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A safety and tolerability laboratory study of the combination of aripiprazole and topiramate in volunteers who drink alcohol

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Objective There are no reports examining the safety of taking both topiramate and aripiprazole together with alcohol. The ultimate aim for this research is to determine whether this combination is safe and is superior to either drug taken alone in reducing alcohol use in alcohol dependent patients.
Method This was an open-label trial. Thirteen heavy drinking participants not seeking treatment for alcoholism were randomized. Participants were titrated up to 300 mg of topiramate and 30 mg of aripiprazole a day over 35 days. Participants reported adverse events (AEs) daily alcohol use and participated in an alcohol challenge session (ACS).
Results The eight participants who completed the study achieved the maximum doses of drugs. The AEs of the drugs would suggest that the AEs profile is broader but not additive. Alcohol use from the 28 days before screening to the seven days before the ACS was reduced ($p = 0.08$).
Conclusion There was no evidence that AEs of aripiprazole and topiramate are additive and can, therefore, be administered safely together with a modest amount of alcohol. There was also a trend for a reduction of alcohol use by participants. This finding has implications for further investigation of this combination of drugs for alcohol dependence.

KEY WORDS — aripiprazole; topiramate; alcohol; alcohol dependence; alcoholism; lab studies

INTRODUCTION

Alcohol has diffuse mechanisms of action. Notable neurotransmitters and their receptors involved in the neurobiological action of alcohol include at least γ-amino-butyric acid (GABA), glutamate, dopamine (DA), serotonin (5-HT), adenosine, neuropeptide-Y (NPY), norepinephrine, endocannabinoids, and opioid peptides. Subsequently, each of these neurotransmitters or their receptors is a potential target for pharmacotherapy. Given the complex pharmacology of alcohol, one approach for alcohol researchers is to investigate the efficacy of medications, manipulating multiple neuronal systems, to reduce craving or block the reinforcing effects of alcohol (Kenna *et al*., 2004).

Topiramate is approved for the indications of epilepsy and migraine headaches (Ortho-McNeil Neurologics Inc, 2005). Topiramate is demonstrated to have multiple mechanisms of action including antagonism of AMPA/kainate glutamate receptors, potentiation of GABA, enhancement of $GABA_A$ receptor function, blockade of voltage-sensitive sodium and calcium channels (White *et al*., 2000), and inhibition of carbonic anhydrase (Morrow *et al*., 2001; Papadeas *et al*., 2001). It is theorized that the net effect of these actions could decrease DA facilitation in the midbrain and normalize depleted DA levels (Morrow *et al*., 2001).

Johnson and colleagues (2003) in a double-blind placebo-controlled trial used an escalating dose of upto 300 mg per day of topiramate or matching placebo in 150 alcohol dependent men and women. The results demonstrated a significant reduction in drinks per day ($p < 0.01$), drinks per drinking day ($p < 0.01$), per cent heavy drinking days ($p < 0.001$), per cent days abstinent ($p < 0.01$), and plasma γ-glutamyl-transferase (GGT)-log ratio (0.0112) in the participants taking topiramate compared to placebo. A larger multi-site trial confirmed the effectiveness of topiramate compared to placebo in the treatment of alcohol-dependent patients (Johnson *et al*., 2007). Further analyses reported significantly decreased alcohol related obsessions and compulsions regarding alcohol use, increased psychosocial well-being, and improved some aspects

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of quality of life, thus reducing the risk of relapse and continuing negative outcomes (Johnson *et al*., 2008). Though important questions were raised at the time (Swift, 2003), regarding what the appropriate dose and length of titration for topiramate might be to successfully treat patients *in the initial pilot trial* (Johnson *et al*., 2003), the findings in total suggest significant promise for continued study of topiramate for alcohol dependence (Kenna *et al*., 2009).

Aripiprazole is a partial D_2 and 5-HT_{1A} agonist, and a 5-HT_{2A} receptor antagonist. Each of these actions has been linked independently to reducing alcohol preference and reinforcement in animals (Singh *et al*., 1993; Bono *et al*., 1996; Otsuka Pharmaceutical Co, 2006; Van Oekelen *et al*., 2003) and was hypothesized to be a potential pharmacotherapy for alcohol dependence in humans (Kenna, 2003). The mechanism of action of partial DA agonists may become more pronounced in conditions of rebound reduction of DA activity in the mesolimbic area that may be associated with alcohol abstinence. As hypothesized, partial DA agonists may provide a means to reverse DA depletion observed during alcohol abstinence, modulate DA increases seen in craving and because of its flexible activity represents a novel strategy for normalizing DA neurotransmission along the behavioral continuum of alcoholism (Kenna, 2003). Moreover as a neuroleptic, aripiprazole may enhance DA receptor D_2 up-regulation further attenuating alcohol consumption (Martinotti *et al*., 2007).

