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Gender-specific effects of comorbid depression and anxiety on the propensity to drink in negative emotional states

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ABSTRACT

Background and Aims Depression and anxiety are often comorbid with alcoholism and contribute to craving and relapse. We aimed to estimate the prevalence of life-time diagnoses of major depressive disorder (MDD), substance-induced depression (SID), anxiety disorder (AnxD) and substance-induced anxiety (SIA), the effects of these comorbidities on the propensity to drink in negative emotional states (negative craving), and test whether these effects differ by sex. **Design** Secondary analyses of baseline data collected in a single-arm study of pharmacogenetic predictors of acamprosate response. **Setting** Academic medical center and affiliated community-based treatment programs in the American upper mid-west. **Participants** A total of 287 males and 156 females aged 18–80 years, meeting DSM-IV criteria for alcohol dependence. **Measurements** The primary outcome measure was 'propensity to drink in negative emotional situations' (determined by the Inventory of Drug Taking Situations) and the key predictors/covariates were sex and psychiatric comorbidities, including MDD, SID, AnxD and SIA (determined by Psychiatric Research Interview of Substance and Mood Disorders). **Findings** The prevalence of the MDD, SID and AnxD was higher in females compared with males (33.1 versus 18.4%, 44.8 versus 26.4% and 42.2 versus 27.4%, respectively; $P < 0.01$, each), while SIA was rare (3.3%) and did not differ by sex. Increased propensity to drink in negative emotional situations was associated with comorbid MDD ($\beta = 6.6$, $P = 0.013$) and AnxD ($\beta = 4.8$, $P = 0.042$) as well as a SID × sex interaction effect ($P = 0.003$), indicating that the association of SID with propensity to drink in negative emotional situations differs by sex and is stronger in males ($\beta = 7.9$, $P = 0.009$) compared with females ($\beta = -6.6$, $P = 0.091$). **Conclusions** There appears to be a higher prevalence of comorbid depression and anxiety disorders as well as propensity to drink in negative emotional situations in female compared with male alcoholics. Substance-induced depression appears to have a sex-specific effect on the increased risk for drinking in negative emotional situations in males.

Keywords Alcohol use disorder, anxiety, craving, depression, gender, substance-induced.

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INTRODUCTION

Alcohol use disorders (AUDs) and depression are the main contributors to the global burden of mental and neurological disorders [1]. Clinical [2–6] and epidemiological [7–9] findings indicate frequent comorbidity of AUDs with depression and anxiety, resulting in poor treatment outcomes and frequent complications, including suicide. Analyses suggest that such comorbidity may represent an important subtype of AUD and call for development of

diagnostic and therapeutic interventions to improve treatment outcomes [10,11]. Specifically, the distinction between alcohol-induced depression, which often resolves during early abstinence [12], and non-alcohol-induced depression, which is also frequent in alcoholics [13], is challenging and complicates selection between treatment options [14,15]. Hence, studies investigating differential impact of alcohol-induced and non-alcohol-induced depression on phenotypical presentation and course of AUDs are highly important [12,16,17].

Evidence indicates that depression and anxiety combined with alcohol use may create a feed-forward cycle of increasing each other's intensity that develops and supports comorbidity [18]. This feed-forward cycle may include a stress-response system, which contributes to increased craving and corresponding neuroendocrine changes [19,20]. Craving is a major component of AUDs and an important treatment target [21,22]. Based on epidemiological and clinical data, craving was reinstated among diagnostic criteria for AUDs [23,24]. Our recent findings and previous reports associated craving intensity with the post-treatment relapse [25–28]. Available self-rating instruments [21,29,30] assess the intensity of craving, while leaving aside its emotional and motivational dimensions [31]. Conversely, the Inventory of Drinking Situations [32] and its revised version Inventory of Drug Taking Situations (IDTS) [33] identify negative and positive reinforcing motives versus temptation corresponding to preferred drinking situations [32,34–36]. This approach is consistent with a three-pathway model of craving: attributing the desire for rewarding properties of alcohol (i.e. positive/reward craving); the desire for drinking to reduce tension, stress reactivity and negative emotions (i.e. negative/relief craving); and obsessive thoughts about drinking (i.e. temptation craving) to corresponding dysregulation in dopamine/opioid, glutamate/gamma-aminobutyric acid (GABA) and serotonin neurotransmission systems, respectively [37].

