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Levetiracetam for the Treatment of Co-Occurring Alcohol Dependence and Anxiety: Case Series and Review

John J. Mariani, M.D.[1,2] and **Frances R. Levin, M.D.**

[1]Division on Substance Abuse, New York State Psychiatric Institute, New York, New York, USA

[2]Department of Psychiatry, College of Physicians and Surgeons, Columbia University New York, New York, USA

Abstract

Objectives—Alcohol dependence is frequently associated with anxiety disorders. The exact nature of the relationship between alcohol dependence and anxiety disorders is unknown, but emerging evidence suggests that in a majority of cases, the anxiety disorder is independent of the alcohol use disorder. There is pre-clinical and clinical evidence that levetiracetam, a newer generation anticonvulsant medication, may be efficacious in the treatment of co-occurring alcohol use and anxiety disorders.

Methods—In an open label clinical trial, three patients with alcohol dependence and a co-morbid anxiety disorder were treated with levetiracetam in doses up to 1500 mg twice daily for up to 8 weeks.

Results—All three participants reported reductions in alcohol consumption and anxiety symptoms during the study period. Levetiracetam was generally well tolerated.

Conclusion—This study suggests that levetiracetam deserves further study in the treatment of alcohol dependence and co-occurring anxiety disorders.

Keywords

Alcohol dependence; anticonvulsants; anxiety disorders

INTRODUCTION

Alcohol dependence is frequently associated with anxiety disorders in both community-based epidemiological studies (1-5) and studies of clinical populations (6-8). The Epidemiologic Catchment Area data showed that 12.2% of alcohol-dependent individuals had a comorbid anxiety disorder (OR = 1.8) (1). The National Comorbidity Study found that 35.8% (OR = 2.2) of the males and 60.7% (OR = 3.1) of females diagnosed with alcohol dependence met criteria

Address correspondence to John J. Mariani, M.D., NYSPI-Division on Substance Abuse, 1051 Riverside Drive, Unit 66, New York, NY 10032, USA. E-mail: jm2330@columbia.edu.

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for an anxiety disorder (9). More recently, the National Epidemiologic Survey on Alcohol and Related Conditions found that individuals with alcohol dependence had an odds ratio of 2.6 (2.2–3.0) of having any co-occurring anxiety disorder as compared to individuals without alcohol dependence (4). A multicenter clinical survey of 2713 alcohol dependent subjects and 919 controls found that the life-time prevalence of an independent anxiety disorders was significantly higher among individuals with alcohol dependence than controls (9.4% vs. 3.7%), with most of the differential related to panic disorder (4.2% vs. 1.0%) and social phobia (3.2% vs. 1.4%), but there were no significant group differences for agoraphobia or obsessive-compulsive disorder (6).

The association between anxiety disorders and alcohol use disorders remains an area of active investigation and contention (10). One perspective has been that independent anxiety disorders do not develop at an increased frequency in alcohol dependence, but that the observed association is due to alcohol-induced anxiety syndromes (11,12). However, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) indicates that the vast majority of individuals with alcohol dependence and who report anxiety symptoms had an independent anxiety disorder (4), which presumably would require specific treatment. The theoretical framework for approaching the relationship between alcohol use disorders and anxiety disorders is of great clinical significance since a substance-independent model suggests that treating the anxiety symptoms from the outset is appropriate and may influence treatment outcome (13), whereas a substance-dependent model suggests that clinical attention should be focused on the alcohol use disorder and the anxiety symptoms will improve as alcohol consumption decreases or remits.

Pharmacotherapy studies of individuals with comorbid alcohol dependence and anxiety disorders have been limited. Four double-blind placebo-controlled trials have studied the use of buspirone to treat alcohol dependence and co-morbid generalized anxiety disorder or anxiety symptoms (14-17). Two randomized placebo-controlled trials have evaluated paroxetine for alcohol use disorders and comorbid social phobia (18,19). In three of the four buspirone studies, the medication was effective in reducing anxiety symptoms (14,15,17). Of the two buspirone studies that used alcohol consumption as an outcome measure, one study found some benefit on alcohol use outcomes (17) and the other showed no benefit on drinking behavior (16). In summary, while there is evidence that buspirone is safe and effective in reducing anxiety symptoms in actively drinking alcohol-dependent patients with comorbid generalized anxiety disorder, there is little evidence to suggest that it increases abstinence rates or reduces drinking behavior. Similarly, in the first paroxetine trial, anxiety symptoms improved a significantly greater degree in the active medication group, but there was no effect on drinking outcome measures (18). The second paroxetine trial had similar results in reducing anxiety symptoms, but alcohol use outcomes were not reported (19).

Anticonvulsant medications have been studied as potential therapies for alcohol dependence (20). Within this class of medications, the best evidence of efficacy exists for topiramate, which has been shown to reduce drinking and promote abstinence in actively drinking individuals with alcohol dependence (21,22). Levetiracetam is a newer generation anti-seizure medication, which is safe and generally well tolerated (23,24). The most commonly reported adverse events are somnolence and asthenia (25). The Food and Drug Administration has approved levetiracetam for use with other anti-seizure medications in the treatment of epilepsy in adults. The metabolism of levetiracetam is less complicated than older anti-seizure medications, which makes it easier to use and better tolerated, and it is not likely to interact with other medicines (26). Levetiracetam has been shown to cause less cognitive function impairment than topiramate (27).