In an open-label study, 13 recently detoxified alcohol-dependent patients received flexible doses of aripiprazole for 16 weeks (Martinotti *et al*., 2007). Six of the patients were abstinent for the entire study. In addition, all of the patients experienced a reduction of craving as assessed by the obsessive compulsive drinking scale (OCDS; $p < 0.05$) and visual analog scale (VAS; $p < 0.05$), and a decrease in the SCL-90 general severity index ($p < 0.05$). In a double-blind placebo controlled trial, 295 patients with alcohol dependence were randomized to treatment with aripiprazole (titrated to a maximum dose of 30 mg daily by day 28) or placebo for 12 weeks (Anton *et al*., 2008). Drop-outs (40.3% vs. 26.7%) and treatment-related AEs (82.8% vs 63.6%) were higher with aripiprazole than with placebo. The primary efficacy measure, mean percentage of days abstinent, was not significantly different between aripiprazole and placebo (58.7% vs. 63.3%; $p = 0.227$), however, the aripiprazole group reported fewer drinks per drinking day compared to placebo (4.4 vs. 5.5 drinks; $p < 0.001$).

The results of animal and human studies suggest that aripiprazole attenuates DA during craving, facilitates DA activation in hypodopaminergic states during withdrawal and DRD2 up-regulation associated in prolonged abstinence. Aripiprazole also targets 5-HT_{1A} and 5-HT_2 serotonin receptors associated with reduced alcohol consumption and tolerance. Topiramate blocks AMPA receptors, enhances GABAergic function and targets abstinence initiation. Putatively, taking advantage of the complex mechanisms of action of these two drugs at different stages of abstinence may produce an additive reduction in alcohol consumption. Our hypotheses for this pilot were that: (1) combining these drugs with alcohol was safe, thereby facilitating future double-blind placebo controlled trials; (2) that the number of AEs of combining these two drugs may be increased, but are not additive; and (3) that there was no evidence there would be specific AEs created by having the participants drink a modest dose of alcohol. As a Phase 1 trial, the primary aim of this study was to evaluate the safety and tolerability of combining *high dose* (30 mg) aripiprazole and *high dose* (300 mg) topiramate with alcohol in non-treatment seeking heavy drinking volunteers. Our ultimate aim for this initial study was to verify in a larger trial that lower doses of these medications were comparatively just as effective to reduce alcohol use as higher doses. Note that, since this research was performed, studies of topiramate (Miranda *et al*., 2008) and aripiprazole (Voronin *et al*., 2008) have been reported demonstrating that lower doses of these drugs taken alone, may be just as effective or in the case of aripiprazole, perhaps even more effective to reduce alcohol urge and consumption. Ultimately, the goal of this study was to first demonstrate the safety of the upper limit of these two medications given together with alcohol. The long-term purpose of this pilot research is to determine whether a particular combination of these two drugs in a *multi-dose trial* is superior to either drug taken alone in reducing alcohol use in alcohol dependent patients.

SUBJECTS AND METHODS

This study used an alcohol administration design as a method to determine the safety and tolerability of 300 mg of topiramate and 30 mg of aripiprazole in heavy drinking volunteers. Procedures for human experimentation were approved by the hospital and university Institutional Review Boards. Subjects were recruited through local newspapers to meet criteria for heavy drinking and not seeking treatment for alcoholism. Adverse events (AEs) were recorded at each visit and assessed during each alcohol challenge session (ACS). Volunteers were compensated $720 for their participation.