Evidence also supports gender-related differences in relationships between alcohol craving, stress, anxiety and depression [38,39]. We previously identified a positive correlation between craving intensity and depression severity [40] and between depression severity and tendency to drink in negative emotional situations in treatment-seeking alcoholics, especially females [41]. This last association in our study was no longer significant after adjusting for depressive symptoms' severity [41], which supports a hypothesis that depressive symptomatology may serve as a 'mediator' in the relationship between gender and situational drinking [42].

Thus, converging evidence supports the association of comorbid depression and anxiety with the intensity and context of craving (e.g. the tendency to drink in negative emotional situations), which may explain the increased relapse risk in AUD subjects with these comorbidities. In this study we aimed to (1) estimate the prevalence of comorbid substance-induced and non-substance-induced depression and anxiety disorders in male and female treatment-seeking alcoholics; (2) estimate the association between comorbid substance-induced and non-substance-induced depression and anxiety disorders and propensity for propensity to drink in negative emotional situations; and (3) test whether these effects differ by sex and whether the combined presence of more than one of these conditions results in additive effects on propensity to drink in negative emotional situations.

METHODS

Study design

To investigate the relationships between propensity to drink in negative emotional situations and the life-time diagnoses of substance-induced and non-substance-induced depression or anxiety, we analyzed clinical and demographic data collected during baseline evaluation of male and female participants in a prospective study searching for genetic markers associated with sobriety in alcoholics treated with acamprosate in community-based programs [43]. The study was approved by the Institutional Review Boards of Mayo Clinic Rochester and Mayo Clinic Health System. All participants signed informed consent after a full explanation of the study procedures.

Study subjects

We included male and female participants aged 18–80 years with a primary diagnosis of current alcohol dependence treated in community-based programs affiliated with Mayo Clinic Rochester, MN and Mayo Clinic Health System sites in Austin, MN, Albert Lea, MN and La Crosse, WI. Each program and referral numbers are described in the Supplemental materials for an earlier publication [43]. We excluded subjects unable to provide informed consent or speak English, or those with unstable medical (e.g. renal or hepatic impairment) or psychiatric (e.g. psychotic disorder or active suicidal ideation) conditions. Individuals taking disulfiram and those with a history of an allergic reaction to acamprosate, pregnant or lactating women, or women planning to become pregnant during the subsequent year were also excluded in accordance with the requirements of the original study [43].

Complete IDTS and Psychiatric Research Interview of Substance and Mood Disorders (PRISM) data were available for 414 of 443 subjects enrolled into the study (Table 1). All 414 participants included in the analyses met diagnostic criteria for current alcohol dependence.

Assessments

A semi-structured interview (PRISM) [44], conducted by trained and certified interviewers, was used to assess systematically for the life-time presence of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) diagnostic

Table 1 Demographic and clinical characteristics of the study sample.

