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A Retrospective Study of Gender Differences in Depressive Symptoms and Risk of Relapse in Patients with Alcohol Dependence

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Abstract

Background and Objectives—The aim of this study was to investigate potential gender differences in situations associated with heavy alcohol drinking

Methods—Data from 395 alcohol dependent patients participating in the Mayo Clinic Intensive Addiction Program were evaluated. Each participant completed the Inventory of Drug Taking Situations (IDTS), Penn Alcohol Craving Scale (PACS), Patient Health Questionnaire (PHQ-9), and/ or Beck Depression Inventory (BDI). Gender differences in IDTS scores representing three domains (negative, positive, and temptation) of situations associated with heavy alcohol use were examined.

Results—Women with alcohol dependence report a higher frequency of heavy drinking in unpleasant emotional (IDTS negative scores mean $\pm$ SD women vs. men: 52.3 ± 22.1 vs. 43.8 ± 21.8 ; $p = 0.0006$), and as a result of temptation (IDTS temptation scores mean $\pm$ SD women vs. men: 40.4 ± 23.0 vs. 35.3 ± 20.8 ; $p = 0.035$). Upon admission, women also scored significantly higher on depressive symptoms as measured by the BDI (23.4 ± 11.4 vs. 18.2 ± 9.8 , $p < .001$). After controlling for depressive symptom severity as a covariate, the IDTS gender differences were no longer significant.

Conclusion and Scientific Significance—Our results suggest that unpleasant or temptation based emotional situations are a vulnerability risk factor for heavy drinking particularly in females. This risk appears to be at least partially driven by depressive symptom burden. Future research is needed to further investigate this finding.

Introduction

Alcohol consumption among women has increased dramatically over the past century¹. This trend has been accompanied by a corresponding increase in serious alcohol-related medical complications² and a telescoping phenomena where women³ tend to develop more medical complications faster and at lower drinking threshold compared to men.^{4–7} Since alcoholism is frequently associated with intense cravings, and cravings are initiated by certain internal cues in response to environmental triggers, a three-pathway psychobiological model of craving was proposed by Verheul et al⁸. In accordance with this model, craving may present in the context of (1) positive emotional situations and desire for stimulating and/or

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rewarding properties of alcohol (reward craving), (2) negative emotional situations and desire for reduction of tension, arousal or stress (relief craving) or (3) a lack of control over obsessive thoughts about drinking (obsessive craving). It has been hypothesized that “relief craving” results from hyperactive glutamate neurotransmission, “reward craving” results from dysregulation in dopamine or opioid related neurotransmission, while “obsessive craving” is controlled by the pathophysiological changes in serotonergic neural regulation⁸. Research findings also indicate that all three types of craving can be successfully measured by the Inventory of Drinking Situations (IDS).⁹

Gender differences in clinical course of alcohol dependence are only beginning to be explored. In a recent post hoc analysis of the PROJECT COMBINE study, women were found to have differences in drinking pattern prior to randomization and involvement in prior treatment (i.e. overall and primary care vs specialty substance abuse program)¹⁰. Gender differences in craving and subsequent risk for relapse have been less well studied. Our group, has previously reported that alcohol dependent women had higher cravings as measured by the Penn Alcohol Craving Scale (PACS) which correlated with the Beck Depression Inventory (BDI) in females ($r=0.78$).¹¹

The Inventory of Drug Taking Situation (IDTS) was developed to help patients with drug addiction identify their own high-risk situations for heavy drinking.¹² The IDTS contains eight categories of heavy drinking situations: (1) negative emotional states, (2) negative physical states, (3) positive emotional states, (4) testing personal control, (5) urges and temptations and (6) interpersonal conflicts, (7) social pressures, and (8) positive emotional states in interpersonal situations. Problem index scores for these eight sub-scales can be used to calculate scores for three second order factors, representing positive, negative, and temptation situations. Previous reports indicate that women with alcoholism tend to drink more in response to negative emotions,^{13–15} while men drink more in response to positive affect.^{14,16} These early studies did not measure comorbid depressive symptoms. A more recent report¹⁷ used a scoring algorithm for the Reasons for Drinking Questionnaire, 16 self-report, retrospective questions that were designed to assess the 13 categories and subcategories of the Marlatt relapse taxonomy¹⁸ to classify alcohol relapses into one of three types (negative affect, social pressure, or craving/cued) and measured depressive symptoms using the Beck Depression Inventory (BDI). The authors found women more likely to have negative affect associated relapses that were predicted by the Alcohol Dependence Scale¹⁹ score, but not by the BDI scores.

