Effects of Topiramate on Urge to Drink and the Subjective Effects of Alcohol: A Preliminary Laboratory Study

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Background: Topiramate was recently reported to be efficacious in reducing drinking rates and craving among individuals with alcohol dependence in a randomized controlled trial, but dose effects could not be determined. This laboratory study systematically examined the dose-dependent effects of topiramate on cue-elicited craving and other putative mechanisms of its pharmacotherapeutic effects on drinking.

Methods: Male and female heavy drinkers ($n = 61$) were randomized to 1 of 3 medication conditions (200 mg/d; 300 mg/d; placebo) in a double-blind study. Participants reached the target dose after a 32-day titration period, then were stabilized for approximately 1 week. All then participated in a laboratory assessment of alcohol cue reactivity and of the subjective effects of a moderate dose of alcohol.

Results: Both doses of topiramate reduced the frequency of heavy drinking during the titration period as compared to placebo. However, topiramate did not affect self-reported craving for alcohol during the titration period, during the cue reactivity protocol, or in response to the alcohol challenge procedure. Topiramate reduced the stimulating effects of alcohol ingestion compared to placebo, but only in the 200 mg group.

Conclusions: The results of this study support previous findings that topiramate reduces drinking, but the behavioral mechanism underlying this effect does not appear to be attenuation of craving for alcohol as measured using the approaches employed in this study. Rather, the results tentatively suggest that topiramate may exert its beneficial effects by altering the subjective experiences of alcohol consumption. Limitations of the current study are discussed and complementary methods are recommended for future studies, such as the use of behavioral economic paradigms and ecological momentary assessment.

Key Words: Topiramate, Medication Action, Cue Reactivity, Alcohol Challenge, Craving.

TOPIRAMATE IS AN anticonvulsant medication that was recently identified as a potentially efficacious treatment for alcohol dependence based primarily on results of 1 double-blind randomized clinical trial (Johnson et al., 2003). In this 12-week study, individuals with alcohol dependence who received topiramate in doses titrated up to 300 mg/day reported reductions in their quantity and frequency of alcohol consumption, with large magnitude effect size differences compared to placebo. In addition, results of 2 open-label trials found similarly positive results on alcohol use after treatment with topiramate (250 to 300 mg/d; Rubio et al., 2004; Raguraman et al., 2005). Although the efficacy cannot be

determined from open-label studies, these latter reports provide further support for the tolerability and safety of topiramate for treating alcoholism.

Despite considerable interest in topiramate as a promising pharmacotherapy for alcohol dependence, the mechanisms by which this medication reduces drinking are not well characterized. Pharmacotherapeutic strategies for treating alcoholism generally aim at reducing withdrawal symptoms, reducing craving or urge to drink, attenuating the pleasurable effects of alcohol ingestion, and intensifying the unpleasant effects of alcohol ingestion (Davidson et al., 1999). Identifying the mechanisms by which different pharmacological agents impact drinking would allow for more targeted use of medications and expand our understanding of the underlying neurobiology of alcoholism. Moreover, different medications may reduce drinking through different mechanisms. Understanding how particular medications affect drinking would suggest which types and combinations of medications may be most beneficial for treating alcohol use disorders.

It has been hypothesized that topiramate reduces alcohol intake by attenuating alcohol craving and motivation to drink (Johnson et al., 2003, 2004). This hypothesis is based largely

on the medication's neuropharmacological actions, which include facilitation of gamma aminobutyric acid (GABA) neurotransmission and blockade of AMPA/kainite glutamate receptors. Acute dopamine release from mesocorticolimbic neurons plays a critical role in determining the motivational significance of stimuli in general (see Hyman and Malenka, 2001) and in alcohol reward (e.g., Dodd et al., 2000; Weiss et al., 1993; Weiss & Porrino, 2002). According to Johnson et al. (2003), because mesocorticolimbic DA release is under tonic inhibitory control via GABAergic neurons and excitatory control via glutamatergic neurons, topiramate's concurrent GABAergic agonism and glutamatergic antagonism may inhibit acute motivation for alcohol (i.e., craving). The one published placebo-controlled clinical trial of topiramate's effects on drinking reported that topiramate reduced urge to drink and this attenuation of craving was significantly correlated with decreased alcohol use (Johnson et al., 2003).