	n (%) or mean ± SD			
Characteristic	*All subjects n = 443*	*Males n = 287*	*Females n = 156*	*P-value*[a]
Race				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)	42.1 ± 11.8	42.3 ± 11.8	41.8 ± 11.9	0.661
IDTS-negative score	57.0 ± 21.7	55.4 ± 21.3	59.9 ± 22.3	**0.045**
IDTS-positive score	56.6 ± 24.0	57.9 ± 23.1	54.0 ± 25.4	0.110
IDTS temptation score	49.4 ± 23.2	49.9 ± 22.4	48.5 ± 24.6	0.575
Drinks per drinking day[b]	9.8 ± 9.6	11.3 ± 10.5	7.1 ± 7.0	**<0.0001**
Drinking days per month	8.9 ± 8.4	8.8 ± 8.3	9.1 ± 8.6	0.887
Withdrawal symptoms history (%)	312 (72.4%)	198 (63.5%)	114 (74.0%)	0.571
PRISM diagnoses				
MDD	102 (23.7%)	51 (18.4%)	51 (33.1%)	**0.0006**
SID	142 (33.0%)	73 (26.4%)	69 (44.8%)	**<0.0001**
Any AnxD	141 (32.7%)	76 (27.4%)	65 (42.2%)	**0.0017**
Generalized anxiety disorder	10 (2.3%)	5 (1.8%)	5 (3.3%)	0.341
Obsessive–compulsive disorder	22 (5.1%)	14 (5.1%)	8 (5.2%)	0.949
Social phobia	54 (12.5%)	33 (11.9%)	21 (13.6%)	0.605
Post-traumatic stress disorder	79 (18.3%)	35 (12.6%)	44 (28.6%)	**<0.0001**
Panic disorder	31 (7.2%)	17 (6.1%)	14 (9.1%)	0.255
SIA	14 (3.3%)	10 (3.6%)	4 (2.6%)	0.919
Nicotine dependence	177 (41.1%)	112 (40.4%)	65 (42.2%)	0.720
Other substance dependence	159 (36.9%)	110 (39.7%)	49 (31.8%)	0.104
Cannabis	79 (18.3)	60 (21.7)	19 (12.3)	–
Cocaine	79 (18.3)	51 (18.4)	28 (18.2)	–
Heroin	4 (0.9)	3 (1.1)	1 (0.7)	–
Hallucinogen	17 (3.9)	14 (5.1)	3 (2.0)	–
Sedatives	23 (5.3)	17 (6.1)	6 (3.9)	–
Stimulant	52 (12.1)	36 (13.0)	16 (10.4)	–
Prescription opioids	33 (7.7)	20 (7.2)	13 (8.4)	–
Other	4 (0.9)	3 (1.1)	1 (0.7)	–

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; SD = standard deviation. [a]*P*-value for comparison between male and female groups; [b]average number of drinks per drinking day. *P*-values below 0.05 are presented in bold.

criteria for alcohol dependence and comorbid disorders including major depressive disorder (MDD), substance (alcohol)-induced depression (SID), anxiety disorders (AnxD) and substance-induced anxiety (SIA), as well as other Axis I diagnoses determined by the PRISM. The presence or absence of alcohol withdrawal history was also determined by the PRISM.

In the PRISM version designed to incorporate DSM-IV criteria [45], the disorder was classified as substance-induced when: (1) all DSM-IV criteria for the disorder were met, (2) the episode occurred entirely during a period of heavy substance use or within the first 4 weeks after cessation of use, (3) substance use is relevant to the disorder and (4) the symptoms are greater than the expected effects of intoxication or withdrawal. A primary mental disorder was diagnosed when (1) the episode occurred during a sustained period of abstinence or occasional use, (2) the episode began at least 2 weeks prior to the onset of heavy substance use or (3) the episode began during heavy substance use and continued for 4 or more weeks after cessation of use. PRISM showed good to excellent reliability (kappas from 0.66 to 0.75) for primary and substance-induced major depressive disorder [46]. Kappas for any life-time primary anxiety disorder was 0.56, and for the either/or category of life-time primary and substance-induced anxiety disorder was 0.55, while kappa for life-time PTSD was 0.58 [46]. In accordance with DSM-IV criteria, diagnoses of substance-induced depressive or anxiety disorders were assessed independently (i.e. the same person may have more than one diagnosis) and accounted for the timing of development and other diagnostic characteristics [46]. As recommended [14], results obtained by the PRISM interview were reviewed by the

study psychiatrist to ensure that participants met eligibility criteria and that the diagnosis represented a clinically relevant syndrome. To avoid excessively small groups and loss of power in the analysis, we combined all non-substance-induced types of anxiety (including generalized anxiety disorder, obsessive compulsive disorder, social phobia, post-traumatic stress disorder, agoraphobia and panic disorder) into a single category defined as anxiety disorder (AnxD). For the same reason, we did not differentiate between alcohol and non-alcohol-related SID and SIA.

The IDTS [33] was used to establish a propensity to drink in negative emotional situations over the past year. As recommended [36], the raw scores of the IDTS subscales of unpleasant emotions, physical discomfort and conflict with others were averaged to construct the 'IDTS-negative factor score', which was then used as a measure of propensity to drink in negative emotional situations (and potentially reflective of negative craving). Effects of depression and anxiety on IDTS-positive or temptation craving scores (reflecting propensity to drink in response to positive emotions or urges/temptation, respectively) were not investigated.

Alcohol consumption information for 30 days prior to enrollment was collected using the time-line follow-back form [47]. For statistical analyses, consumption was quantified as the average number of drinks per drinking day, and the number of drinking days in the month prior to enrollment.

