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A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence

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ABSTRACT

Background: Topiramate increases GABAergic activity and antagonizes the AMPA/kainate subtype of glutamate receptors. Through these mechanisms of action, topiramate may reduce alcohol and cocaine reward and may reduce alcohol and cocaine craving. Topiramate has been shown to reduce drinking in persons with alcohol dependence, and reduce relapse in stimulant-dependent patients. The current trial was intended to test the ability of topiramate to promote cocaine and alcohol abstinence among patients addicted to both drugs.
Methods: The study was a double-blind, placebo-controlled, 13-week trial involving 170 cocaine and alcohol dependent subjects. After achieving a period of cocaine and alcohol abstinence, subjects were randomized to topiramate, 300 mg daily, or identical placebo capsules. In addition, subjects received weekly individual psychotherapy. Primary outcome measures included self-reported alcohol and cocaine use, and thrice weekly urine drug screens. Secondary outcome measures included cocaine and alcohol craving, Addiction Severity Index results, cocaine withdrawal symptoms, and clinical global improvement ratings.
Results: Topiramate was not better than placebo in reducing cocaine use on the a priori primary outcome measure, or in reducing alcohol use. Topiramate was not better than placebo in reducing cocaine craving. Topiramate-treated subjects, compared to placebo-treated subjects, were more likely to be retained in treatment and more likely to be abstinent from cocaine during the last three weeks of the trial. Subjects who entered treatment with more severe cocaine withdrawal symptoms responded better to topiramate.
Discussion: Topiramate plus cognitive behavioral therapy may reduce cocaine use for some patients with comorbid cocaine and alcohol dependence.

1. Introduction

The co-occurrence of cocaine and alcohol dependence is common and patients suffering from both disorders are extremely difficult to treat. Studies have shown that 60–80% of cocaine dependent patients are also alcohol dependent (Carroll et al., 1993; Regier et al., 1990). Patients with both cocaine and alcohol dependence tend to have more psychosocial problems and worse treatment outcomes compared to patients addicted to either cocaine or alcohol alone (Brady et al., 1995; Carroll et al., 1993; Heil et al., 2001; Walsh et al., 1991). The combined use of alcohol and cocaine is fostered by a variety of factors including both conditioning (Wallace, 1989) and pharmacodynamic interactions between cocaine and alcohol (McCance-Katz et al., 1993). Thus, treatments aimed specifically at reducing either cocaine use or alcohol use alone may be inadequate and the best strategy for treating cocaine and alcohol dependent patients may be one that targets both addictions simultaneously.

Topiramate is a promising medication for either alcohol or stimulant dependence. Topiramate is an anticonvulsant medication with several different mechanisms of action. Topiramate increases cerebral levels of GABA and facilitates GABA neurotransmission through a non-benzodiazepine-associated binding site on the GABA A receptor (Kuzniecky et al., 1998; Petroff et al., 1999; White et al., 1997). By increasing GABAergic activity in the nucleus accumbens, topiramate may reduce the dopamine release associated with cocaine or alcohol use and reduce the reinforcing effects of cocaine and alcohol. In addition, topiramate inhibits glutamate neurotransmission through a blockade of AMPA/kainate receptors

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(Gibbs et al., 2000). This may reduce craving for alcohol and cocaine associated with exposure to conditioned cues. In animal models of cocaine relapse, topiramate's blockade of AMPA receptors in the nucleus accumbens prevented reinstatement of cocaine self-administration (Cornish and Kalivas, 2000). Cocaine-dependent patients who experience cocaine withdrawal symptoms report a greater "high" from experimentally-administered cocaine (Newton et al., 2003; Sofuoglu et al., 2003; Uslaner et al., 1999). Therefore, a reduction in euphoria produced by topiramate may be particularly helpful in cocaine and alcohol dependent patients with more severe cocaine withdrawal symptoms.

In two placebo-controlled clinical trials, topiramate promoted abstinence from alcohol by reducing heavy drinking days among alcohol-dependent individuals (Johnson et al., 2003, 2007b). Topiramate was also efficacious in promoting stimulant abstinence in three placebo-controlled trials of stimulant dependence treatment. First, in a 13-week pilot trial, topiramate reduced relapse to cocaine use in 40 cocaine dependent patients (Kampman et al., 2004). Levin and colleagues showed that the combination of topiramate and mixed amphetamine salts was more effective in promoting cocaine abstinence in patients with more severe cocaine dependence, defined as having more cocaine use days in the month prior to entering the trial (Mariani et al., 2012). Finally, Elkashef and colleagues found that topiramate reduced methamphetamine use and reduced the relapse rate in methamphetamine-dependent patients who attained a period of abstinence prior to starting topiramate (Elkashef et al., 2012).

2. Methods

2.1. Subjects

The subjects were 170 DSM-IV cocaine dependent men and women drawn from treatment-seeking cocaine users between the ages of 18 and 70. Drug dependence diagnoses were obtained using the Structured Clinical Interview for DSM IV (SCID-IV) (First et al., 1996). Other psychiatric diagnoses were obtained using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). In the 30 days prior to study entry, subjects used no less than $200-worth of cocaine and met the following drinking criteria as measured by the Timeline Followback (TLFB; Sobell and Sobell, 1995): (a) drank within 30 days of intake day, (b) reported a minimum of 48 standard alcoholic drinks (avg. 12 drinks/wk) for women and 60 standard drinks (15 drinks per week) for men in a consecutive 30-day period over the 90-day period prior to starting intake, and (c) had 2 or more days of heavy drinking (defined as 5 or more drinks per day in males and 4 or more drinks per day in females) in this same pre-treatment period.

Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood count, urinalysis, and a 12 lead EKG. Women received urinary pregnancy testing prior to starting medications, and at monthly intervals throughout the study. Chemistry screening, CBC, urinalysis and EKG were repeated at the end of the trial. Liver function tests and carbon dioxide levels were obtained monthly during the trial.

Subjects with current dependence (DSM-IV criteria) on any additional drug except nicotine and cannabis were excluded. Psychiatric exclusion criteria included psychosis, dementia, and the use of other psychotropic medications. Medical exclusion criteria included unstable medical illnesses, impaired renal function, and a history of hypersensitivity to topiramate. Subjects with a history of kidney stones or subjects taking carbonic anhydrase inhibitors or any other antiepileptic drug were excluded from the study.

2.2. Procedures

Subjects were treatment-seeking cocaine and alcohol users recruited at the University of Pennsylvania Treatment Research Center (TRC). The TRC recruits through advertisement in the local media as well as through professional referrals. All subjects signed informed consent prior to participation in the trial, after an investigator explained to them the study procedures. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Pennsylvania. Subjects were reimbursed $5.00 at each visit for completing all research procedures; at the last visit of the medication phase of the trial and at the follow up visit they received $25.00 because of the greater number of research procedures done at those two visits. Subjects received an additional $5.00 each week for returning the previous week's medication package in order to facilitate the pill-count compliance check. If needed, two transit tokens were provided at each visit.

Table 1
Dose titration schedule.

Wk.	A.M. dose (mg)	P.M. dose (mg)	Total (mg)
1	0	25	25
2	0	50	50
3	0	75	75
4	25	75	100
5	50	100	150
6	100	100	200
7	100	150	250
8	150	150	300
9	150	150	300
10	150	150	300
11	150	150	300
12	150	150	300

Eligible subjects entered a baseline phase during which all pretreatment measures were obtained and subjects began psychosocial treatment. The baseline phase could last up to three weeks during which time subjects were required to attain baseline abstinence from cocaine and alcohol. This was defined as three consecutive days of abstinence from cocaine and alcohol, determined by self-reports and confirmed by negative urine drug screens, a negative breathalyzer tests, and collateral report, a Clinical Institute Withdrawal Scale for Alcohol (CIWA-AR; Sullivan et al., 1989) score below eight. Eligible subjects were then randomized to receive either topiramate or placebo. The dose was titrated to 300 mg daily following the schedule shown in Table 1. Subjects attended the clinic three days per week.

The Investigational Drug Service of the University of Pennsylvania prepared study medication by overencapsulating topiramate tablets and preparing identical appearing placebo capsules. Capsules were placed in blister packs with each day's dose clearly marked. Medications were dispensed by a nurse practitioner each week and the previous week's blister pack was collected. Compliance was measured by pill count. None of the dose ingestions were observed in the clinic.

In addition to medication or placebo, subjects received weekly individual cognitive-behavioral relapse prevention therapy utilizing a Cognitive-Behavioral Coping Skills Therapy (CBT) manual. The CBT therapy manual and supporting materials were developed for the National Institute on Alcohol Abuse and Alcoholism Project MATCH (Kadden et al., 1992). The basic format was accepted, although specific procedures were adapted for treatment of comorbid cocaine dependence by our group. Master's level therapists with additional training in CBT provided therapy.

2.3. Measures

Self-reported alcohol and cocaine use were measured using the Timeline Followback (Sobell and Sobell, 1995). Self-reported cocaine use was verified by qualitative urine benzoylecgonine tests (UBT) obtained thrice weekly. Urine collection was monitored by temperature checks. Samples less than 90 degrees, or greater than 100 degrees Fahrenheit were considered invalid and were not accepted. Samples were analyzed for benzoylecgonine by fluorescent polarization assay. Samples containing equal to or greater than 300 ng/ml of benzoylecgonine were considered to be positive.

Treatment retention was determined by attendance at research visits. Subjects were considered dropouts if they stopped attending research visits and did not return within the 14 weeks of the trial. Severity of addiction-related problems was measured by the Addiction Severity Index (ASI; McLellan et al., 1992) administered at baseline and three more times during the trial. The study nurse practitioner rated overall improvement weekly using the Clinical Global Impression Scale (CGI; Guy, 1976). The Minnesota Cocaine Craving Scale (MCCS) was used to measure cocaine craving intensity (MCCS-I), cocaine craving frequency (MCCS-F) and cocaine craving duration (MCCS-D) (Halikas et al., 1991). Alcohol craving was measured weekly using the Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999). Cocaine withdrawal symptoms were measured weekly using the Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998). Safety measures included adverse events, which were monitored at each visit.

2.4. Statistical analysis

Subjects were first compared on a variety of baseline characteristics to assess randomization balance across the two treatment groups, using chi-square tests for categorical characteristics and t tests for continuous characteristics. The primary analyses did not include additional covariates; characteristics that showed significant imbalance across the groups were examined as covariates in supplementary analyses.

Generalized estimating equation (GEE) models (Diggle et al., 2002) were used to compare the groups on weekly cocaine use, as measured by a combination of three UBT measures, together with self-report based on the TLFB. This was the planned primary outcome measure for cocaine use. Each study week was coded as abstinent or not abstinent based on the following definition: a study week was coded as an abstinent week if the participant reported no cocaine use during the study week, and