



Sex-specific association of depressive disorder and transient emotional states with alcohol consumption in male and female alcoholics

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ABSTRACT

Background: We assessed the impact of comorbid depression and anxiety disorders as well as positive and negative emotional states on alcohol consumption in alcohol dependent men and women.

Methods: Per day alcohol consumption during 90 days before enrolment was assessed by the Time Line Follow Back (TLFB) in 287 men and 156 women meeting DSM-IV-TR criteria for alcohol dependence. Propensity to drink in negative/positive emotional states was assessed using the Inventory of Drug Taking Situations (IDTS). Psychiatric comorbidities, including major depressive disorder (MDD), substance-induced depression (SID), anxiety disorders (AnxD), or substance-induced anxiety (SIA) were identified by Psychiatric Research Interview of Substance and Mood Disorders (PRISM).

Results: In the combined group, increased number of drinks per day and number of heavy drinking days correlated with increased IDTS scores (all $p < 0.0001$), while the lifetime history of MDD was associated with fewer drinking days ($p = 0.045$) but not average number of drinks per day. Male sex was associated with higher alcohol consumption per day ($p < 0.0001$), but not with the number of drinking days ($p > 0.05$). Lifetime MDD history was associated with less drinking days ($p = 0.0084$) and less heavy drinking days ($p = 0.021$) in alcohol dependent men, while current MDD was associated with higher alcohol use per day in alcohol dependent women ($p = 0.044$).

Conclusions: Our findings suggest that emotional states and lifetime MDD history have sex-specific impact on alcohol use in alcohol dependent men and women. The mechanisms underlying these findings and their relevance to treatment outcomes need to be examined in future studies.

1. Introduction

Variation in alcohol use between men and women are influenced by gender-related (socio-cultural) as well as sex-related (biological) factors (Erol and Karpyak, 2015). Mood and emotions are believed to impact drinking differences, with men primarily reporting drinking in the context of pleasant emotions (Connors et al., 1998; Dunne et al., 1993; Lemke et al., 2008; Yankelovitz et al., 2012; Zywiak et al., 2006) and women more often reporting drinking when experiencing negative emotions (Choi and DiNitto, 2011; Lau-Barraco et al., 2009; Rubonis et al., 1994). The impact of negative mood on alcohol intake is even more evident in patients with alcohol use disorders (AUD) and may play a mediator role in sex-specific differences in alcohol consumption in

high-risk situations (Abulseoud et al., 2013; Lau-Barraco et al., 2009).

Evidence indicates high rates of comorbid depressive and anxiety disorders among AUD patients in treatment (Grant et al., 2004; Hasin and Grant, 2002; Hasin et al., 2007; Hesselbrock, 1991; Miller et al., 1996), higher frequency of those comorbidities in alcohol dependent women compared to men (Benishek et al., 1992; Goldstein et al., 2012; Hesselbrock, 1991; Mann et al., 2004; Wu et al., 2010) and poor treatment outcomes with frequent complications including suicide associated with these comorbidities (Alegria et al., 2010; Compton et al., 2007; Conner et al., 2009; Driessen et al., 2001; Grant et al., 2004; Hesselbrock, 1991; Hesselbrock et al., 1985; Yoon et al., 2011).

We have reported a positive correlation between intensity of depressive symptoms and alcohol cravings in women with AUD, and a

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higher propensity for drinking in unpleasant emotional situations in women compared with men (Abulseoud et al., 2013; Boykoff et al., 2010) and replicated the previously described higher prevalence of major depressive disorder (MDD), substance (alcohol)-induced depression (SID), and anxiety disorders (AnxD) in women compared with men (Karpyak et al., 2016).

Thus, converging evidence indicates that negative and positive emotions may impact alcohol consumption in a sex-specific manner. Similarly, evidence indicates that comorbid depression and anxiety disorders, which are frequent among patients with AUDs, also have sex-specific impact on craving intensity and alcohol use. However, no studies have directly evaluated the association of comorbid depressive or anxiety disorders as well as transient emotional states (i.e. tendency to drink while experiencing positive or negative emotions) on the amount and frequency of alcohol consumption in alcoholic men and women. Here, we present analyses testing for these associations in alcohol dependent men and women treated in community-based programs.

2. Methods

2.1. Study design

We analyzed data collected at baseline in a pharmacogenomic study of acamprosate treatment outcomes (Karpyak et al., 2014). The Institutional Review Boards of Mayo Clinic Rochester and Mayo Clinic Health System approved the study. All participants signed informed consent, giving permission to use the collected information in future studies.

2.2. Study subjects

A detailed description of the study sample, recruitment sites, and enrollment procedures is presented elsewhere (Karpyak et al., 2016, 2014). In brief, we included men and women 18–80 years old with a primary diagnosis of current alcohol dependence treated in programs affiliated with Mayo Clinic and Mayo Clinic Health System sites in Minnesota and Wisconsin. We excluded subjects with unstable medical and/or psychiatric (e.g. renal or hepatic impairment, psychotic disorder or active suicidal ideation) conditions and those unable to provide informed consent or speak English. In addition, subjects with a history of an allergic reaction to acamprosate, taking disulfiram, pregnant or lactating women or women planning to become pregnant during the subsequent year were also excluded (Karpyak et al., 2014).

Data from 443 subjects were analyzed for this study. Due to a small amount of missing data for particular variables, some of the analyses included fewer subjects, as indicated in the tables.