Data analyses

Differences in demographic and clinical characteristics between male and female subjects were assessed using *t*-tests or χ^2 tests. We then tested for differences in negative craving scores by the presence of a history of MDD, SID, AnxD or SIA. Multivariable linear regression models were used to investigate the effects of each comorbid disorder (MDD, AnxD, SID, SIA) accounting for age, gender, average number of drinks per day and the presence or absence of withdrawal symptoms. The effect of enrollment site was also considered as a potential confounder, and was evaluated using mixed-effects models. These models were also used to evaluate whether the effect of each disorder on the IDTS-negative scores was the same in men and women by testing for gender × disorder interaction effects on propensity to drink in negative emotional situations. The effects of the mood and anxiety disorders on IDTS-negative scores were similar with and without adjustment for number of drinks per day at baseline and presence/absence of withdrawal history. Furthermore, site was not associated significantly with IDTS-negative scores, and site did not appear to confound the investigated associations. Thus, to maintain a parsimonious model for the effects of interest and to simplify interpretation, the presented multivariable models were adjusted only for age and gender. Finally, we conducted a multivariable linear regression analysis of age, MDD, SID and AnxD, as well as all possible pairwise interactions of comorbid disorder with gender, as predictors of negative IDTS scores. As there was a significant gender interaction effect for SID, a multivariable analysis of comorbidity effects on IDTS-negative scores was then performed separately for males and females. These multivariable analyses also included age as a covariate. All analyses were conducted using SAS version 9.4 (Cary, NC, USA).

RESULTS

Demographic and clinical characteristics of the study sample

The average IDTS-negative score was higher in female compared to male alcoholics (Table 1; 59.9 ± 22.3 versus 55.4 ± 21.3, $P = 0.045$), while there was no difference in IDTS-positive and temptation subscales. The prevalence of MDD and SID were significantly higher in females than in males (33.1 versus 18.4%, $P = 0.0006$; and 44.8 versus 26.4%, $P < 0.0001$, respectively). The frequency of AnxD was also higher in females (42.2 versus 27.4%, $P = 0.0017$), including the frequency of post-traumatic stress disorder (28.6 versus 12.6%, $P < 0.0001$), while prevalence of substance-induced anxiety (SIA) did not differ by gender and was only 3.3% overall. There was no significant difference in the prevalence of history of alcohol withdrawal, nicotine or other substance dependence between subgroups.

Association of the IDTS-negative score with clinical and demographic covariates

Before analyzing the association of IDTS-negative score with mood and anxiety disorders, we investigated associations of IDTS-negative scores with demographic (age, race, and sex) and clinical characteristics (number of drinks per drinking day, drinking days per month and presence/absence of withdrawal history). Increased IDTS- negative scores were associated significantly with younger age ($\beta = -0.22$, $P = 0.015$), increased number of drinks per day ($\beta = 0.64$, $P < 0.0001$) and the presence of withdrawal history ($\beta = 11.47$, $P < 0.0001$). Additional analyses indicated that inclusion of the number of drinks per day and the presence of withdrawal history as covariates did not change the effects of mood or anxiety disorders on IDTS-negative scores. Thus, further analyses of sex as well as mood and anxiety disorder effects on negative craving scores are presented with covariate adjustment for age only.

Association of the IDTS-negative score with comorbid depression and anxiety disorders

Comorbid MDD and AnxD were associated significantly with higher negative IDTS scores (Table 2). Furthermore,

Table 2 Association of Inventory of Drug Taking Situations (IDTS)-negative score with life-time diagnoses of depression and anxiety.