The aim of this study was to further investigate gender differences in the frequency of heavy drinking during various high-risk situations utilizing the IDTS scale and to examine their correlation with craving intensity and mood state in a residential treatment sample.

Methods

Study subjects and setting

The Mayo Institutional Review Board approved this retrospective study (IRB #72-000218). Medical records of 395 patients were reviewed to extract data related to frequency of drinking, cravings, and co-morbid depression. All 395 patients participated in the Mayo Clinic Intensive Addiction Program (IAP) from September 2006 to December 2010 and gave permission to use their records for research purposes. The IAP is a one month physician-led multidisciplinary residential treatment program for patients with alcoholism, other substance dependencies and comorbid psychiatric conditions; treatment interventions primarily include group-based psychotherapies, psychoeducation, and individualized pharmacotherapies for alcohol dependence and psychiatric co-morbid disorders. When

complicated alcohol withdrawal is anticipated upon treatment entry, alcohol detoxification is completed on a general hospital unit before entry into the residential program.

Evaluations

This study included analysis of each of the following instruments from subjects with a primary clinical diagnosis of alcohol dependence: IDTS,¹² PACS,²⁰ BDI,²¹ and the nine-item Patient Health Questionnaire (PHQ-9).²² We utilized three second-order factor scores (negative, positive and temptation) calculated from the short version (50 items) of IDTS, to assess predominant use of alcohol. The *negative states score* is the average score of items (1) Unpleasant emotions, (2) Physical discomfort, and (6) Conflict with others. The *positive states score* is the average of items (3) Pleasant emotions, and (8) Pleasant times with others. The *temptation score* is the average of items (4) testing personal control, (5) urges and temptations, and (7) social pressure to drink. IDTS was generally completed on week 3 of the program after all initial assessments and baseline screenings were completed. Patients are also more able to give more accurate use history at this point in treatment. IDTS scores were not corrected for gender.

PACS data were collected weekly in the course of treatment to assess intensity of craving. BDI was used at the time of admission and discharge to assess presence of depressive symptoms in treatment participants between 2006 and 2009, when the BDI was replaced by the PHQ-9. IDTS data were available for 353 patients, admission PACS for 371, admission BDI for 195 and admission PHQ-9 for 154.

Statistical analysis

T-tests were used to compare mean IDTS score distributions (negative states scores, positive states scores, and temptation scores) between the two gender groups. Wilcoxon rank-sum tests were used to compare the other continuous clinical measures and demographics by gender. Chi-squared statistics were used to evaluate the association of psychiatric comorbidities and gender. Associations of psychiatric comorbidities with IDTS scores in females were further tested using one-way analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was used to study the differences in mean IDTS negative scores between men and women, while controlling for depression (table 2). Since the majority of participants had either the BDI or PHQ-9, two multivariate models of IDTS negative scores with adjustment for depression were used. Gender, PHQ-9 as a covariate, and their interaction were the independent (predictor) variable in one model, while gender, BDI, and their interactions were the independent variable in the other. Non-significant interactions were subsequently dropped from the final models. Pearson's correlation coefficients were used to measure the strength of the relationship between IDTS and PACS scores in males and females. All statistical analyses were performed using SAS® 9.2 software.

Results

A total of 448 patients received treatment in our program from September 2006 through December 2010. Of those, 395 gave permission to use their records for research purposes. All subjects met DSM-IV diagnostic criteria for alcohol dependence as determined in a clinical interview by a board certified addiction psychiatrist. The mean age of the group was 48.1 (± 13.5) years, and the average age at start of regular alcohol consumption was 19.8 (± 7.2) years. The average drinks per drinking day was significantly higher for males (9.9 ± 6.9) compared to females (7.6 ± 4.7) ($P = 0.001$).

As presented in Table 1, the majority of study subjects (55%, $n = 216$) had a co-morbid psychiatric diagnosis without another substance use disorder besides alcohol dependence.