2.3. Assessments

Previous publications (Karpyak et al., 2016, 2014) provide a detailed description of the study assessments, which can be summarized as follows: Certified interviewers conducted a semi-structured interview (PRISM) (Hasin et al., 1996), which was used to determine the presence of lifetime as well as current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. Diagnostic modules included alcohol dependence, MDD, SID, AnxD, and SIA, along with other Axis I diagnoses. To avoid loss of power in the analysis, all non-substance-induced anxiety disorders (i.e. generalized anxiety disorder, social phobia, agoraphobia, panic disorder, obsessive compulsive disorder, and posttraumatic stress disorder) were combined into a single category defined as AnxD. For the same purpose, we elected not to differentiate between alcohol and non-alcohol-related SID or between alcohol and non-alcohol related SIA.

The propensity to drink in positive and negative emotional situations and temptation-related circumstances over the past year were

determined using IDTS (Annis et al., 1997). As recommended (Turner et al., 1997), the “IDTS negative factor score” was constructed by averaging raw scores of the IDTS subscales of physical discomfort, unpleasant emotions, and conflict with others and was used as a measure of tendency to drink in negative emotional circumstances (and potentially reflective of negative craving). Similarly, the “IDTS positive factor score” and the “IDTS temptation factor score,” were constructed by the averaging raw scores of the other two IDTS subscales and were used as measures of tendency to drink in positive emotional states or temptation to drink situations (and potentially reflective of positive or temptation craving, respectively).

The Time Line Follow Back form (Sobell and Sobell, 1992) was used to collect information about alcohol use during the 90 days preceding study enrollment. For statistical analyses, alcohol use was quantified using the following measures: the total number of drinks during 90 days prior to enrollment, the average number of drinks per drinking day, the number of drinking days out of 90 days prior to enrollment, the number of heavy drinking days out of 90 days prior to enrollment, and the maximum number of drinks consumed on a drinking day during the 90 days prior to enrollment. In accordance with the NIAAA guidelines (2005), a heavy drinking day was defined as 4 or more drinks per day for women and 5 or more drinks per day for men.

The intensity of depressive symptoms was measured by the Patient Health Questionnaire 9 (PHQ-9), deemed a reliable and valid measure of depression symptom severity (Kroenke et al., 2001).

The intensity of anxiety symptoms was measured with the 7-item Generalized Anxiety Disorder Screener (GAD-7) (Kroenke et al., 2007), which provides a reliable and valid measure of anxiety symptom severity regardless of specific anxiety disorder (Spitzer et al., 2006; Williams, 2014).

2.4. Data analyses

Demographic and clinical variables, including comorbidities and craving measures, were summarized using mean and standard deviation (SD) or N (%), and were compared between men and women using chi-square tests or t-tests. Consumption measures derived from TLFB were compared between men and women using Wilcoxon rank sum tests. Association of clinical variables with consumption measures was evaluated using linear regression models. Consumption measures were first normalized using Van Der Waerden transformations (to convert ranks to quantiles of the normal distribution). Sex interactions were tested to determine whether the effects of clinical variables on consumption measures differed by sex. Subsequently, sex-stratified analyses were performed. Within sex strata, associations between clinical variables and consumption measures were evaluated, and interactions between MDD and IDTS scores were tested. Additionally, to show the effect of MDD history on alcohol use in men and women, untransformed consumption measures were summarized using median and quartiles 1 and 3 in groups defined by sex and depression history; consumption distributions were then compared between groups defined by MDD history in sex-based strata using Wilcoxon rank sum tests. All analyses were conducted using SAS (version 9.4; Cary, NC).

3. Results

3.1. Demographic and clinical characteristics of the study sample

As shown in Table 1, the study sample included 443 subjects with average age of 42.1 ± 11.8 ; 64.5% of the subjects were men and 93.5% were European Americans. All participants met diagnostic criteria for current alcohol dependence. Common psychiatric comorbidities included MDD (23.6%), SID (32.7%) and AnxD (32.5%). Lifetime MDD and SID were significantly more prevalent in women compared to men (33.6% vs 18.2%, $p = 0.0003$; and 43.9% vs 26.7%, $p = 0.0002$, respectively) as was frequency of an AnxD (42.6% vs 27.2%,

Table 1
Demographic and Clinical Characteristics of the Study Sample^b.