	All subjects (male and female)				*Males*			*Females*		
Disorders	*n*	*IDTS-negative mean ± SD*	*Gender interaction P-value*[a]	*P-value*[b]	*n*	*IDTS-negative mean ± SD*	*P-value*[d]	*n*	*IDTS-negative mean ± SD*	*P-value*[d]
MDD			0.585	**<0.001**						
No	316	54.8 ± 22.1			219	53.8 ± 21.6		97	57.3 ± 23.0	
Yes	98	63.3 ± 19.0			49	62.8 ± 18.2		49	63.9 ± 19.9	
SID			**0.004**	N/A[c]			**<0.001**			0.363
No	280	55.0 ± 22.9			198	52.7 ± 21.7		82	60.7 ± 24.6	
Yes	134	60.6 ± 18.5			70	63.1 ± 18.1		64	58.0 ± 18.6	
AnxD			0.477	**<0.001**						
No	275	54.1 ± 22.4			193	52.9 ± 21.8		89	56.9 ± 23.5	
Yes	139	62.3 ± 19.1			75	62.0 ± 18.5		64	62.7 ± 20.0	
SIA			0.131	0.995						
No	400	56.8 ± 21.8			258	55.6 ± 21.5		142	59.1 ± 22.1	
Yes	14	57.9 ± 19.3			10	51.3 ± 15.4		4	74.2 ± 20.0	

AnxD = anxiety disorders, including generalized anxiety disorder, obsessive–compulsive disorder, social phobia, post-traumatic stress disorder, agoraphobia, panic disorder; MDD = major depressive disorder; SIA = substance-induced anxiety; SID = substance-induced depression. [a]Gender interaction *P* is the *P*-value for the age-adjusted sex × disorder interaction effect on IDTS-negative score (i.e. a test of whether the disorder effect on IDTS differs between men and women). [b]Combined group *P*-value is the *P*-value for the age-adjusted effect of the disorder in males and females combined (without a gender interaction term). [c]For SID, the combined group *P*-value is not presented, as there is significant evidence of a gender interaction effect. Thus it is not appropriate to report a combined marginal effect of SID, which would assume the effect size for SID does not differ by sex. [d]*P*-value is for the age-adjusted effect of the disorder in male or female subgroups—shown only for SID, as this is the only comorbidity with a sex-interaction effect indicating the association with IDTS-negative score differs between men and women. *P*-values below 0.05 are presented in bold.

there was a significant gender × SID interaction, indicating that the relationship between SID and negative IDTS scores is different for male and female alcoholics. In particular, whereas SID was associated with higher negative IDTS scores in males, no such relationship was observed in females. No significant associations were found between negative IDTS scores and SIA. However, as the sample size of subjects with SIA was very small, this study did not have adequate power to detect associations with this comorbid factor. Therefore, SIA effects on IDTS negative-score were not investigated further in the multivariable models.

The multivariable models investigating the joint effects of MDD, SID, AnxD and gender on IDTS-negative score provided evidence of effects of MDD and AnxD as well as an interaction effect of SID by gender on the IDTS-negative score, with no evidence of gender interactions with MDD or AnxD, nor interactions among the different mood and anxiety diagnoses (MDD, SID and AnxD) in their effect on IDTS-negative scores (Table 3).

Because of the presence of a sex–SID interaction effect on the IDTS-negative score, the models investigating the additive effects of MDD, SID and AnxD were constructed separately by sex. As in the combined group of male and female alcoholics, the sex-stratified analyses demonstrated no evidence of interactions among the different mood and anxiety diagnoses in their effect on negative IDTS scores. The multivariable model showed a significant additive effect of MDD, SID and AnxD on negative IDTS score in males, with these three diagnoses combined explaining 7.1% of the score variation ($R^2 = 0.071$). Males with a history of SID have an average negative IDTS score increase of 7.88 points over males without SID. Although the additive effects of MDD and AnxD on negative IDTS scores did not reach statistically significant levels in this analysis, the observed trends suggested that males with MDD had negative IDTS scores 5.35 points greater than males without a history of MDD, while those with AnxD had IDTS scores on average 5.3 points higher than those without AnxD. In females, an additive effect of MDD, SID and AnxD on a negative IDTS score was also significant, with these three diagnoses combined explaining 4.6% of the score variation ($R^2 = 0.046$). However, none of the disorders were statistically significant predictors of elevation of negative IDTS score (Tables 2, 3), although a marginal effect of MDD was detected, with negative IDTS scores being 8.07 points higher in females with MDD ($P = 0.052$). It is possible that this effect did not reach a statistical significance due to a smaller number of females in our sample.

We also found no evidence of interactions between MDD, SID and AnxD in their effect on negative IDTS scores in males, females or the combined group, suggesting that each diagnosis contributes independently to this score.

