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The effects of venlafaxine and cognitive behavioral therapy alone and combined in the treatment of co-morbid alcohol use-anxiety disorders☆

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ABSTRACT

The effects of the antidepressant venlafaxine (VEN-225 mg daily) and transdiagnostic cognitive behavioral treatment (CBT) alone and in combination on alcohol intake in subjects with co-morbid alcohol use disorders (AUDs) and anxiety disorders were compared. Drinking outcomes and anxiety were assessed for 81 subjects treated for 11 weeks with one of 4 conditions: 1) VEN–CBT, 2) VEN-Progressive Muscle Relaxation therapy (PMR), 3) Placebo (PLC)-CBT and 4) a comparison group of PLC-PMR. For subjects who reported taking at least one dose of study medication, the Time × Group interaction was significant for percent days of heavy drinking and drinks consumed per day. For the measure of percent days heavy drinking, the paired comparison of PLC-CBT versus PLC-PMR group indicated that the PLC-CBT group had greater drinking reductions, whereas other groups were not superior to the comparison group. In Week 11, the proportion of subjects in the PLC-CBT group that had a 50% reduction from baseline in percent days heavy drinking was significantly greater than those in the comparison group. Of the 3 "active treatment" groups only the PLC-CBT group had significantly decreased heavy drinking when contrasted to the comparison group. This finding suggests that the transdiagnostic CBT approach of Barlow and colleagues may have value in the management of heavy drinking in individuals with co-morbid alcoholism and anxiety.

Introduction

Alcohol use disorders (AUDs) have been reported to occur with a 12-month prevalence of almost 9% of the adult population in the United States (Grant et al., 2004; Hasin, Stinson, Ogburn, & Grant, 2007). In excess of 33% of treatment seeking individuals with an AUD may have at least one concurrent independent anxiety disorder (Grant et al., 2004). Panic and social phobia are both predictors of later alcohol use problems in adolescents and young adults (Zimmermann et al., 2003). Recent work suggests increases in the number of anxiety and other internalizing disorders, including depression and dysthymia, are directly related to increases in the prevalence of alcohol dependence (Kushner et al., 2012).

The results of several studies suggest that the existence of a co-morbid anxiety disorder can have a significant influence on the outcome of treatment of AUDs. In one study, social anxiety limited the willingness of individuals with AUDs to seek some forms of treatment for their drinking problems (Book, Thomas, Dempsey, Randall, & Randall, 2009). In another investigation, the severity of anxiety symptoms predicted recurrence of alcohol dependence in remitted patients (Boschloo et al., 2012). Phobic anxiety disorders

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also have been reported to predict shorter duration of treatment and discontinuation of treatment (Haver & Gjestad, 2005). Finally, there is evidence that social phobia is a predictor of return drinking after completion of treatment and panic disorder is a predictor of post-treatment alcohol dependence (Kushner et al., 2005).

Based on this empirical and theoretical literature, treatments for alcohol dependence that target anxiety as a mediator of treatment gains and/or relapse are appealing. Empirical evaluations of anxiety-focused treatments among substance-dependent patients (including alcoholics) have yielded mixed results. Several studies have called into question the utility of this approach (Bowen, D'Arcy, Keegan, & Senthilselvan, 2000; Ormrod & Budd, 1991; Schadé et al., 2005). In contrast, other researchers have reported that addressing symptoms of anxiety could be important for the treatment of alcoholism (Fals-Stewart & Schafer, 1992; Modesto-Lowe & Kranzler, 1999).

In addition to behavioral therapies some investigators have examined the use of selective serotonin reuptake inhibitors (SSRIs), which have anxiolytic effects, in the treatment of alcohol use disorders in individuals with co-morbid anxiety disorders. In one study, although anxiety symptoms improved in subjects treated with the SSRI paroxetine, alcohol consumption was not meaningfully altered (Thomas, Randall, Book, & Randall, 2008). In another investigation, the addition of the SSRI fluvoxamine to the treatment regime of cognitive behavioral treatment (CBT) in abstinent subjects who also received an intensive psychological relapse prevention program did not lead to better outcomes with respect to reduction in either alcohol intake or severity of anxiety (Schadé et al., 2005).