Characteristic	N	All Subjects N = 443 N (%) or Mean ± SD	Males N = 287	Females N = 156	p-value ^a
Demographics					
Race	443				0.35
European American		414 (93.5)	267 (93.0)	147 (94.2)	
African American		5 (1.1)	5 (1.7)	0 (0)	
Other		8 (1.8)	6 (2.1)	2 (1.3)	
Unknown		16 (3.6)	9 (3.1)	7 (4.5)	
Age (years)	443	42.1 ± 11.8	42.3 ± 11.8	41.8 ± 11.9	0.66
Emotional state assessment					
IDTS negative score	424	57.0 ± 21.7	55.4 ± 21.3	59.9 ± 22.3	0.045
IDTS positive score	429	56.6 ± 24.0	57.9 ± 23.1	54.0 ± 25.4	0.11
IDTS temptation score	423	49.4 ± 23.2	49.9 ± 22.4	48.5 ± 24.6	0.58
PHQ-9 score	436	9.4 ± 6.1	9.3 ± 6.2	9.6 ± 6.0	0.57
GAD-7 score	441	9.0 ± 5.9	8.5 ± 5.8	9.7 ± 5.8	0.041
Alcohol consumption measures					
Total drinks per drinking day	441	583.4 ± 502.8	664.1 ± 525.8	440.8 ± 425.0	< 0.0001
Avg. drinks per drinking day	412	12.1 ± 7.4	13.6 ± 7.7	9.6 ± 5.9	< 0.0001
Drinking days per 90 days	441	45.8 ± 27.0	46.7 ± 27.4	44.2 ± 26.2	0.33
Max drinks per drinking day	412	17.8 ± 11.2	19.3 ± 11.3	15.0 ± 10.4	< 0.0001
Number of heavy drinking days	441	41.4 ± 27.0	42.7 ± 27.5	39.1 ± 26.0	0.20
Comorbid Depression, Anxiety and Substance use Disorders (PRISM Diagnoses)					
MDD lifetime	440	104 (23.6%)	52 (18.2%)	52 (33.6%)	0.0003
MDD current	440	37 (8.4)	19 (6.7%)	18 (11.6%)	0.074
SID	440	144 (32.7%)	76 (26.7%)	68 (43.9%)	0.0002
Any AnxD	440	143 (32.5%)	77 (27.0%)	66 (42.6%)	0.0009
Generalized anxiety disorder	431	10 (2.3%)	5 (1.8%)	5 (3.3%)	0.34
Obsessive-compulsive disorder	431	22 (5.1%)	14 (5.1%)	8 (5.2%)	0.95
Social phobia	431	54 (12.5%)	33 (11.9%)	21 (13.6%)	0.61
Posttraumatic stress disorder	431	79 (18.3%)	35 (12.6%)	44 (28.6%)	< 0.0001
Panic disorder	431	31 (7.2%)	17 (6.1%)	14 (9.1%)	0.26
SIA	440	14 (3.2%)	10 (3.5%)	4 (2.6%)	0.78
Nicotine dependence	440	180 (40.9%)	115 (40.4%)	65 (41.9%)	0.75
Other substance dependence	440	162 (36.8%)	112 (39.3%)	50 (32.3%)	0.14
Cannabis	440	82 (18.6%)	62 (21.8%)	20 (12.9%)	0.023
Cocaine	440	80 (18.2%)	51 (17.9%)	29 (18.7%)	0.83
Heroin	440	4 (0.9%)	3 (1.1%)	1 (0.7%)	1.0
Hallucinogen	440	17 (3.9%)	14 (4.9%)	3 (1.9%)	0.19
Sedatives	440	23 (5.2%)	17 (6.0%)	6 (3.9%)	0.35
Stimulant	440	53 (12.1%)	36 (12.6%)	17 (11.0%)	0.61
Prescription opioids	440	34 (7.7%)	20 (7.0%)	14 (9.0%)	0.45
Other	440	4 (0.9%)	3 (1.1%)	1 (0.7%)	1.0

PHQ-9, Patient Health Questionnaire 9; GAD-7, Generalized Anxiety Disorder Scale; AnxD, anxiety disorder; IDTS, Inventory of Drug Taking Situations; MDD, major depressive disorder; PRISM, Psychiatric Research Interview of Substance and Mood Disorders; SIA, substance-induced anxiety; SID, substance-induced depression.

^a p-value for comparison between male and female groups. P-values reflecting statistically significant differences (< 0.05) bold and underlined, trend differences (p < 0.1) underlined.

^b Modified from (Karpyak et al., 2016).

p = 0.0009), including posttraumatic stress disorder (28.6% vs 12.6%, p < 0.0001). SIA prevalence was low (3.2%), with no significant difference in prevalence between men and women. There were no significant differences between men and women in age, nicotine dependence or other secondary diagnoses of non-alcohol substance dependence with the exception of cannabis dependence, which was more common in men (p = 0.023).

The average IDTS negative score was significantly higher in alcoholic women compared to men (59.9 ± 22.3 vs 55.4 ± 21.3, p = 0.045), but no significant male/female differences were found in average IDTS positive and temptation scores (Karpyak et al., 2016). The average severity of depressive symptoms (measured by PHQ-9) was similar in men and women (p = 0.57), while severity of anxiety symptoms (measured by GAD-7) was higher in women (9.7 ± 5.8 vs 8.5 ± 5.8; p = 0.04).

3.2. Correlations among alcohol consumption measures

As expected, the total number of drinks consumed is correlated with per-day quantity (average drinks per day and maximum drinks per day) and even more strongly with frequency (number of drinking days); total

drinks is most strongly correlated with the number of heavy drinking days, a frequency measure that also incorporates information on quantity (Supplementary Table S1). The two frequency measures are strongly correlated with each other, and the two per-day quantity measures are correlated with each other. However, the number of drinking days (i.e. frequency) is not correlated with the two per-day quantity measures.

3.3. Association of alcohol consumption measures with clinical and demographic covariates in the combined sample of study participants

As shown in Table 2, all three IDTS subscales were strongly and positively associated with total alcohol consumption, average number of drinks per drinking day, maximum number of drinks per drinking day and number of heavy drinking days (all p ≤ 0.0001). Number of drinking days was also positively associated with all three IDTS subscales, with IDTS negative showing the strongest evidence of association (p = 0.0002), IDTS positive weakest (p = 0.024) and IDTS temptation in between (p = 0.0055). Male sex was associated with higher total alcohol consumption (p = 0.0002), number of drinks per drinking day (p < 0.0001) and maximum number of drinks per drinking day

Table 2
Association of alcohol consumption measures (transformed to normal variables) with comorbid depression or anxiety disorders and propensity to drink in positive and negative emotional states in a combined sample of male and female alcoholics.

