>26</sup> As a result, care providers might assume that referral to residential substance abuse treatment might not be effective for this group. Medi-Cal beneficiaries were observed to be less likely to be referred to residential treatment. This can be explained by Medi-Cal's strict criteria for inpatient rehabilitation admission and continuation,<sup>27</sup> which might make healthcare providers unwilling to refer Medi-Cal beneficiaries to residential treatment.

With regard to legal supervision, in contrast to our findings, a study investigating the 2002 data of National Survey on Drug Use and Health has demonstrated that history of criminal justice involvement in the previous year increases the likelihood of substance abuse treatment admission.<sup>28</sup> The authors of this study divided criminal justice involvement to three groups (arrest only, arrest with criminal justice supervision, and criminal justice supervision only) and have reported no significant difference between the arrest only group and the general population with regard to type of treatment (outpatient, residential, mental health clinic, and hospital based).<sup>28</sup> One reason for the apparent disagreement between the results of this study and our study might be that the authors have assessed the impact of arrest in the previous year rather than criminal justice referral. In addition, this study investigated the national level data in 2002, while we have assessed the 2005-2010 data of Los Angeles County. However, in collaboration with outpatient and residential treatment facilities, authorities in criminal justice are in a unique position to leverage a court visit as teachable moment in encouraging change in the substance behaviors of individuals.<sup>29,30</sup>

Association of gender with treatment completion. Our findings revealed no significant difference in gender regarding treatment completion. Similar findings were reported by Bird,<sup>8</sup> who found no differences between male and females who received substance abuse treatment in mixed- vs. singlegender programs. Likewise, Greenfield et al.<sup>7</sup> found that while gender did not predict treatment completion, individual characteristics such as education, employment, income, mental health, and social support predicted treatment completion differentially by gender. It is evident from previous studies that substance abuse treatment services that offer womenspecific programs such as childcare, prenatal and postnatal care, transportation, supplemental assistances such as domestic



violence services, empowerment and self-efficacy workshops, and mental health counseling and offer age-specific treatment module are more likely to reduce barriers to treatment utilization and enhance treatment completion rates.<sup>5,31-33</sup> Others have suggested that directing resources toward social support and childcare for female alcoholics might improve treatment completion rates.<sup>34-38</sup> It is also argued that the dynamic of treatment completion may be the function of within-treatment factors. For example, Fiorentine et al.<sup>39</sup> found that women attended significantly more in group treatment sessions compared to men, though treatment completion rates were similar. The lack of a significant gender disparity in treatment completion rates in our study may imply that patients in the study were properly assigned to the needed treatment services, and treatment providers were able to address problems unique to their patients.

Other factors that increased the odds of treatment completion in the sample were being referred to residential services, being older, unemployed, having part-time or full-time jobs, having Medi-Cal, and being referred to the treatment by court, school, or an employer. Factors that decreased the odds of treatment completion in this sample were being African-American or Hispanic, using heroin, amphetamines, cocaine/crack, or marijuana, as well as more frequent drinking. In a large study on African-American and Hispanic alcoholics in Los Angeles, Bluthenthal et al.<sup>40</sup> observed links between treatment completion rates and patient placement in residential vs. outpatient facilities and showed that racial differences in completion rates would be eliminated if African-Americans and Hispanics were referred to residential treatment at the same rates as Whites. Others have supported racial disparity in treatment completion, highlighting the role of culturally appropriate treatment programs and eclectic model of care for enhancing treatment retention and posttreatment outcomes.41-43

Limitations. Our study had the inherent limitations of a cross-sectional study. We could not establish any causal relationship between gender and referral status. Another shortcoming of our study was having a smaller sample size for women compared to men, which may have influenced our results. Also, the data set did not contain information about other factors known to influence treatment referrals, eg, available community resources such as childcare facilities, social support, patients' attitude toward the residential or outpatient treatments, social workers' and/or counselors' attitudes, and the society's attitudes toward the preferred treatments for men and women. In addition, it was unclear whether men had a tendency to self-elect the residential treatment facilities for other reasons such as gaining a better position in the court. Moreover, the potential biases due to self-reporting and different treatment effectiveness across the study sites could not be anticipated. We suggest that future studies on gender disparities in the type of alcohol treatment referral and completion rates focus on identifying gender and cultural barriers for completing treatment for women assigned to residential



treatment, as well gender and cultural barriers or biases of healthcare professional who make such referrals.

# Conclusions

Our results shed more light on how gender affects patient placement and treatment completion among those suffering from alcohol abuse, and it showed that the gender disparities in referrals are still in place. Based on our observations, women are less likely to be referred to residential treatment for alcoholism. However, we observed no significant difference between men and women with regard to treatment completion rates.

A key implementation for practice is to aim for higher referral rates of alcoholic women to residential treatment facilities in order to better address alcohol abuse among women and to eliminate such a gender disparity in patient placement considering the fact that gender is not among the ASAM criteria for patient placement while such a disparity currently exists in patient referrals. It seems necessary to train providers to better understand gender issues and on how to better assess referrals. However, whether higher referrals to residential treatment facilities would actually lead to decreased morbidity and increased quality of life among alcoholic women should be further tested in future studies, particularly in randomized controlled trials.

Future studies should incorporate gender-specific motives for treatment seeking as well as the attributes considered by the providers and referring agencies to place men and women in a given treatment setting. Finally, considering the empirical evidence pointing to the importance of women-focused substance abuse treatments,<sup>5</sup> it is just as important to validate which specific therapeutic aspects and programmatic components of women-focused treatments are essential to augment positive treatment outcomes.<sup>3</sup>

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### **Author Contributions**

SBH and VDL conceived and designed the study, and drafted the initial version of the manuscript. DP and MB analyzed

the data. SBH, MM, ER, SJ and GZ participated in drafting different versions of the manuscript. SBH and MB drafted the final version. All the authors reviewed and approved the final manuscript.

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