There is pre-clinical and clinical evidence that levitiracetam has anxiolytic effects. Levitiracetam has been shown in animal models of anxiety to have anxiolytic actions (28,29). In open-label studies, levetiracetam has shown promise for the treatment of social anxiety disorder (30) and panic disorder (31). There is also pre-clinical and clinical evidence that levetiracetam may have utility in the treatment of alcohol withdrawal. Levetiracetam has been shown to prevent anxiety during sedative withdrawal, a syndrome similar to alcohol withdrawal, in a laboratory study using mice (32). In an open-label study of 15 patients levetiracetam was safe and efficacious in the treatment of alcohol withdrawal (33). However, these data are preliminary and the utility of levetiracetam for the treatment of alcohol withdrawal needs to be studied more rigorously.

Given that other anti-seizure medications have been shown to be helpful in treating alcohol dependence (21,22), that levetiracetam has a favorable pharmacokinetic profile, and that there is pre-clinical and clinical evidence that suggests levetiracetam may have utility in treating both alcohol dependence and anxiety, we believed it should be studied for the treatment of alcohol-dependent patients with anxiety disorders. We hypothesized that alcohol-dependent individuals with co-occurring anxiety disorders have difficulty reducing or discontinuing alcohol use because of the significant anxiety that accompany such reductions, and that treatment with levetiracetam would have favorable effects on both alcohol use and anxiety outcome measures.

METHODS

Procedures

This was an 8-week open-label evaluation of the efficacy and tolerability of levetiracetam for the treatment of alcohol dependence with comorbid anxiety. The protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute. Patients who met the study eligibility criteria were assigned to treatment with levetiracetam under open label conditions.

Levetiracetam was initiated at 500 mg twice a day for one week, then increased to 1000 mg twice a day for one week, and then increased to 1500 mg twice a day and maintained at that dose for 6 weeks. All patients needed to take a minimum of levetiracetam/placebo 500 mg BID to remain in the study. All patients had weekly individual supportive psychotherapy sessions with the research psychiatrist using a structured compliance enhancement manual designed for pharmacotherapy trials in patients with substance use disorders (34).

Patients

Individuals with current alcohol dependence and comorbid anxiety were recruited through clinical referrals and newspaper, radio, and internet advertisements. Men and non-pregnant women between the ages of 18 and 65 who meet DSM-IV criteria for 1) alcohol dependence and 2) an anxiety disorder, (including panic disorder, social phobia, generalized anxiety disorder, substance-induced anxiety disorder or anxiety disorder, NOS); 3) had a baseline Hamilton Anxiety Rating Scale (HAM-A) (35) $\geq$ 14; and 4) were drinking $\geq$ 4 days per week, with men drinking $\geq$ 5 standard drinks/drinking day and women drinking $\geq$ 5 standard drinks/drinking day, were eligible for enrollment. Patients were excluded for any of the following reasons: 1) the presence of any other clinically significant psychiatric disorders, including post-traumatic stress disorder or obsessive-compulsive disorder; 2) a Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) score $\geq$ 15 (36); 3) co-occurring cocaine or opioid dependence; 4) unstable medical conditions; 5) currently prescribed psychotropic medications; 6) known sensitivity to levetiracetam; 7) elevated suicide risk; 8) physiologic dependence on

other substances (excluding nicotine or caffeine); or 9) a history of hazardous drinking behavior.

RESULTS

Three participants were enrolled in this clinical trial. Participant demographic information and outcome measures are presented in Table 1. All three participants experienced improvement in their alcohol use and anxiety symptoms. Levetiracetam was well-tolerated with no drop-outs due to adverse effects or clinical worsening. One of the three patients did not complete the trial; the patient discontinued the trial for personal reasons that involved him needing to move to another location and was unrelated to adverse medication side effects or psychiatric worsening. This same patient was only able to tolerate doses of levetiracetam of 1000 mg twice daily; higher doses caused sedation.

DISCUSSION

This case series of 3 patients presents preliminary data suggesting that levetiracetam may have beneficial effects on alcohol use and anxiety symptoms in patients with alcohol dependence and co-occurring anxiety disorders. The open-label design and small number of patients present significant limitations to interpreting the potential efficacy of levetiracetam, but these results at a minimum suggest that further study is warranted.

The frequent co-occurrence of alcohol dependence with anxiety disorders presents a challenging pharmacotherapy prescribing dilemma. Benzodiazepines are inappropriate for many patients with alcohol dependence in the outpatient setting given their abuse liability and potential for dangerous interactive effects with alcohol. Development of non-addictive treatments for these commonly comorbid conditions remains an important unmet public health need. Given the limited pharmacotherapy options available for patients with alcohol dependence and co-occurring anxiety disorders, levetiracetam represents a potential area for further study.

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Table 1

Demographics and Study Outcome Measures

Patients	Anxiety Disorder	Maximum Tolerated Dose[1]	Study Weeks[2]	Drinking Days/Week[3]	Drinks/ Drinking Day[3]	% Heavy Drinking Days[3]	% Days Abstinent[3]	HAM-A	
31 y/o White Female	Generalized Anxiety Disorder	1500 mg Twice-Daily	8	4.8	11.2	64.3%	32.1%	22	Baseline
				3.0	3.5	14.3%	57%	6	Study End
37 y/o Hispanic Male	Panic Disorder without Agoraphobia	1000 mg Twice-Daily	6	5.5	7.8	17.9%	21.4%	21	Baseline
				1.0	1.2	0	85.7%	10	Study End
45 y/o White Female	Panic Disorder without Agoraphobia	1500 mg Twice-Daily	8	4.0	9.5	46.4%	42.9%	20	Baseline
				2.0	12.8	28.6%	71.4%	6	Study End

[1]The maximum possible dose of levetiracetam was 1500 mg twice-daily;

[2]The maximum possible study weeks completed was 8 weeks;

[3]Baseline timeline follow-back (TLFB) was calculated over 28-day period and end-of-study TLFB was calculated over the last 7 days of the study period.