Although the report from Johnson et al. (2003) provides provisional support for the hypothesis that topiramate reduces alcohol use by attenuating craving, no controlled laboratory study has systematically tested this hypothesis. Furthermore, other putative mechanisms of topiramate's actions, such as alterations in the subjective reinforcing effects of alcohol, have not been examined. In the Johnson et al. (2003) study of topiramate's effects, it is unclear whether topiramate first reduced craving which in turn reduced drinking, or whether topiramate affected another aspect of alcohol use which reduced drinking and these changes subsequently attenuated desire for alcohol.

The primary objective of the present study was to systematically examine the effects of topiramate on several putative mechanisms of pharmacotherapy action using 2 well-established human laboratory paradigms, one that focused on alcohol craving and one that examined subjective responses to alcohol. The cue reactivity paradigm was developed to examine urge to drink in response to alcohol-associated stimuli in a controlled setting, as exposure to alcohol cues can simulate a high-risk situation for alcohol use. Indeed, the cue reactivity paradigm has demonstrated substantial utility in eliciting urge to drink (e.g., Monti et al., 1987; for a review, see Carter and Tiffany, 1999) and reactivity to alcohol cues has been shown to predict treatment outcome (Monti et al., 2000). Similarly, an important advantage of the alcohol administration paradigm is that it allows for the assessment of a medication's action on the subjective effects of alcohol ingestion under carefully controlled alcohol administration conditions. Furthermore, by assessing effects in close proximity to drinking, bias because of memory decay involved in retrospective reporting is prevented.

In the present study, participants were randomly assigned to receive 1 of 3 targeted medication conditions (200 mg/d, 300 mg/d, or placebo). We tested the dose-dependent effects of topiramate because Johnson et al. (2003) found that significant reductions in drinking emerged while participants were at the 200 mg/day dose, however, doses continued to escalate. As such, the effects of time and dose on drinking were con-

founded in that study and the potential efficacy of doses stabilized at lower than 300 mg/day remains unclear. In the present study, medication was titrated over a 32-day period to 1 of 2 stable target doses or placebo. After dose stabilization, participants completed a laboratory session that involved in vivo exposure to alcohol beverage cues followed by alcohol administration procedures. We examined the dose-dependent effects of topiramate on: (i) alcohol use and craving during the titration period; (ii) craving in response to alcohol cue exposure in the laboratory; and (iii) craving and other subjective responses to alcohol administration in the laboratory. Based on previous findings, it was hypothesized that topiramate would reduce alcohol use and craving during the titration period, and attenuate urge to drink in response to alcohol cues in the laboratory. Although no previous laboratory studies have been conducted on topiramate and alcohol consumption, we explored its effects on the stimulant and sedative effects of alcohol, since these should be related to the reinforcement value of drinking (Swift et al., 1994).

MATERIALS AND METHODS

Participants

To be eligible for the study, participants needed to be between 21 and 65 years of age, consume 18 to 60 standard alcoholic drinks/ week during the 90 days prior to enrollment, if male (14 to 53 drinks/week, if female), to score < 14 on the Beck Depression Inventory-II (Beck et al., 1996), and, for purposes of the alcohol challenge, to like beer. Potential participants were excluded if they had recent treatment or expressed interest in current treatment for alcoholism, if they had medical contraindications to study participation, if they used medications that could affect mood or drinking, or if they were living with someone who was enrolled in the study.

Of 78 individuals enrolled in the study and sequentially randomized into medication condition, 14 voluntarily withdrew from the study for various reasons, including side effects ($n = 6$), misgivings about participating in a medication trial ($n = 2$), or miscellaneous personal reasons (e.g., relocation; $n = 6$). Three additional participants in the 300 mg group who completed the study were determined to have zero topiramate levels by serum assay. These participants were considered to be noncompliant and their data were excluded from analyses, leaving the final sample at 61 participants (PLA $n = 20$, 200 mg $n = 20$, 300 mg $n = 21$).

Participants were typically white (89%), with smaller proportions of minority participants (5% African-American, 2% Native American, 5% biracial); ethnically, participants were 90% non-Hispanic. The percentage with current alcohol use disorders was not significantly different across conditions: overall, 14% met criteria for alcohol abuse and 46% met criteria for dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR; American Psychiatric Association, 2000). 1 participant met criteria for current marijuana dependence, but no other current substance use disorders were present. Diagnostic interviews were conducted by a trained doctoral level psychologist using the Structured Clinical Interview for DSM-IV (First et al., 1995). Other axis I psychopathology was not assessed.