The majority of women had a co-morbid psychiatric diagnosis (64% of women vs. 49% of men), and frequencies of the different comorbidities differed significantly between men and women ($\chi^2=9.3$, 3 df, $p = 0.025$). Women had significantly higher BDI (mean $\pm$ SD for women vs. men: 23.4 ± 11.4 vs. 18.2 ± 9.8 , $p = 0.003$) and PACS (mean $\pm$ SD for women vs. men: 15.5 ± 8.0 vs. 12.6 ± 7.6 , $p < 0.001$) scores, but there was no significant gender difference in PHQ-9 scores. At discharge, no significant gender differences in BDI, PHQ-9, or PACS scores were observed. As shown in Table 1 and Figure 1, there was no significant gender difference in the frequency of drinking during positive emotional situations: IDTS positive mean score (mean $\pm$ SD for women vs. men: 43.4 ± 24.2 vs. mean for men 46.1 ± 24.7 ; $p = 0.39$). However, compared to men, women had significantly higher IDTS negative scores: (mean $\pm$ SD women vs. men: 52.3 ± 22.1 vs. 43.8 ± 21.8 ; $p = 0.006$) and temptation scores (mean $\pm$ SD women vs. men: 40.4 ± 23.0 vs. 35.3 ± 20.8 ; $p = 0.035$). This gender difference was not detected after adjusting for depressive symptoms measured by either BDI or PHQ-9 scores (table 2). After adjusting for BDI or PHQ-9 scores by incorporating them as covariates in the model, the magnitude of the depressive (beta) coefficients for the gender effect was reduced in the BDI and PHQ-9 adjusted analyses (table 2), suggesting that at least some of the gender effect may be explained by the higher depressive symptoms observed in women. However, the negative coefficient estimates in the adjusted model (albeit of smaller magnitude) suggest that a weaker gender effect may still be present, independent of depressive symptoms. The availability of data may, however, not provide adequate power for detecting this remaining effect.

Given the well documented association between bipolar diagnosis and heavy drinking in women, we looked for differences in IDTS scores (positive, negative or temptation) between unipolar ($n=80$) and bipolar ($n=10$) alcoholic women, however no significant differences were found, perhaps due, at least in part, to the small number of bipolar women in our cohort (table 3). We also found a significant positive correlation between IDTS negative and PACS scores: IDTS negative and PACS upon admission, [all subjects ($n = 332$, $r=0.39$, $p < 0.0001$), females ($n = 116$, $r=0.48$, $p < 0.0001$) and males ($n = 216$, $r=0.31$, $p < 0.0001$)], and with PACS at discharge, [all subjects ($n = 331$, $r=0.21$, $p < 0.0001$), females ($n = 216$, $r=0.29$, $p < 0.0001$), and males ($n = 115$, $r=0.32$, $p = 0.001$)].

Discussion

With women developing medical complications earlier in their course of drinking and at lower drinking thresholds compared to men,³⁻⁷ the issue of gender difference in high risk situations for heavy drinking warrants careful investigation. In this study of a large retrospective sample of treatment-seeking alcohol dependent patients, a significant gender difference in mean IDTS scores as measured by second-order factors of the 50-item scale.¹² Women were shown to be more likely than men to engage in drinking when experiencing unpleasant emotional situations or as a result of temptation.

These results are consistent with previous studies that have demonstrated that psychological variables, such as mood and affect, could play a role in craving and drinking behavior among women. Olenick and Chambers¹⁵ found that women (74%) were significantly more likely than men (59%) to answer yes to “do you drink when you feel depressed” in the Alcohol Use Inventory.²³ The AUI is a set of 16 first-order factor scales developed to characterize drinking styles²⁴, and to “do you drink in order to change you mood” ($F = 6.2$, $P < 0.01$). In another sample of alcoholic inpatients ($n=125$), Women followed prospectively over 12 weeks following treatment ($n=35$) were found to be more likely (48% of women vs. 31% of males) to experience relapse crises in situations involving negative emotional states.²⁵ Using the Relapse Questionnaire²⁶, Connors et al¹⁴ found that 25% of women in a mixed cohort of inpatient and outpatient alcoholics ($n=142$) met criteria for major

depression. These women reported more cravings when feeling down. Zywiak et al¹⁷ looked at the impact of negative affect and depressive symptoms, as measured by the BDI, on relapse in both men (n=74) and women (n=64) in outpatient and residential alcohol treatment program. They reported that most women (88%) had negative affect or craving/cued relapses, but the relapse could not be predicted by the BDI scores.