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Subjects

Inclusion criteria for enrolling volunteers in this study included that they should: (a) be between 21 and 65 years old (inclusive); (b) be in good health as confirmed by medical history, baseline physical examination, an electrocardiogram, laboratory tests, urinalysis and vital signs; female participants must be postmenopausal for at least 1 year, surgically sterile, or practicing an effective method of birth control before entry and throughout the study; have a negative urine pregnancy test at baseline screening and prior to the ACS; must understand that this was not a treatment study for alcoholism; be heavy drinking (Babor *et al*., 2001) as defined by an Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8, men consumed ≥ 18, and women ≥ 14 alcoholic beverages a week in the previous 90 days; had a body mass index (BMI) $\geq 18\,kg/m^2$ and not lose $\geq 10\%$ of their BMI during the study; willing to take oral medication, adhere to the medication regimen and willing to return for weekly visits and the ACS; able to read and comprehend written instructions and comprehend and complete all scale and inventories required by the protocol; must have signed an informed consent indicating they understand the purpose of and procedures required for the study which was not for alcohol dependence treatment, and their willingness to participate.

Exclusion criteria included: Alcohol consumption of > 45 alcoholic beverages per week for men or > 40 drinks per week for women; pregnancy or women breast feeding; a positive urine drug screen for any illegal substance other than marijuana. (If the subject had a positive drug screen, a re-test was performed. If the retest was positive the subject was excluded); current use of psychotropic medications; medical contraindications for use of aripiprazole or topiramate (e.g., kidney stones, history of seizures or suicide, cardiovascular disease); taking drugs that interfere with the metabolism of either drug that could not be stopped per study physician; allergic to either drug; a creatinine clearance ≤ 60 dl/min.; bilirubin $> 150\%$ of the upper limit of normal or ALT or AST elevations $> 300\%$ the upper limit of normal; individuals with a reasonable expectation of being institutionalized during the course of the trial or pending legal charges; individuals anticipating moving during the course of the study; participants who have significant alcohol withdrawal symptoms as measured by the Clinical Institute for Withdrawal Assessment of Alcohol Scale-Revised $>$ 10 (CIWA-Ar; Sullivan *et al*., 1989); and participants with a history of renal impairment or nephrolithiasis.

General procedures

Blood and urine samples consisted of complete blood count, serum electrolytes, liver function tests, alkaline phosphatase, lactate dehydrogenase (LDH), direct and total bilirubin, uric acid, serum creatinine, creatinine phosphokinase, and urinalysis including drug test and pregnancy test in all women of childbearing potential. Pharmacokinetic levels of the medications were assessed midway through the study and before the ACS. Self reported alcohol use was determined by the timeline follow-back (TLFB) method (Sobell and Sobell, 1992) then standardized with the formula: (ounces of alcoholic beverage $\times$ per cent of alcohol content/0.5) = standard drinking units (SDUs). Heavy drinking was assessed by an AUDIT score ≥ 8. Alcohol withdrawal was assessed by the CIWA-Ar. The Hamilton Depression Scale (HAM-D; Hedlung and Veiweg, 1979) assessed weekly changes in mood or suicidality. The Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) was used weekly to monitor the development or worsening of extrapyramidal symptoms. At each visit, participants were assessed using a revised version of the SAFTEE (Levine and Schooler, 1986; Rabkin *et al*., 1992), a standardized AEs measure. The collection of adverse reaction data was the primary aim of this study.

Two measures assessed craving for alcohol. The Obsessive Compulsive Drinking Scale (OCDS; Anton *et al*., 1995) is a 14-item scale that assesses obsessive thoughts and compulsions associated with alcohol craving. The OCDS measured the average severity of overall craving for the 7-day period prior to the time of assessment. The Alcohol Urge Questionnaire (AUQ; Bohn *et al*., 1995) is a validated eight-item questionnaire to assess craving (desire to drink), expectation of positive effect from drinking, and inability to avoid alcohol consumption if available. The AUQ was assessed during screening and during the ACS. The Profile of Mood States (POMS; McNair *et al*., 1971) is a self-report questionnaire to identify and assess transient affective mood states. The Biphasic Alcohol Effects Scale (BAES; Martin *et al*., 1993) is a validated self-report rating scale used to measure the stimulant and sedative effects of alcohol and was used during the ACS only.

After the study physician reviewed the medical history and lab tests, the volunteer was scheduled for an initial visit. Volunteers who were excluded at any point in the recruitment process were asked if they wanted to be referred for treatment in accordance with the National Institute on Alcohol Abuse and Alcoholism National Advisory Council recommended guidelines

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for the administration of ethyl alcohol (National Council on Alcohol, 1988). Because change of mood, depression, and suicidal thoughts have been reported with topiramate (Ortho-McNeil Neurologics Inc, 2005), a flyer listing local community mental health resources was given to all randomized participants.