Medication and Compliance

Participants underwent a 32-day titration period, followed by up to 7 days at target dose (see Table 1) during which time the laboratory session took place. The 7-day window permitted some flexibility in scheduling the laboratory session. Modal duration at target dose

Table 1. 200 and 300 mg Topiramate Titration Schedules

	Dose	
Days	200 mg/d	300 mg/d
Escalation schedule		
1–3	50	50
4–7	50	75
8–10	75	100
11–14	75	125
15–17	100	150
18–21	100	175
22–24	125	200
25–28	150	225
29–31	175	250
32–39	200	300
Reduction schedule		
1–2	100	200
3–4	75	100
5–6	50 mg	50 mg
7	0 mg	0 mg

at the time of the laboratory session was 4 days. Immediately following the laboratory session, participants underwent a 7-day dose reduction period (see Table 2) for safety reasons. The placebo capsules were compounded by the same pharmacy and were identical in all dimensions except the topiramate content. All medication was compounded from bulk topiramate to our specifications. Specifically, the amounts of topiramate as described were compounded with Avicel filler, which is a nonlactose, pharmacologically inert, microcrystalline cellulose filler. Active and placebo capsules were identical in appearance across all doses and conditions, and all participants were instructed to take 2 capsules daily, 1 in the morning and 1 in the evening. The capsules were individually labeled by dose (e.g., Day 4, Morning) and individually sealed in plastic wrappers.

Medication compliance was assessed using 2 methods. Electronic medication bottle caps [Medication Event Monitoring System (MEMS); Aardex Inc., Geneva, Switzerland] prompted participants to take capsules and recorded the date/time that the medication bottles were opened. In addition, blood samples were taken during week 3 and at the laboratory session and analyzed for plasma levels of topiramate.

Weekly Assessments

Alcohol use prior to and during the study was assessed using the Timeline Follow Back (Sobell et al., 1979), with heavy drinking days defined as 6/4 standard drinks in a day for males/females (Flannery et al., 2002). Craving on average over days during the titration period was assessed using 2 measures, the Drinking Obsessions subscale of

Table 2. Baseline Descriptive Statistics for the 3 Experimental Conditions (total $n = 61$)

Variable	Placebo ($n = 20$)	200 mg ($n = 20$)	300 mg ($n = 21$)
Sex (M/F)	60%/40%	70%/30%	62%/38%
Alcohol use disorder	58%	58%	62%
Smoker	55%	40%	24%
Age	45.30 (12.56)	45.65 (12.36)	37. 76 (13.18)
Years of education	13.70 (3.94)	14.40 (2.48)	14.50 (2.27)
Drinks/week	29.12 (15.72)	31.17 (13.52)	25.55 (10.46)
% Drinking days	64.50% (19.39)	77.28% (25.32)	67.99% (21.83)
% Heavy drinking days	40.11 (27.39)	48.83 (29.34)	35.87 (29.94)

Note: Percentage or mean (±SD) is provided, as appropriate.

the Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995; Bohn et al., 1996) and the Penn Alcohol Craving Scale (PACS; Flannery et al., 1999), which explicitly assesses experiential craving. The compulsive subscale of the OCDS was not used because its content is largely not craving-related. In addition, to allow direct comparisons with Johnson et al. (2003), the Automaticity of Drinking and Interference due to Drinking subscales of the OCDS, as derived by Bohn et al. (1996), were also used. During the titration period, side effects were rated for severity (i.e., none, mild, moderate, and severe) using an interview that assessed 38 specific side effects (Johnson et al., 2005; Levine and Schooler, 1986) and used open-ended questions to assess any additional unexpected side effects.

Laboratory Assessments

The immediate state of craving was assessed using the Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995), an 8-item measure validated for use in laboratory research (MacKillop, 2006). During the cue reactivity procedure, the AUQ was complemented by the modified Alcohol Attention Scale (AAS), two 10-point Likert-type scales assessing attention to the sight and smell of water and alcohol cues (Rohsenow et al., 1992). These scales were modified by omitting an item pertaining to thoughts about drinking. In addition, psychophysiological arousal was assessed via measures of mean arterial pressure (MAP) and heart rate in beats per minute (BPM) using a Criticare© Scholar II 507EP blood pressure monitor.