DISCUSSION

Consistent with epidemiological data [7,13,48] and clinical observations [5,49], we found a high prevalence of depression and anxiety disorders in alcoholics treated in our

Table 3 Multivariable regression models predicting negative IDTS scores.

	Predictors of IDTS-negative score	*Estimated effect (β)*[a]	*Standard error*	*P-value*	*Partial R^2*	*Model R^2*	*Overall model P-value*
Total sample (n = 414)	Age	−0.21	0.09	**0.019**	0.015	0.083	<**0.001**
	Male gender	−6.92	2.77	**0.013**	0.008		
	MDD	6.57	2.64	**0.013**	0.025		
	SID	−6.08	3.59	0.092	0.003		
	AnxD	4.79	2.34	**0.042**	0.011		
	Male[a] SID	13.81	4.56	**0.003**	0.021		
Males (n = 268)	Age	−0.17	0.11	0.118	0.012	0.083	<**0.001**
	MDD	5.35	3.47	0.125	0.029		
	SID	7.88	4.00	**0.009**	0.031		
	AnxD	5.30	3.01	0.080	0.011		
Females (n = 146)	Age	−0.28	0.16	0.076	0.022	0.068	**0.042**
	MDD	8.07	4.12	0.052	0.020		
	SID	−6.61	3.88	0.091	0.017		
	AnxD	4.16	3.78	0.272	0.008		

AnxD = anxiety disorders; IDTS = Inventory of Drug Taking Situations; MDD = major depressive disorder; SID = substance-induced depression. [a]Presented as average change in IDTS-negative scale points. *P*-values below 0.05 are presented in bold.

community-based programs. Also consistent with epidemiological data [50–52] was the higher prevalence of MDD, SID and AnxD (including post-traumatic stress disorder) in female compared with male alcoholics. Previous reports indicate that female alcoholics report drinking in response to unpleasant emotions more often than males [53,54], and interpret these associations as a result of depression severity [42]. However, our findings indicate that drinking in response to unpleasant emotions is elevated significantly in female compared with male alcoholics regardless of the presence or absence of depression or anxiety disorders. Further research is needed to determine whether a subsyndromal presentation and/or specific symptoms of depression and/or anxiety contribute to elevation of IDTS-negative scores in female alcoholics.

In contrast to female alcoholics, propensity to drink in negative emotional situations in male alcoholics was increased significantly only in the presence of a life-time history of comorbid MDD, SID or AnxD. Moreover, we found a significant interaction effect between SID and sex, indicating that the association between SID and negative IDTS scores differs between male and female alcoholics. Similarly, we found that the presence of more than one comorbid condition further increases the propensity to drink in negative emotional situations, and that this effect appears to be stronger in male compared with female alcoholics.

These male–female differences are intriguing, as they suggest that etiopathogenesis of propensity to drink in negative emotional situations and negative craving may be impacted by direct alcohol effects (e.g. toxicity and/or resetting of allostatic threshold) as well as vulnerability to comorbid mood and anxiety disorders and, especially, SID in male but not female alcoholics. Interestingly, recent analyses of genetic effects on alcoholism-related phenotypes also indicate the presence of sex-dependent effects that are also phenotype-specific: for example, the same genetic variant being associated with alcoholism in males, and with increased propensity to drink in negative emotional situations, negative craving and shorter time for post-treatment relapse in female but not male alcoholics [55]. Further research is needed to determine which genetic, toxic or other underlying biological and psychosocial mechanisms are responsible for associations between propensity to drink in negative emotional situations and life-time history of comorbid MDD, SID or AnxD in male and female alcoholics.

Our findings are significant in the context of the following practical considerations. First, an elevated negative IDTS score should alert the treatment team to the potential presence of comorbid depression and/or anxiety, especially in male alcoholics. Screening for these conditions may trigger a referral to psychiatry for safety assessment and medication considerations. Prospective studies are necessary to determine the utility of the negative IDTS score for the purpose of such screening.

Secondly, a potential benefit of early initiation of antidepressant treatment in alcoholics with comorbid depression has been demonstrated [15]. Evidence also suggests improvement of alcohol and depression-related outcomes with the combined use of antidepressants and anti-dipsotropics [56,57] and effectiveness of pharmacotherapy for mood symptoms in patients with substance dependence [58]. However, not everyone treated responds to antidepressants or anti-dipsotropics, and predictors of treatment response are needed. Our finding of a gender-specific

impact of comorbid depression and anxiety on negative IDTS score may be among positive antidepressant response predictors in alcoholics, which is consistent with reports that gender is among the factors affecting decreased alcohol consumption in response to antidepressants [59]. This compelling hypothesis requires further investigation in prospective studies.