There were five phases of the study: (1) a 1-week screening period; (2) a 32-day titration period, (Table 1) which consisted of 11 more visits. Participants remained eligible as long as they exceeded thresholds of 100 mg per day of topiramate and/or 10 mg of APZ (33% of the maximum target dose); (3) a minimum of 3 days at the maximum dose with a +3 day window to perform the ACS; (4) an ACS on the last day of treatment at the maximum dose for the ACS; (5) and follow-up call at 7 days post ACS. Immediately after the day of the ACS, the medication was discontinued (this study was completed before there was a manufacturer warning regarding titrating all patients off topiramate over 16 days due to reports of seizures in patients who had no previous medical history of seizures (Ortho-McNeil Neurologics Inc, 2005)).

Regular visits (titration weeks)

As the goal of the study was to demonstrate safety and tolerability of the medications with alcohol, the study was an open-label medication trial but the dose was blinded to the participant. The study received an IND #70 603 from the Food and Drug Administration (FDA) to administer topiramate and aripiprazole together with alcohol. Tablets were not altered or crushed. Instructions were provided to the volunteer at each visit and on the prescription bottle. Each dose titration was performed within the capsules dispensed but without discussion with any of the participants as the number of capsules taken each day was consistent throughout the titration period.

Table 1. Dosing schedule for aripiprazole and topiramate pilot study

Study visits	Days	TPMT total dose	APZ total dose
1	7	On-site screening	
2	3	Placebo	Placebo
3	3	25 mg (25 mg daily)	10 mg (10 mg daily)
4	4	50 mg (25 mg bid)	20 mg (10 mg bid)
5	7	100 mg (50 mg bid)	20 mg (20 mg daily)
6	7	150 mg (75 mg bid)	20 mg (20 mg daily)
7	7	200 mg (100 mg bid)	20 mg (20 mg daily)
8	3 (+ 3 days)	300 mg (100 mg in a.m./200 mg in p.m. daily)	30 mg (30 mg daily)
9	1	Alcohol challenge session	
10	7	7 day follow-up	
Total	42		

TPMT = topiramate; APZ = aripiprazole.

Each visit, the participant received a breath alcohol concentration (BrAC), weight check, and vital signs. Participants were advised not to drink prior to study visits. Subjects each week were monitored for AEs, changes in mood, and evaluation of concomitant medication use. After consultation with a physician, dose adjustments to study medication were made. Subjects filled out questionnaires at each weekly visit, and alcohol use was assessed using the TLFB method for the time period since the previous visit. The dose of medication was started with a placebo dose for 3 days and then the study medication was started at the next visit and increased over 32 days to a maximum dose of 300 mg per day of topiramate (100 mg in the morning and 200 mg at night), and 30 mg per day of aripiprazole administered in the morning. Adherence was confirmed with capsule counts at each visit and medication blood levels midway and at the end of the study.

Alcohol challenge session

On the day of the ACS, participants arrived at 10 a.m. and had a number of assessments to complete, urinalysis, and blood work (see Table 2). Beginning at about noon, participants were then administered alcohol (about three beers) adjusted by gender, height, and weight, such that each drink was equivalent to 0.15 g/kg of alcohol for men and 0.11 g/kg for women with a goal of achieving a BrAC of 0.06 mg% (Watson, 1989). The modest dose of alcohol was chosen as we were unsure of the severity of any potential interaction that may potentially occur. However, based on the lack of reports in the literature regarding taking either drug alone or in drug combination with alcohol, we were confident this particular amount of alcohol was safe. During the ACS participants were asked to complete each drink in 12 min, then complete a few short assessments after each drink including AEs with the SAFTEE. Our experience suggested that AEs would be most intense when the subjects reached peak alcohol level which we approximated was 20 min after the last drink. The volunteers then had 8 min to complete the assessments before the next drink was served. The participants had to wait until their BrAC was 0.00 mg% before they could depart. We telephoned participants 1 week after the ACS to assess any post-study AEs.