During the alcohol administration, breath alcohol (BrAC) was assessed using an Intoximeters© Alco-Sensor IV breathalyzer. Stimulation and sedation were assessed using the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993). Craving was assessed using the AUQ and affect was assessed using the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988).

The measures administered during the laboratory session are presented in Table 3.

Procedure

All procedures were approved by the Brown University Institutional Review Board. Participants were recruited via advertisements placed in the community. Potential participants underwent a telephone screening and those who met initial criteria were invited to attend an in-person screening interview that included a physical examination and urine toxicology screen. Individuals who met criteria provided written informed consent and received their first week of medication. The instructional set was that the study was examining the effects of 2 doses of topiramate on craving in response to alcohol cues and while drinking modest doses of alcohol; no instructions about potential effects on participants' drinking in their daily life were given. Subsequently, participants attended weekly sessions during which they were assessed for alcohol use, craving, and side effects, and were given their next 7-day supply of medication.

The individual laboratory session took place in the afternoon, typically starting at noon, and lasted approximately 5 hours. Participants

Table 3. Laboratory Session Experiential and Psychophysiological Measures

Procedure	Measures
Cue reactivity paradigm	Alcohol Urge Questionnaire (AUQ)
	Alcohol Attention Scale (AAS)
	MAP/BPM
Alcohol administration	AUQ
	Biphasic Alcohol Effects Scale (BAES)
	Positive and Negative Affect Scales (PANAS)

Note: MAP/BPM = mean arterial pressure/beats per minute.

Table 4. Effects of Topiramate on Drinking and Craving During the Titration Period

Variable	Topiramate F (2, 57)[a]	η_p^2	Time F (3, 171)	η_p^2	Topiramate × Time F (6, 171)	η_p^2
Alcohol use variables						
Drinks/week	2.12	0.07	0.55	0.01	2.37*	0.08
% Drinking days	1.42	0.04	0.12	0.00	0.38	0.01
% Heavy drinking days	3.73*	0.12	1.98	0.03	3.21**	0.10
Craving and related variables						
Drinking obsessions	0.36	0.01	1.45	0.03	1.67	0.06
Penn Alcohol Craving Scale	1.06	0.04	0.36	0.01	1.46	0.05
Automaticity of drinking	0.06	0.00	0.09	0.00	1.20	0.04
Interference of drinking	0.48	0.02	2.53†	0.04	1.89†	0.06

[a]The degrees of freedom for the Penn Alcohol Craving Scale are: (2, 56), (3, 168), and (6, 168), respectively.
†$p < 0.10$, * $p < 0.05$, ** $p < 0.01$.

were transported by taxi to the laboratory, where they completed their weekly assessments, had blood drawn to determine topiramate levels and alcohol breath testing to ensure recent abstinence. They then underwent the cue reactivity and alcohol challenge protocols. No participant had a positive breath alcohol level upon arrival. All experimental manipulations took place in a sound-attenuated testing room equipped with a one-way mirror to monitor participants' behavior. The cue reactivity procedure was similar to that of previously published protocols (e.g., McGeary et al., 2006; Monti et al., 1993). Participants were fitted with the blood pressure cuff on their nondominant arm and habituated to the inflation cycle (approximately every 40 seconds) during an audio taped instruction period, which included a demonstration of the procedures without a beverage. Trials were presented in the same order for all participants because of known carryover effects (Monti et al., 1987).

Participants first underwent a 3-minute relaxation period ("please sit quietly and do nothing") to collect baseline levels of urge and physiological arousal. Following relaxation, a research assistant (RA) entered the room with a tray containing a glass half full of water and a commercially labeled bottle of water, both covered by an inverted pitcher. The pitcher was removed, the RA left the room, and the audio tape instructed the participant to sniff the glass of water when s/he heard high tones and stop sniffing when s/he heard low tones. This protocol included thirteen 5-second olfactory exposures during each 3-minute trial, with variable intervals between each exposure. In this way, participants were exposed to visual, tactile, olfactory, and proprioceptive stimuli associated with the beverage. At the end of the trial, the participant completed an assessment packet (described above in *Laboratory Assessments*), the RA removed the tray, bottle, and glass, and another 3-minute relaxation period began. Participants next underwent two 3-minute alcohol cue exposure trials that were identical to the water trial except the glass of water was replaced with their preferred alcohol beverage (Staiger and White, 1991), and the bottle of water was replaced with the appropriate commercially-labeled alcohol bottle. Two alcohol trials were conducted to gain a stable estimate of participants' reactions to alcohol cues and because two exposures have proven sensitive to differential effects in previous studies (e.g., Rohsenow et al., 2000). Consistent with recommendations by Wertz and Sayette (2001), participants were clearly informed they would receive alcohol to consume following the cue exposure procedure.