Thirdly, our findings suggest that teaching psychosocial coping strategies addressing propensity to drink in negative emotional situations and negative craving to alcoholics with diagnoses of MDD, SID or AnxD may be a particularly important part of treatment. Psychotherapy research has demonstrated that targeted interventions providing strategies to cope with craving and urges result in decrease of anxiety, negative mood and frequency of heavy drinking [60–63]. Our findings indicate that selection of the therapeutic interventions targeting craving and relapse in alcoholics with comorbid depression or anxiety should be considered in the context of gender-specific differences (e.g. significantly elevated propensity to drink in negative emotional situations in depressed and non-depressed female alcoholics versus direct impact of comorbid depression or anxiety on propensity to drink in negative emotional situations in male alcoholics). Prospective studies are necessary to clarify whether the use of an IDTS-negative score may guide selection of such therapeutic interventions and improve treatment outcomes.

Finally, we also found that drinking in negative emotional states is associated with increased alcohol consumption and with the presence of physiological withdrawal. This finding is consistent with the original conceptual model of negative (relief) craving [37] and with reports that individuals with high IDTS-negative scores have higher alcohol dependence scores [36]. Further studies should investigate whether a 'craving factor independent from emotional state' [36] may be associated with development of tolerance and alcohol withdrawal.

Our study has the following limitations. The sample size was sufficient to detect described associations but insufficient to detect the effects of less frequent conditions on negative IDTS score. The smaller number of females in our sample may have also precluded some of the association effects—which had similar direction and magnitude as in males—from reaching a statistically significant level. The analyses presented in this paper are limited to life-time diagnoses of anxiety or depressive disorders and did not differentiate between alcohol and other substance-induced disorders. However, it is possible that the effect of depression or anxiety on a negative IDTS score may differ depending on the proximity in time (e.g. current, recent or remote episode of depression) and/or effect of specific substance. Future studies in larger samples may allow investigating these possibilities further. Although validity and reproducibility of PRISM diagnoses have been demonstrated, it is also important to consider potential limitations of this approach in the context of evolving knowledge about mental illness and operationalization of clinical findings [64,65]. Finally, our association findings are based on retrospective (at the point of treatment entry) assessment of the life-time history of anxiety and depressive disorders. Therefore, our analyses are confined to the relationship between described phenotypical and demographic characteristics collected at one point in time, while it is also possible that more complex interactions may exist between craving and mood disorders in male and female subjects. The biological underpinnings of the reported findings and their association with the treatment outcomes will be tested in ongoing research projects.

CONCLUSION

Our findings support a high prevalence of comorbid depression and anxiety in treatment-seeking alcoholics. Our data also indicate that the presence of these comorbid conditions in male alcoholics results in an increased propensity to drink during negative emotional states (negative craving), whereas in female alcoholics IDTS-negative scores (and propensity to drink in negative emotional situations) seems to be elevated regardless of the presence/absence of a formally diagnosed depression or anxiety disorder. These findings underscore the need to account for gender effects in selection of individualized treatment recommendations for males and females suffering from AUD with comorbid mood and anxiety disorders. Understanding the biology of reported associations may guide the development of novel targeted interventions necessary to improve treatment outcomes in this group of patients with AUD.

Clinical trial registration

ClinicalTrials.gov, Identifier: NCT00662571, http://clinicaltrials.gov

Declaration of interests

Two co-authors disclose relationships with funding sources, which may be perceived as potential conflicts of interest. Specifically, M.A.F. had a past consultancy with Janssen Research and Development LLC, Mitsubishi Tanabe Pharma Corporation, Myriad Genetics, Sunovion, Supernus Pharmaceuticals and Teva Pharmaceuticals; he has also received past grant support from Johnson & Johnson and AssureRx (although not for this publication). The late David A. Mrazek had (and Mayo Clinic has) a financial interest in technology unrelated to this research. The remaining authors report no conflicts of interest.

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