RESULTS

After obtaining informed consent screened 15 non-treatment seeking, heavy alcohol-drinking participants in person with interviews, physical exam, and clinical labs. Thirteen of these (11 male, 2 female) were

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Table 2. Timeline for alcohol challenge session

Assessment/Event	10 : 00	12 : 00	12 : 20	12 : 40	13 : 00	Midway	BrAC = 0.00
Habituation	x						
Drink 1		x					
Drink 2			x				
Drink 3				x			
Post drink					x		
BrAC	x	x*	x*	x*	x**	x	x
SAFTEE checklist	x				x		
POMS	x				x	x	
AIMS	x				x		
AUQ	x	x	x	x			
MOS Sleep	x						
BAES		x	x	x	x	x	x
Discharge							x

Note: Midway = Midway between peak and zero breath alcohol concentration (BrAC).
*BrAC taken after wash mouth out and before beer.
**BrAC taken every 15 min post-assessments. See text for complete names of assessments.

randomized, and eight (seven male and one female) completed the study (mean age of 38 years, range 22–58 years old).

Adherence

For the eight participants who completed the study, all achieved the maximum dose of aripiprazole 30 mg and topiramate 300 mg with pill counts > 90% adherence at all visits. All participants except one were verified to have achieved detectable blood levels of both drugs midway though the study. One of the participants who was confirmed to be taking the medication halfway though the study refused to have blood work performed at study completion so that we cannot pharmacokinetically verify the participant took the medications until the study completion.

Dropouts/early terminations

There were a total of five dropouts in the study. Two participants discontinued the study because of AEs that were most likely medication related. One male participant taking 20 mg APZ and 150 mg TPMT stopped taking the medications because he was experiencing akinesia. One woman participant also taking 20 mg APZ and 150 mg TPMT stopped taking her medication due to feeling restless, inability to concentrate, insomnia, and headache all of which were most likely medication related. Both reported that the AEs were completely gone within a week after discontinuing the medications. A third participant went out of town unexpectedly, ran out of study medication, and discontinued the study.

Two terminations were not medication related and both were hospitalized. A participant was hospitalized for a previously un-reported to study staff and untreated diagnosis of attention-deficit hyperactivity disorder (ADHD) and depression. The second significant AE occurred when a participant was hospitalized due to a previously broken foot that flared up.

Adverse events reported

There were no unexpected AEs during this pilot trial. Table 3 displays the per cent of AEs and AEs possibly or probably attributed to the medications during the course of the study. Additionally presented are AEs greater than 1% and greater than placebo for a study using 200–400 mg dose of topiramate as an adjunctive therapy as well as pooled AEs for aripiprazole 15–30 mg doses in short (3 weeks) and longer (6 weeks) trials in patients with bipolar disorder and schizophrenia, respectively. The majority of the AEs in the current study reported were not ''probably'' drug related. The most common AEs were insomnia (17%), fatigue (33%), headache (33%), change in taste (25%), paresthesias (33%), somnolence (8%), dizziness (17%), restlessness (25%), increased (8%) or decreased (8%) appetite, dry mouth (8%), lack of energy (8%), vomiting (8%), and weak legs (17%). Comparing these AEs to the AEs reported in the professional literature (Ortho-McNeil Neurologics Inc, 2005; Otsuka Pharmaceutical Co, 2006; Johnson *et al*., 2007; Anton *et al*., 2008) is limiting in such a small sample size, however, the AEs of the two drugs together would suggest that the AEs profile is broader but not additive or synergistic as predicted. No new AEs were reported during the ACS. The incidence of the AEs reported during the ACS included 16.66% insomnia, fatigue, and paresthesia, and 8.33% fatigue, change in taste, diarrhea, dizziness, and weak legs. Any

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Table 3. Adverse events possibly or probably related to topiramate or aripiprazole compared to other reported trials