The role played by noradrenergic systems in both AUD and anxiety remains to be more fully delineated. There is evidence, however, of the involvement of these systems in both AUDs (Kash, 2012; Smith and Aston-Jones, 2008) and anxiety disorders (Bremner, Krystal, Southwick, & Charney, 1996; Dell'Osso, Buoli, Baldwin, & Altamura 2010; Rasmussen, Wilkinson, & Raskind, 2006). Thus, agents that modify the activity of brain noradrenergic systems may be value in the management of co-morbid AUD and anxiety disorders. The present study examined the use of the NSRI (norepinephrine serotonin reuptake inhibitor) antidepressant venlafaxine for this purpose. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of both norepinephrine and serotonin uptake and weak inhibitors of dopamine reuptake. It is of particular interest that the chronic administration of venlafaxine does not alter basal levels of norepinephrine within the prefrontal cortex, but does significantly lower the amount of this neurotransmitter released by a stressor such as foot shock (Dazzi et al., 2002). Chronic administration of venlafaxine has also been found to desensitize frontal cortical β-adrenoreceptor-coupled adenylase cyclase systems in animals selectively depleted of serotonin (Nalepa et al., 1998). These results indicate that treatment with venlafaxine can reduce the activity of noradrenergic receptor systems in certain conditions.

Several studies support the efficacy of venlafaxine in generalized anxiety disorder (Allgulander, Hackett, & Salinas, 2001; Gelenberg et al., 2000; Rickels, Pollack, Sheehan, & Haskins, 2000), panic disorder (Kjernisted & McIntosh, 2007; Liebowitz, Asnis, Mangano, & Tzanis, 2009), social phobia (Stein, Pollack, Bystritsky, Kelsey, & Mangano, 2005), and obsessive-compulsive disorder (Denys, van der Wee, van Megen, & Westenberg, 2003; Grossman & Hollander, 1996). The objective of the present investigation was to determine whether venlafaxine administered alone or in combination with CBT using the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders (UP) developed by Barlow et al. (Barlow, Allen, & Choate, 2004; Barlow et al., 2011) would reduce alcohol intake and anxiety compared to either CBT in combination with placebo (PLC) or PLC in combination with a "control" behavioral therapy, i.e. progressive muscle relaxation (PMR). For safety reasons all subjects were provided with an initial platform treatment of motivational enhancement therapy (MET), and were required to achieve four days of abstinence prior to randomization to reduce the potential for alcohol–venlafaxine interactions. The primary study hypothesis was that in comparison to the PLC-PMR treatment condition, the other treatment combinations would produce greater decreases during the treatment period in both alcohol consumption and anxiety. It was also hypothesized that the combination of venlafaxine and CBT would show greater improvements in decreasing alcohol consumption and anxiety than did these treatments when they were administered alone.

Methods

Men and women were recruited into an outpatient anxiety treatment program via radio, web, and newspaper advertisements. Telephone screenings determined initial eligibility, and potential research participants were invited to the Center for Anxiety and Related Disorders at Boston University for a more extensive assessment of alcohol use and emotional symptoms.

Inclusion criteria for subject eligibility included: 1) DSM-IV diagnosis of alcohol abuse or dependence (alcohol use disorder: AUD) and a diagnosis of anxiety disorder (panic disorder, social phobia, or generalized anxiety disorder); 2) minimum age of 18 years; and 3) expressed desire to stop drinking alcohol completely or to reduce alcohol consumption with the possible long-term goal of abstinence. Exclusion criteria were: 1) DSM-IV diagnosis of bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or other substance dependence, with the exception of nicotine, marijuana, and caffeine dependence; 2) medical contraindication to the use of venlafaxine; 3) currently taking anti-craving agents, anti-depressant medications, or medication known to reduce anxiety or alcohol consumption; 4) ongoing concurrent treatment for alcohol problems; 5) currently taking medication that has significant interactions with venlafaxine; 6) previously received venlafaxine; 7) currently prescribed medication with known abuse potential; and 8) having experienced severe depression or suicidal behaviors in the past 30 days.

The objective of this study was to compare the efficacy and safety of using venlafaxine and CBT to facilitate abstinence from alcohol consumption in individuals with co-morbid AUDs and anxiety disorders, as compared to combined treatment with placebo and PMR, the control treatment condition. The flow diagram for this study is presented in Fig. 1. This study, with respect to medication therapy, followed a double-blind, randomized, placebo-controlled study design.

All procedures used in this study were approved by the Boston University and Boston University Medical Center"s Institutional Review Boards (IRBs), as well as the Central Texas Veterans Health Care System IRB. Subjects provided informed consent in accordance with IRB requirements. Participants who were unable to continue the drug treatment due to adverse effects were discontinued from the medication but continued to attend clinic for psychological treatment and assessment.

Following telephone screening, subjects completed an in-clinic baseline assessment to determine eligibility for inclusion in the study. Eligible subjects were assigned to a counselor who provided MET (Miller, 2004) to aid the subject in achieving an initial period of four days of complete abstinence from alcohol (as a safety precaution due to 50% chance of receiving venlafaxine). MET feedback was given based on normative data published in the Combined Behavioral Intervention Manual.