We found that women experience more depressive symptoms as measured by BDI or PHQ-9. Interestingly, after adjusting for depressive symptoms using either BDI, or PHQ-9 scores, the gender difference in mean scores for drinking when experiencing unpleasant emotional situations or as a result of temptation was not significant. This may partly reflect a mediating effect of depressive symptoms in the relationship between gender and situational triggers of heavy drinking. However, it is also important to note that the smaller sample size in the BDI and PHQ-9 adjusted analyses may have contributed to a loss of power to detect gender differences in IDTS scores after correction for the effect of depression scores. Inferring causality in the relationship among gender, depressive symptoms and negative craving will require further investigation. This finding highlights the potential negative impact of depression on the course of alcoholism among women. A rich body of literature documents the high rates of depression among individuals with alcohol dependence²⁷ especially among women^{28–33}. Patients with alcoholism have a much higher risk (6.5 times higher) of attempted suicide compared to those without alcoholism³³. Despite the well documented observation that many of these depressive symptoms tend to improve within 2–4 weeks of abstinence³⁴, comorbid depression seems to be a factor associated with relapse²⁹. Moreover, the degree of depressive symptoms tends to have a positive association with the level of current alcohol use and related impairment as shown in a meta-analysis of 74 studies of adults with alcohol abuse or dependence which included data on depression and substance²⁷. In a systematic review and meta-analysis to quantify the efficacy of antidepressant medications for treatment of depressed alcoholics on the outcome of substance use, the authors³¹ found favorable effects of antidepressant medication for treatment of depressed alcoholics on the outcome of substance use, the authors³⁵ found favorable effects of antidepressant medication on measures on quantity of substance use, but rates of sustained abstinence were low. In a more recent 14-week double-blind, placebo-controlled trial that evaluated the efficacy of combining sertraline and naltrexone in treating patients with both disorders,³⁰ the sertraline plus naltrexone combination produced a higher alcohol abstinence rate (53.7%) and demonstrated a longer delay before relapse to heavy drinking (median delay=98 days) than the naltrexone (abstinence rate: 21.3%; delay=29 days), sertraline (abstinence rate: 27.5%; delay=23 days), or placebo (abstinence rate: 23.1%; delay=26 days) treatments.

We also found a significant gender difference in the IDTS temptation score. Previous studies examining the impact of gender on temptation-driven drinking yield inconsistent results. Cox et al³⁶ utilized The Temptation and Restraint Inventory (TRI) and Cognitive and Emotional Preoccupation (CEP) Scales to assess alcohol consumption in 113 American (71.7% females) and 70 German (71.4% females) undergraduate students. Men scored higher on temptation-related drinking compared to women [$F(1,176)=7.61$, $P<.006$]. Lawyer et al³⁷ studied 309 university students (60% female) to evaluate the influence of gender on relationships between Anxiety total scores and IDS higher-order factor scores. No significant gender difference was found in moderating the relationship between anxiety and temptation-motivated drinking. Temptation drinking could also be viewed as a sign of impulsivity,^{38,39} or could be influenced by an underlying bipolar diagnosis, or could be driven by other factors. We did not find significant difference in situationally triggered drinking in women with bipolar disorder, however, only 10 bipolar women were found in our sample. A large sample size of alcoholic women with bipolar disorder is needed to investigate this possibility.

The results of this study should be considered in the context of several limitations. We have used the 50-item IDTS, while others have used the long version, both the short and long versions of IDS were designed to assess frequency of heavy drinking in each of Marlatt and Gordon's⁴⁰ eight situations with documented excellent convergent validity⁴¹. Another limitation was the retrospective nature of the study and absence of structured interview to diagnose alcohol dependence or major depression. However, each of the study patients stayed for one month and had a comprehensive diagnostic evaluation performed by experienced board certified psychiatrists. Moreover, our study did not control for the preceding alcohol withdrawal or detoxification treatment prior to admission or the effect of medications at time of admission.

This study, nonetheless, adds an important understanding to the previously reported gender difference in drinking situations.^{14, 15, 17, 25} Our data indicate that alcoholic women respond to negatively emotions and to temptation by drinking; at the same time, they tend to have more depressive symptoms compared to men. The role that depressive symptoms play in perpetuating this cycle is not yet fully understood, however the results have several important clinical implications. First, they reinforce the importance of examining gender effects and considering gender difference in the design of addiction treatment programs. Most of the current evidence-based treatment for alcoholism has been built on research focused primarily on alcoholic men. Second, it may be beneficial to implement psychosocial and pharmacological interventions targeting negative affect. Finally, measuring and treating comorbid depressive symptoms early during the course of abstinence may be warranted. Further prospective studies are urgently needed to assess the role of early treatment of depressive symptoms, and ultimately to probe the underlying neurobiological basis of drinking situations and cravings.