Alcohol consumption measures	Predictor	N	Estimate	SE	p-value
Total drinks	IDTS negative	414	0.0149	0.002	< 0.0001
	IDTS positive	418	0.0111	0.002	< 0.0001
	IDTS temptation	412	0.0117	0.002	< 0.0001
	PHQ-9	425	0.0149	0.008	<u>0.057</u>
	GAD-7	430	0.0033	0.034	0.68
	Sex (M)	430	0.3652	0.097	0.0002
	Age	430	0.0064	0.004	0.11
	MDD	430	-0.2000	0.111	<u>0.072</u>
	SID	430	-0.0581	0.101	0.56
	AnxD	430	-0.0777	0.101	0.44
	Current MDD (12mo)	430	0.0597	0.167	0.72
	Number of drinking days	IDTS negative	414	0.0081	0.002
IDTS positive		418	0.0045	0.002	0.024
IDTS temptation		412	0.0058	0.002	0.0055
PHQ-9		425	0.0127	0.008	0.10
GAD-7		430	0.0062	0.008	0.44
Sex (M)		430	0.0769	0.099	0.44
Age		430	0.0127	0.004	0.0015
MDD		430	-0.2225	0.111	<u>0.045</u>
SID		430	-0.1187	0.101	0.24
AnxD		430	-0.0822	0.101	0.41
Current MDD (12mo)		430	-0.1409	0.167	0.40
Number of heavy drinking days		IDTS negative	414	0.0103	0.002
	IDTS positive	418	0.0076	0.002	0.0001
	IDTS temptation	412	0.0082	0.002	< 0.0001
	PHQ-9	425	0.0142	0.008	<u>0.067</u>
	GAD-7	430	0.0095	0.008	0.24
	Sex (M)	430	0.1074	0.098	0.27
	Age	430	0.0103	0.004	0.0093
	MDD	430	-0.2242	0.110	<u>0.042</u>
	SID	430	-0.0788	0.100	0.43
	AnxD	430	0.9755	0.033	0.41
	Current MDD (12mo)	430	-0.0609	0.166	0.71
	Avg. drinks/drinking day	IDTS negative	414	0.0112	0.002
IDTS positive		418	0.0105	0.001	< 0.0001
IDTS temptation		412	0.0116	0.002	< 0.0001
PHQ-9		425	0.0130	0.008	<u>0.094</u>
GAD-7		430	0.0015	0.008	0.85
Sex (M)		430	0.4899	0.095	< 0.0001
Age		430	-0.0054	0.004	0.17
MDD		430	-0.0622	0.033	0.57
SID		430	-0.0314	0.100	0.75
AnxD		430	-0.0425	0.100	0.67
Current MDD (12mo)		430	0.2789	0.165	<u>0.091</u>
Max drinks/drinking day		IDTS negative	414	0.0086	0.002
	IDTS positive	418	0.0093	0.002	< 0.0001
	IDTS temptation	412	0.0105	0.002	< 0.0001
	PHQ-9	425	0.0106	0.008	0.17
	GAD-7	430	-0.0021	0.008	0.79
	Sex (M)	430	0.3702	0.097	0.0001
	Age	430	-0.0127	0.004	0.0013
	MDD	430	-0.0537	0.111	0.63
	SID	430	0.0180	0.100	0.86
	AnxD	430	0.0354	0.100	0.72
	Current MDD (12mo)	430	0.2190	0.165	0.19

SE, Standard Error; PHQ-9, Patient Health Questionnaire 9; GAD-7, Generalized Anxiety Disorder Scale; AnxD, anxiety disorder; IDTS, Inventory of Drug Taking Situations; MDD, major depressive disorder; SIA, substance-induced anxiety; SID, substance-induced depression. P-values reflecting statistically significant differences (< 0.05) bold and underlined, trend differences (p < 0.1) underlined.

(p = 0.0001).

Age was positively associated with the number of drinking days (p = 0.0015) and heavy drinking days (p = 0.0093), but was negatively associated with the maximum number of drinks per drinking day (p = 0.0013). Alcohol use measures (i.e., total alcohol use, per day alcohol use, number of drinking days or heavy drinking days) were not associated with current MDD, SID, or AnxD diagnoses in the entire cohort of men and women. However, marginal evidence was observed for negative association of the number of drinking days and number of heavy drinking days with lifetime MDD history (p = 0.045, p = 0.042, respectively).

Considering the strong association between male sex and alcohol consumption, and in order to evaluate whether the associations described above differ by sex, we tested for the association of consumption measures with interactions between sex and the other predictors of consumption shown in Table 2. Given the limited power to detect interactions, it was not surprising that no interactions were statistically significant at the 0.05 level. However, marginal evidence of sex interaction was observed for the effect of lifetime MDD on the number of drinking days (p_{interaction} = 0.054) and the effect of IDTS temptation score on the maximum drinks in a drinking day (p_{interaction} = 0.055). These results suggest possible differences in predictors of consumption between men and women, which motivated further sex-stratified analyses.

3.4. Association of alcohol consumption with clinical and demographic covariates in male and female study participants

As shown in Table 3, the total alcohol consumption in male alcoholics was strongly and positively associated with IDTS negative and temptation scales (p < 0.0001, each) and IDTS positive scale (p = 0.0002). Moreover, the average number of drinks per drinking day was associated with IDTS negative (p = 0.0002), temptation (p = 0.0011), and positive (p = 0.0063) scales. The maximum number of drinks per drinking day and number of drinking days were also associated with the three IDTS subscale scores, though the associations were slightly weaker for these consumption measures (Table 3).

The evidence for association between the lifetime MDD history and decreased number of drinking days was stronger in the male subgroup (p = 0.0084) than in the combined sample (p = 0.045). Also, the association between the number of heavy drinking days and IDTS negative (p = 0.0001), temptation (p = 0.0022), and positive (p = 0.0061) scores in alcohol dependent men was stronger than the association with the average number of drinking days. In contrast, the evidence for association between the lifetime history of MDD and decreased number of heavy drinking days in this subgroup (p = 0.021) was weaker compared to association with the number of drinking days (p = 0.0084).

The age of male study participants was positively associated with the number of drinking days (p = 0.027) and the number of heavy drinking days (p = 0.036), and it was negatively associated with the maximum reported number of drinks per drinking day (p = 0.011). In alcohol dependent men, we again found no associations between alcohol consumption measures (i.e., total alcohol use, per day alcohol use, number of drinking days or heavy drinking days) and current MDD, AnxD or SID diagnoses.