Reported adverse events	Total reported percentage (%)	Possible or probable med related (%)	TPMT*	APZ*	*TPMT***	*APZ***
Insomnia	58.30	16.60	n.r.	20%	*19.1%*	*21.9%*
Fatigue	66.60	33.30	15%	n.r.	*22.4%*	*24.7%*
Headache	58.30	33.30	n.r.	31%	*24.0%*	*20.6%*
Change in taste	25.00	25.00	2%	n.r.	*23.0%*	*n.r.*
Paresthesia	33.30	33.00	11%	n.r.	*50.8%*	*n.r.*
Somnolence/sleepiness	41.60	16.66	29%	12%	*12.0%*	*17.1%*
Dizziness (lightheaded)	33.30	16.60	25%	11%	*11.5%*	*7.5%*
Nervousness/restlessness	25.00	25.00	16%	25%	*14.2%*	*18.5%*
Increased appetite	16.60	8.33	n.r.	n.r.	*n.r.*	*5.5%*
Decreased appetite	16.60	8.33	n.r.	n.r.	*19.7%*	*n.r.*
Difficulty concentrating	8.33	8.33	6%	n.r.	*14.8%*	*9.6%*
Nausea	8.33	8.33	10%	16%	*10.4%*	*6.9%*
Dry mouth	16.60	8.33	2%	n.r.	*n.r.*	*n.r.*
Lack of energy (apathy)	16.60	8.33	1%	n.r.	*n.r.*	*n.r.*
Dyspnea	8.33	8.33	1%	15%	*n.r.*	*n.r.*
Abnormal vision	8.33	8.33	13%	3%	*n.r.*	*n.r.*
Vomited	25.00	8.33	n.r.	11%	*n.r.*	*n.r.*
Weak legs	16.60	16.60	n.r.	n.r.	*n.r.*	*n.r.*
Swollen tongue	8.33	8.33	n.r.	n.r.	*n.r.*	*n.r.*
Language problems	8.33	8.33	6%	n.r.	*n.r.*	*n.r.*

Notes: $N = 8$; TMPT = Topiramate; APZ = Aripiprazole;
*Pooled AEs reported that were greater than placebo where rate was > 1% are reported for topiramate at 200–400 mg doses where the drug was used as an add-on during clinical trials (Ortho-McNeil Neurologics Inc, 2005). Pooled AEs reported for aripiprazole are for 15–30 mg doses in trials up to 3 weeks for bipolar disorder and 6 weeks for schizophrenia (Otsuka Pharmaceutical Co, 2006).
**AEs reported by Johnson *et al*., 2007 and Anton *et al*., 2008.

of the AEs reported at the ACS dissipated by the follow-up contact 1 week later.

Other measures

Rarely were any scores for participants greater than 0 for either the CIWA-AR or for the AIMS throughout the trial. Only one participant was occasionally assessed as demonstrating a score on the AIMS. HAM-D scores varied no more than 2 points from baseline during the course of the study.

Alcohol consumption

Data are available for eight participants who completed the ACS. All of the participants consumed the entire quantity of alcohol available. Mean peak BrAC during the ACS was 0.042 mg%. Although the study was not designed to reduce alcohol use, of those who completed the study the mean number of SDUs during the prior 28 days to starting medication was 6.12 SDUs per day. During the 7 days prior to the ACS the mean number of SDUs reported decreased to 1.79 daily, paired samples *t*-test, $t\ (7) = 2.00$, $p = 0.08$.

DISCUSSION

The results of this study generally demonstrate that 30 mg of aripiprazole and 300 mg of topiramate are well tolerated and can be administered safely together with a modest amount of alcohol. Furthermore, there is little evidence from this study that the AEs of these two drugs are additive or synergistic. If there were an additive number of AEs for combining topiramate and aripiprazole, then one would suspect a noticeably higher percentage of AEs compared to other trials in Table 3 though attempting to compare the AEs from this study to pooled results from clinical trials and the two trials with alcohol dependent patients is speculative. For example, the incidence of ''headache'' was reported one-third of the time in this pilot study which was consistent with the rate reported in 4 and 6 week pooled clinical trials for aripiprazole but slightly higher than reported in either trial with alcohol dependent patients. On the other hand, the 50.8% incidence of ''paresthesia'' reported by Johnson et al. (2007) was higher than reported by this pilot, however one must keep in mind the length of the treatment period in the Johnson *et al*. (2007) study was twice a long.

Notably though patients who are alcohol dependent and are prescribed topiramate and/or aripiprazole for co-morbid psychiatric problems relapse to drinking, there are no published anecdotal reports or case studies reported examining the AEs associated with taking both topiramate and aripiprazole, and the subsequent combination of these drugs with alcohol. Aripiprazole and topiramate are prescribed together (off-label) without reports of intolerance and have already been

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shown safe to administer to samples of alcohol dependent individuals who are expected to relapse to alcohol use in lab studies (Kranzler *et al*., 2008; Miranda *et al*., 2008; Voronin *et al*., 2008) and clinical trials (Johnson *et al*., 2007; Anton *et al*., 2008; Martinotti *et al*., 2009). However, the combination of both drugs in a population of heavy drinkers receiving alcohol under closely monitored conditions has never been reported. Additionally there is no common metabolic mechanism for or reports of drug interaction between the two drugs, and under strict laboratory conditions there is no current evidence to suggest an increased risk in combining these drugs with a modest dose of alcohol.