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Figure 1.
IDTS subscale score for males and females

Table 1

demographics and clinical characteristics

	All	Females	Males	P-value
	N=395	N=134	N=261	
Age (mean $\pm$ SD)	48.1 $\pm$ 13.5	47.0 $\pm$ 13.3	48.6 $\pm$ 13.5	0.206
Years education (mean $\pm$ SD)	15.3 $\pm$ 2.5	14.9 $\pm$ 2.3	15.5 $\pm$ 2.6	0.056
Age regular use (mean $\pm$ SD)	19.8 $\pm$ 7.2	20.9 $\pm$ 8.5	19.2 $\pm$ 6.4	0.117
Average drinks per day (mean $\pm$ SD)	9.1$\pm$6.3	7.6$\pm$4.7	9.9$\pm$6.9	0.002
Clinical Diagnosis				
Alcohol dependence only	73 (18%)	17 (13%)	56 (21%)	0.025
Alcohol dependence + Other substance use disorder	18 (5%)	7 (5%)	11 (4%)	
Alcohol dependence + Other substance use disorder + co-morbid psychiatric diagnosis	89 (22%)	24 (18%)	65 (25%)	
Alcohol dependence + co-morbid psychiatric diagnosis	215 (54%)	86 (64%)	129 (49%)	
IDTS scores (mean $\pm$ SD)				
IDTS Positive	45.1 $\pm$ 24.5	43.2 $\pm$ 24.2	46.1 $\pm$ 24.7	0.274
IDTS Negative	46.7$\pm$22.2	52.3$\pm$22.1	43.8$\pm$21.8	<0.001
IDTS Temptation	37.0$\pm$21.7	40.4$\pm$23.0	35.3$\pm$20.8	0.035
PACS scores (mean $\pm$ SD)				
PACS admit	13.6$\pm$7.8	15.5$\pm$8.0	12.6$\pm$7.6	<0.001
PACS discharge	4.8 $\pm$ 4.5	5.4 $\pm$ 5.2	4.4 $\pm$ 4.0	0.307
Depressive Symptoms scores (mean $\pm$ SD)				
BDI at admission	19.9$\pm$10.6	23.4$\pm$11.4	18.2$\pm$9.8	0.003
BDI at discharge	6.9 $\pm$ 6.3	7.2 $\pm$ 6.8	6.8 $\pm$ 6.1	0.927
PHQ at admission	12.1 $\pm$ 6.4	12.2 $\pm$ 6.9	12.0 $\pm$ 6.1	0.981
PHQ at discharge	4.6 $\pm$ 3.9	4.8 $\pm$ 4.3	4.4 $\pm$ 3.7	0.801

Table 2

Gender difference in IDTS negative scores based on linear regression without or with depression symptom ratings as a covariate.

Outcome	Predictors [*]	N	R ²	Beta ^{**}	p-value
IDTS Negative	Gender	353	0.033	-8.51	0.001
IDTS Negative	BDI	174	0.122	0.68	<0.001
	Gender			-3.07	0.388
IDTS Negative	PHQ-9	137	137	1.49	<0.001
	Gender			-5.87	0.105

^{*} The model with only gender as a predictor evaluates the difference in IDTS negative scores between men and women, without adjustment for any covariates, while the models with BDI/PHQ-9 and gender as predictors, allows for the evaluation of gender differences in IDTS scores while accounting for the effect of BDI/PHQ-9 on the IDTS score.

^{**} Beta = estimated regression coefficient representing the effect size of the predictor.

Table 3
IDTS scores in alcoholic females with unipolar, bipolar diagnosis and those without comorbid psychiatric conditions

	Alcoholic No comorbid psychiatric condition (n=37) (Mean ± SD)	Alcoholic Unipolar females (n=80) (Mean ± SD)	Alcoholic Bipolar females (n=10) (Mean ± SD)	ANOVA		
				df	F-value	p-value
IDTS positive	42.1±24.8	44.2±23.5	38.3±29.1	2	0.29	0.742
IDTS negative	48.8±22.3	52.9±21.8	63.2±22.3	2	1.34	0.265
IDTS temptation	39.0±24.3	42.3±22.3	31.3±23.1	2	1.10	0.336