In alcohol dependent women (Table 4), all three IDTS subscales were positively associated with total alcohol consumption (p < 0.0001, each). Similarly, the average number of drinks per day and maximum number of drinks per day were strongly and positively associated with all three IDTS subscales (p < 0.0001, each). Our sample provided no evidence of association between IDTS scales and the number of drinking days in alcohol dependent females with only a trend toward positive association with IDTS negative scale (p = 0.057). Yet, significant positive associations with IDTS negative (p = 0.0027), temptation (p = 0.012), and positive (p = 0.0063) scores were found when the number of heavy drinking days was considered. No

Table 3
Association of alcohol consumption measures (transformed to normal variables) with comorbid depression or anxiety disorders and propensity to drink in positive and negative emotional states in male alcoholics.

Alcohol consumption measures	Predictor	N	Estimate	SE	p-value
Total drinks	IDTS negative	268	0.0156	0.003	<u>< 0.0001</u>
	IDTS positive	270	0.0099	0.003	<u>0.0002</u>
	IDTS temptation	267	0.0027	0.017	<u>< 0.0001</u>
	Age	277	0.0043	0.005	0.41
	PHQ-9	273	0.0125	0.010	0.21
	GAD-7	277	0.0048	0.011	0.65
	MDD	277	-0.2621	0.157	<u>0.096</u>
	SID	277	0.1119	0.139	0.42
	AnxD	277	-0.0015	0.137	0.99
	Current MDD (12mo)	277	-0.0708	0.217	0.74
	Number of drinking days	IDTS negative	268	0.0093	0.003
IDTS positive		270	0.0055	0.003	<u>0.037</u>
IDTS temptation		267	0.0075	0.003	<u>0.0061</u>
Age		277	0.0113	0.005	<u>0.027</u>
PHQ-9		273	0.0098	0.010	0.32
GAD-7		277	0.0057	0.010	0.58
MDD		277	-0.4094	0.154	<u>0.0084</u>
SID		277	-0.1279	0.137	0.35
AnxD		277	-0.1314	0.136	0.33
Current MDD (12mo)		277	-0.2912	0.215	0.18
Number of heavy drinking days		IDTS negative	268	0.0109	0.003
	IDTS positive	270	0.0073	0.003	<u>0.0061</u>
	IDTS temptation	267	0.0084	0.003	<u>0.0022</u>
	Age	277	0.0108	0.005	<u>0.036</u>
	PHQ-9	273	0.0106	0.010	0.28
	GAD-7	277	0.0095	0.010	0.36
	MDD	277	-0.3591	0.155	<u>0.021</u>
	SUD	277	-0.0317	0.138	0.82
	AnxD	277	-0.1112	0.136	0.41
	Current MDD (12mo)	277	-0.2213	0.216	0.31
	Avg. drinks/drinking day	IDTS negative	268	0.0103	0.003
IDTS positive		270	0.0071	0.003	<u>0.0063</u>
IDTS temptation		267	0.0086	0.003	<u>0.0011</u>
Age		277	-0.0055	0.005	0.27
PHQ-9		273	0.0113	0.010	0.24
GAD-7		277	-0.0008	0.010	0.94
MDD		277	-0.0321	0.153	0.83
SID		277	0.1466	0.134	0.27
AnxD		277	0.0698	0.133	0.60
Current MDD (12mo)		277	0.1987	0.210	0.34
Max drinks/drinking day		IDTS negative	268	0.0074	0.003
	IDTS positive	270	0.0062	0.003	<u>0.018</u>
	IDTS temptation	267	0.0071	0.003	<u>0.0082</u>
	Age	277	-0.0128	0.005	<u>0.011</u>
	PHQ-9	273	0.0095	0.010	0.33
	GAD-7	277	-0.0048	0.010	0.64
	MDD	277	-0.0819	0.154	0.59
	SID	277	0.1031	0.135	0.45
	AnxD	277	0.060	0.133	0.65
	Current MDD (12mo)	277	0.0674	0.212	0.75

PHQ-9, Patient Health Questionnaire 9; GAD-7, Generalized Anxiety Disorder Scale; AnxD, anxiety disorder; IDTS, Inventory of Drug Taking Situations; MDD, major depressive disorder; SIA, substance-induced anxiety; SID, substance-induced depression. P-values reflecting statistically significant differences (< 0.05) bold and underlined, trend differences (p < 0.1) underlined.

association was found between lifetime MDD history with the number of drinking days or heavy drinking days in alcohol dependent females. However, current MDD was associated with increased average number of drinks per drinking day and the maximum number of drinks per drinking day (p < 0.05, each) in alcohol dependent women.

The age of female study participants was positively associated with the number of drinking days (p = 0.018) and negatively associated

Table 4
Association of alcohol consumption measures (transformed to normal variables) with comorbid depression or anxiety disorders and propensity to drink in positive and negative emotional states in female alcoholics.