Topiramate has been approved for migraine prophylaxis, initial monotherapy of partial onset, or primary generalized tonic–clonic seizures in patients 10 years of age or older and as an adjunct for seizure disorder (Ortho-McNeil Neurologics Inc, 2005). The most commonly reported AEs experienced by subjects associated with topiramate include paresthesia, tiredness, dizziness, somnolence, weight loss, and difficulty with memory, with less common AEs that include difficulty concentrating, nervousness, slow thinking, a change in taste which seems to be more pronounced with those drinking carbonated beverages, abnormal vision, confusion, and language problems. Aripiprazole has been approved by the FDA for use in schizophrenia and bipolar disorder (Otsuka Pharmaceutical Co, 2006). Across short-term double-blind placebo-controlled schizophrenia studies, the AEs profile of aripiprazole was generally comparable to that of placebo. The only notable differences in AE incidences between aripiprazole and placebo were headache, nausea, vomiting, insomnia, lightheadedness, and blurred vision. Most AEs were reported as mild or moderate in intensity.

Sedatives such as alcohol taken in large quantities may produce central nervous system depression in patients when taken with topiramate or aripiprazole, therefore, patients must be advised to use caution. Furthermore, other than this standard precaution there were no special warnings against alcohol use and the use of topiramate or aripiprazole for the manufacturer sponsored trials. However, as the data report, some patients drank heavily while taking topiramate in the Johnson and colleague studies (2003; 2007; 2008) and Anton *et al*. (2008) studies, and while neither study reported an increased number nor intensity of AEs that may have occurred due to alcohol use, it is difficult to tease apart AEs as a result of their alcohol consumption.

We wished to demonstrate that combining topiramate and aripiprazole with alcohol was safe enough to explore in larger more fully powered studies. This study indicates that future laboratory studies can be safely conducted to investigate whether the combination of topiramate and aripiprazole would alter alcohol craving and actual alcohol consumption, using self-administration or choice studies in alcohol dependent individuals. Furthermore, though the primary aim of this study was to assess the safety and tolerability of combining aripiprazole and topiramate with alcohol, there was a trend for a reduction of alcohol use by participants not seeking to reduce their use. This was not the main purpose of this study *per se* but as previously noted, still the underlying factor for performing this study. This is potentially important, as the effect was fairly robust for a study not powered for such a reduction in alcohol use. This result may therefore have long-term implications for potential study of future treatments for alcohol dependence.

LIMITATIONS

The small sample size is a limitation of this pilot trial. However, one must keep in mind the substantial drug costs involved in performing this trial and no study of this type had previously been performed. As neither drug company was in a position to donate the drugs, the drugs were procured at what was a reduced price, however, the cost for the drug alone was in excess of $22 000, making a larger sample financially prohibitive. Finding a drug or combination of drugs that can successfully reduce craving and alcohol consumption in alcohol dependent individuals is important to pursue regardless of initial costs. The drugs will eventually be available as generics and will be less cost prohibitive to patients if a particular combination of the drugs are found to be effective. This study was a first step toward that pathway and to ensure that the combination of aripiprazole and topiramate were safe in subjects who drink even a modest dose alcohol.

There are several significant AEs that occur with these two drugs and 35 days is a short course of therapy to properly assess the full extent of potential AEs of these drugs. It is also possible that long-term exposure to these drugs would show a dramatic drop-off in compliance in an alcohol dependent population. Additionally there are no data to justify the use of a 30 mg per day dose of aripiprazole (Anton *et al*., 2008) and using a lower dose may reduce side effects. Furthermore, there is growing support to suggest the usefulness of a lower dose in both lab studies (Kranzler *et al*., 2008; Voronin *et al*., 2008) and clinical trials (Martinotti *et al*., 2009). Our future studies, therefore, will be using lower doses of both drugs.

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It should also be stressed that the dose of alcohol given was modest for heavy drinkers of alcohol. Therefore, making assumptions about the safety of combining these two drugs particularly with any dose of alcohol was not the purpose of this study nor is it considered or condoned as a safe practice. This lab experiment was conducted under strict supervision and does not attempt to reflect what patients will do outside of such constant monitoring. Moreover, though there was a trend toward a reduction in alcohol use, there is no way to know if these participants were really volunteering or looking for help with their alcohol use and reduced their alcohol use on their own.

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