Alcohol consumption measures	Predictor	N	Estimate	SE	p-value
Total drinks	IDTS negative	146	0.0158	0.003	<u>< 0.0001</u>
	IDTS positive	148	0.0113	0.003	<u>< 0.0001</u>
	IDTS temptation	145	0.0117	0.003	<u>< 0.0001</u>
	Age	153	0.0088	0.006	0.13
	PHQ-9	152	0.0211	0.012	<u>0.073</u>
	GAD-7	153	0.0088	0.012	0.47
	MDD	153	0.0211	0.149	0.89
	SID	153	-0.1325	0.141	0.35
	AnxD	153	-0.0500	0.142	0.72
	Current MDD (12mo)	153	0.0962	0.200	0.63
	Number of drinking days	IDTS negative	146	0.0065	0.003
IDTS positive		148	0.0028	0.003	0.35
IDTS temptation		145	0.0029	0.003	0.35
Age		153	0.0148	0.006	<u>0.018</u>
PHQ-9		152	0.0185	0.012	0.14
GAD-7		153	0.0090	0.013	0.49
MDD		153	0.0250	0.159	0.88
SID		153	-0.0795	0.151	0.60
AnxD		153	0.0159	0.152	0.92
Current MDD (12mo)		153	-0.0406	0.214	0.85
Number of heavy drinking days		IDTS negative	146	0.0099	0.003
	IDTS positive	148	0.0079	0.003	<u>0.0063</u>
	IDTS temptation	145	0.0076	0.003	<u>0.0117</u>
	Age	153	0.0091	0.006	0.1382
	PHQ-9	152	0.0213	0.012	<u>0.079</u>
	GAD-7	153	0.0122	0.013	0.33
	MDD	153	-0.0270	0.155	0.86
	SUD	153	-0.1017	0.147	0.49
	AnxD	153	-0.0047	0.148	0.97
	Current MDD (12mo)	153	0.0138	0.209	0.95
	Avg. drinks/drinking day	IDTS negative	146	0.0155	0.003
IDTS positive		148	0.0133	0.003	<u>< 0.0001</u>
IDTS temptation		145	0.0151	0.003	<u>< 0.0001</u>
Age		153	-0.0070	0.006	0.24
PHQ-9		152	0.0183	0.012	0.12
GAD-7		153	0.0165	0.012	0.17
MDD		153	0.1088	0.148	0.46
SID		153	-0.0561	0.141	0.69
AnxD		153	-0.0164	0.142	0.91
Current MDD (12mo)		153	0.3986	0.197	<u>0.044</u>
Max drinks/drinking day		IDTS negative	146	0.0128	0.003
	IDTS positive	148	0.0121	0.003	<u>< 0.0001</u>
	IDTS temptation	145	0.0150	0.003	<u>< 0.0001</u>
	Age	153	-0.0138	0.006	<u>0.023</u>
	PHQ-9	152	0.0143	0.012	0.24
	GAD-7	153	0.0108	0.013	0.39
	MDD	153	0.1375	0.154	0.37
	SID	153	0.0731	0.146	0.62
	AnxD	153	0.1479	0.147	0.31
	Current MDD (12mo)	153	0.4201	0.204	<u>0.041</u>

PHQ-9, Patient Health Questionnaire 9; GAD-7, Generalized Anxiety Disorder Scale; AnxD, anxiety disorder; IDTS, Inventory of Drug Taking Situations; MDD, major depressive disorder; SIA, substance-induced anxiety; SID, substance-induced depression. P-values reflecting statistically significant differences (< 0.05) bold and underlined, trend differences (p < 0.1) underlined.

with the maximum reported number of drinks per drinking day (p = 0.023). There was no evidence of association with the average number of drinks per drinking day, number of heavy drinking days or the total number of drinks consumed during three months prior to evaluation. We found no associations between alcohol consumption measures (i.e., total alcohol use, per day alcohol use, number of drinking days or heavy drinking days) and SID or AnxD diagnoses in

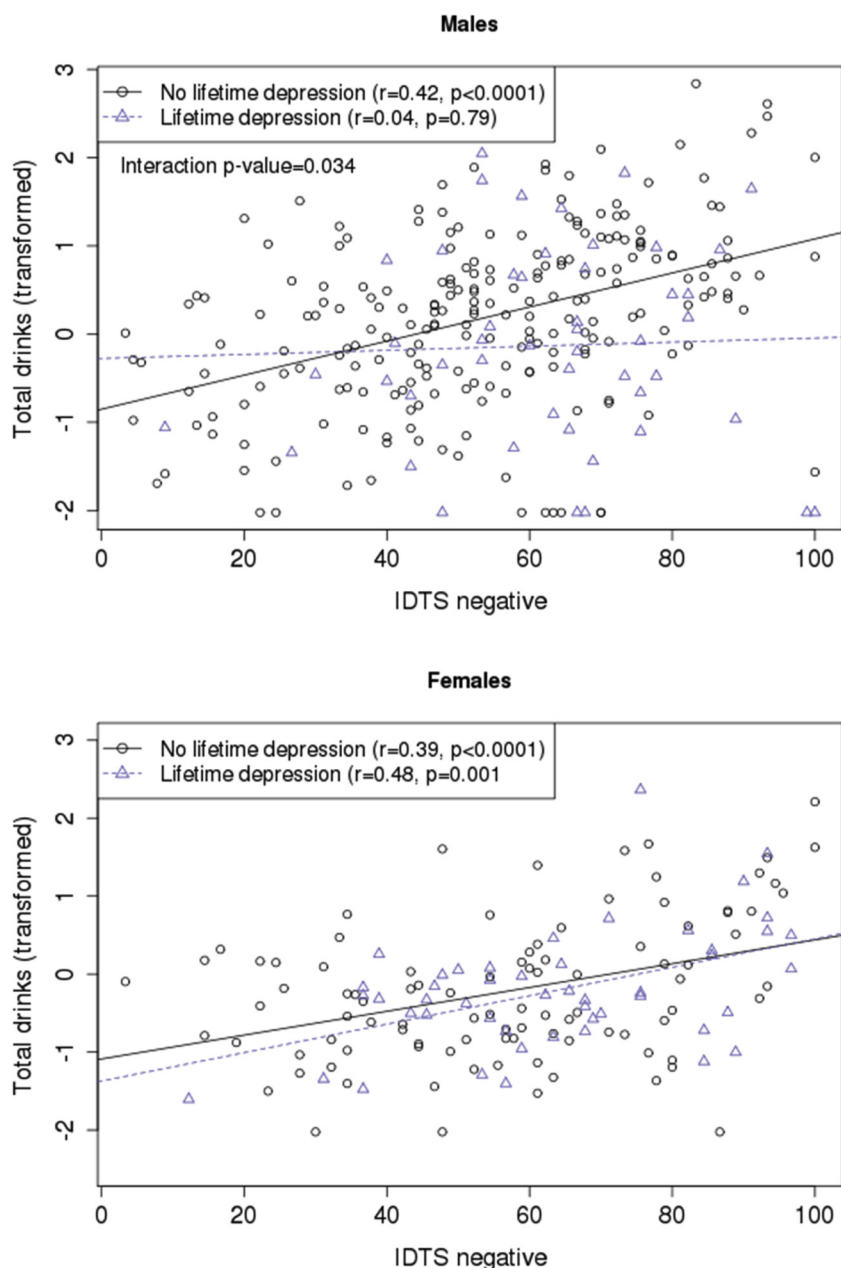


Fig. 1. The relationship between total alcohol consumption (transformed to a standard normal variable) and IDTS negative and life time MDD history in alcoholic men and women. The slope of the line representing alcohol consumption in male alcoholics without MDD history is positive, while the slope of the line representing alcohol consumption in male alcoholics with MDD history is almost flat, suggesting that the positive correlation between IDTS negative score and total alcohol consumption is modified (decreased) by lifetime MDD history. On the contrary, in female alcoholics, slopes of the lines reflect a positive correlation between IDTS negative score and total alcohol consumption regardless of the presence or absence of lifetime MDD history.

alcohol dependent women.

3.5. The interaction of IDTS negative and depression as predictors of consumption measures

Since our data suggested that IDTS negative scale and male sex were the strongest predictors of increased alcohol consumption, while lifetime MDD history was the only predictor of decreased alcohol consumption, we tested for the interaction of IDTS negative subscale and lifetime MDD history as predictors of consumption measures in men and in women. An interaction was observed for total drinks in men ($p = 0.034$), suggesting that the association of IDTS negative score with the total alcohol consumption in men may be modified (decreased) by MDD history (Fig. 1a). Depression-stratified analysis showed IDTS negative score is associated with total alcohol consumption only in men without MDD history ($r = 0.42, p < 0.0001$), whereas no association between IDTS negative score and total consumptions was detected in men with MDD history ($r = 0.04, p = 0.79$). This difference is illustrated by the different slopes of regression lines in Fig. 1a. As shown in

Fig. 1b, IDTS negative score was significantly associated with increased total alcohol consumption in women with and without history of MDD ($r = 0.48, p = 0.001$ and $r = 0.39, p < 0.0001$, respectively), with no evidence of interaction between MDD history and IDTS negative score in their effect on total alcohol consumption ($p = 0.24$).

Because our analyses (Tables 3 and 4) revealed an impact of MDD history on alcohol use in males but not females, we present the summary statistics (mean and IQR) for consumption measures separately in men and women with and without MDD history (Table 5). Table 5 also shows results of Wilcoxon rank sum test analyses comparing consumption measures by MDD history in male and female strata. Consistent with the findings presented in Tables 3 and 4, the results in Table 5 show no difference in the total number of drinks or the average number of drinks per drinking day between male subjects with and without MDD history. Yet, the number of drinking days and the number of heavy drinking days are significantly lower in men with lifetime history of MDD ($p = 0.013$ and $p = 0.022$, respectively). On the contrary, there is no difference in the alcohol consumption measures between female subjects with and without MDD history.

Table 5
Alcohol consumption in male and female alcoholics by lifetime history of MDD.

Alcohol consumption (TLFB 90)	Median	Q1, Q3	Median	Q1, Q3	p-value
Men					
MDD (N = 51)			No MDD (N = 226)		
Total drinks	380	102, 935	549	263, 938	0.12
Heavy drinking days	27	10, 60	46	22, 71	0.022
Drinking days	35	17, 64	55	25, 72	0.013
Average drinks/drinking day	12	6, 20	11	8, 16	0.87
Max drinks/drinking day	16	10, 23	16	11, 22	0.72
Women					
MDD (N = 51)			No MDD (N = 102)		
Total drinks	326	178, 487	291	127, 571	0.79
Heavy drinking days	39	17, 57	36	13, 66	0.99
Drinking days	48	23, 68	47	20, 67	0.78
Average drinks/drinking day	8	5, 12	8	5, 11	0.57
Max drinks/drinking day	12	10, 20	12	8, 18	0.47

MDD, major depressive disorder; Q1, Q3, quartiles 1 and 3, respectively; TLFB90, time line follow back for 90 days before assessment. P-values reflecting statistically significant differences (< 0.05) bold and underlined.

4. Discussion

We previously observed that comorbid depressive and anxiety disorders are associated with tendency to drink in negative emotional states in a sex-specific manner (Karpyak et al., 2016). Here we investigated the impact of preferred drinking states as well as presence/absence of comorbid depressive and anxiety disorders on alcohol use in alcohol dependent males and females during 90 days before enrollment in a treatment study. Consistent with previous reports (Turner et al., 1997; Victorio-Estrada and Mucha, 1997; Victorio-Estrada et al., 1996), our findings revealed strong association between emotional states (measured by magnitude of positive, negative and temptation subscales of IDTS) and the amount (average per day and total) of alcohol consumption during 90 days prior to assessment in both men and women. Yet, the strength of associations between IDTS subscales and the frequency of use (number of drinking days) was weaker and insignificant in women; these associations became stronger when the number of heavy drinking days was considered, once again suggesting that association of IDTS scales with total consumption is driven by the amount of alcohol use per drinking day. Furthermore, sex-specific effect on alcohol use (higher in males compared to females with AUD) was also restricted to per day consumption and no sex differences were observed in the number of drinking days.

Our findings also indicate that the IDTS negative score consistently shows strong association with alcohol consumption measures. This is consistent with previous findings of association between IDTS negative score and the intensity of depressive symptoms (Abulseoud et al., 2013; Lau-Barraco et al., 2009) and supports contextual validity of the IDTS negative scale—i.e., drinking in an effort to achieve relief from negative feelings (Turner et al., 1997). Yet, association between alcohol use measures and intensity of depressive symptoms at the time of evaluation was not statistically significant in our study. The delay in assessment of the intensity of depressive symptoms completed on average 21 days after beginning treatment (at the time of enrollment in the parent study) may have contributed to this lack of association.

We found no association of alcohol use measures with a history of AnxD, SID or current MDD (within last 12 months) in the combined group of alcoholics, although there was a weak trend toward positive association between average per day alcohol consumption and current MDD in the combined group; this association was nominally significant in women, as was the association of current MDD with maximum drinks per drinking day. This finding is consistent with previous reports of stronger association between alcohol consumption and negative

emotional states in women (Abulseoud et al., 2013; Lau-Barraco et al., 2009).

Contrary to our expectations, lifetime MDD history was associated with decreased total alcohol consumption; further analyses indicated that this association was driven by decreased number of drinking days in alcohol dependent men with lifetime (but not current) history of MDD. Prior longitudinal studies suggest that having more depressive symptoms predicts less alcohol consumption later in life (Schutte et al., 1995). Moreover, negative genetic correlation between MDD history and alcohol consumption (measured by AUDIT-C score) was recently reported in a large population-based cohort (Sanchez-Roige et al., 2018). However, to our knowledge, this is the first report demonstrating the phenotypic association between MDD and alcohol consumption (rather than genetic correlation) and showing that the negative association between MDD and total consumption is driven by frequency of drinking (as opposed to per day consumption), and that these relationships are specific to alcohol dependent men. Furthermore, this is the first report indicating that presence of MDD also modifies (decreases) the association of the IDTS negative scores with alcohol consumption in alcoholic men. The underlying mechanisms of this association are not clear. One possible explanation is that decreased number of drinking days results from successful treatment of depressive symptoms with antidepressant medications in some male alcoholics. However, our post-hoc analyses with adjustment for antidepressant use suggested that the association with MDD was not driven by antidepressant use (results not shown). Thus, other psychological and physiological mechanisms may have contributed to this finding.

We also found that older age was associated with a higher number of drinking days and a lower reported maximum number of drinks per drinking day. These findings were consistently present in the combined sample as well as in stratified analyses in the male and female subsamples. An association between older age and higher number of heavy drinking days was present only in men and combined sample but not in the female subsample.

These findings further delineate the differential impact of negative emotional states on alcohol consumption in alcoholic women and men, such that women seem especially prone to increased amount and frequency of alcohol use when negative emotions are present (as measured by elevated scores of PHQ-9, IDTS negative scale, or current MDD diagnosis by PRISM). This difference should be accounted for in individualized treatment planning. More research is needed to understand the complex relationship between a lifetime diagnosis of MDD and alcohol consumption in male alcoholics.

Despite the high correlations among the alcohol consumption measures used in this study, differences in their association with clinical features were observed. For example, in women significant positive associations of IDTS negative, temptation, and positive scores were found with the average and maximum per day consumption as well as with the number of heavy drinking days, but not with the number of drinking days. Meanwhile, in men, lifetime MDD was associated with the number of drinking days, but not with the average or maximum per day consumption. These results demonstrate that it is important to consider different consumption measures, which account for both frequency and quantity, to better understand the impact of craving on alcohol consumption.

Our findings should be considered in the context of the following limitations. The smaller number of women and men with certain characteristics (e.g. MDD) in our sample may have precluded the detection of some association effects. Also, because our results were not corrected for multiple testing, associations with weaker statistical evidence (e.g. $p > 0.005$) should be interpreted cautiously and warrant replication. In addition, the design of the parent study resulted in some of the assessments (e.g., the intensity of depressive and anxiety symptoms) being conducted after 3 weeks of treatment, which could have limited our ability to detect association between PHQ-9 or GAD-7 scores and the IDTS negative subscale. Finally, reported association

findings are based on retrospective assessment of self-reported history of alcohol consumption and history of anxiety and depressive disorders and preferred drinking situations, which were collected at the time of enrollment in parent study. Therefore, our findings are limited to relationships among clinical and demographic variables collected at single time point, and it is important to extend these findings based on prospective monitoring of those characteristics. The biological mechanisms underlying the reported findings and their relevance to treatment outcomes also need to be investigated in order to develop relevant treatment strategies.

In conclusion, our findings demonstrate important differences in the impact of state-dependent (present at the time of alcohol use) factors (e.g., negative or positive emotions as well as temptation to drink and current MDD diagnosis) compared to the impact of the trait-related characteristic (e.g., life-time history of MDD) on alcohol consumption in alcoholic men and women. Unlike the state-dependent factors, which seem to be strongly and positively associated with the amount and frequency of alcohol consumption in alcoholics of both sexes, trait-related characteristics are associated with decreased number of drinking days (e.g., propensity for initiation of drinking episode) in alcoholic men, without impact on the per-day amount of alcohol consumed. This difference should be accounted for in clinical research and prompt investigation of underlying biological mechanisms that may guide individualized treatment planning and relapse-prevention recommendations.

Contributors

VK and JB conceived of the study. VK, MF, and JB designed the study. VK, DHF, LL, TS, MS, and MF generated the data. JB and JG prepared and analyzed the data. VK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

Co-authors disclosed relationships with funding sources, which may be perceived as potential conflicts of interest. Specifically, Dr Frye had a past consultancy with Janssen Research & Development LLC, Mitsubishi Tanabe Pharma Corporation, Myriad Genetics, Sunovion, Supernus Pharmaceuticals, and Teva Pharmaceuticals; he also has received past grant support from Johnson & Johnson and AssureRx (although not for this publication). Other authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.12.010>.

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