After the conclusion of the cue reactivity procedure, participants underwent an alcohol challenge (e.g., Drobes et al., 2004; King et al., 1997; Swift et al., 1994). Individuals were given high-alcohol content (7.2%) beer in a volume that was designed for them to reach a

blood-alcohol level of 0.06% based on a nomogram incorporating their gender and weight (Rohsenow et al., 2006). Total alcohol administered was .647 g/kg for males and .548 g/kg for females; this was typically 2 to 3 16 oz. bottles of 7.2% alcohol beer. Participants were asked to consume the alcohol over a 20-minute period, which was followed by a 20-minute absorption period. Participants were then assessed for BrAC after rinsing their mouths with water to eliminate residual oral alcohol. At this time, the assessment packet was administered to participants who were at a BrAC of 0.06 g % or higher. For those who were still below 0.06 g %, BrAC was assessed 10 minutes later to allow further absorption. At that point, the assessment packet was administered. Following the assessment, participants were provided with a meal and were permitted to relax in the laboratory until their BrAC had dropped to below 0.04 g %, at which time they were provided with the dose reduction medication and transported home in a taxi. All individuals were compensated for their participation.

Data Analysis

All data were initially examined for distribution normality and outliers, and the psychophysiological data were examined for movement artifacts. Potential differences on dependent variables between conditions were examined using univariate analyses of variance (ANOVAs). Differences in side effects among the 3 groups were examined using Kruskal–Wallis H-tests and significant effects were clarified using follow-up chi-square tests. Consistent with Johnson et al. (2003), effects of topiramate during the titration period were examined on a weekly basis and titration effects were examined using 3 (PLA, 200 mg, 300 mg) × 4 (weeks 1 to 4) analyses of covariance (ANCOVAs), while covarying initial baseline values. Effects of topiramate were examined for weeks 1 to 4 only, because after week 4 participants' duration of enrollment varied, generating potentially nonrepresentative data. Topiramate's effects on alcohol cue reactivity were examined using 3 (PLA, 200 mg, 300 mg) × 3 (Water cues, Alcohol Cues 1, Alcohol Cues 2) mixed ANOVAs. Medication effects on reactions to alcohol were examined using one-way between-subjects analyses of covariance (ANCOVAs), while covarying pre-administration values and BrAC. For all analyses, planned follow-up pairwise comparisons and simple effects tests were conducted to characterize significant main effects and interactions. All analyses were conducted using SPSS 14.0 (SPSS, Inc., Chicago, IL, USA), using partial eta-squared (η_p^2) as an index of effect size, and a significance criterion of $p < 0.05$. Multiple-test error-correction was not employed because of the exploratory nature of this study.

RESULTS

Preliminary Analyses

Less than 1% of data were missing and no data were imputed. All dependent variables were normally distributed, without outliers. Movement artifacts were removed from the MAP and BPM data. Univariate ANOVAs revealed no differences between the conditions in terms of baseline values of drinking quantity and frequency measures or of other dependent variables. Of those participants who withdrew because of side effects, 4 were in the 300 mg condition, 1 was in the 200 mg condition, and 1 was in the placebo condition. No medication-related serious adverse events occurred.

According to MEMS data, all participants met the medication compliance criterion of taking 80% of their assigned medication, with a mean compliance rate of 96.5% (range = 82 to 100%) for the full duration of the study,

including the decreasing titration period. Of 41 participants randomized to active drug, 32 were verified as compliant by serum assay; samples from the remaining 9 participants hemolyzed in transit and were nonviable for analysis. The 300 mg group had significantly higher topiramate serum levels compared to 200 mg [200 mg $M = 4.45$ mcg/ml (SD = 1.41) vs. 300 mg $M = 6.98$ mcg/ml (SD = 2.16); F (1, 23) = 12.55, $p < 0.005$, $\eta_p^2 = 0.35$).

With respect to side effects once participants reached their target dose, significant main effects of medication condition were evident for dizziness (χ^2 [2, $N = 60$] = 7.00, $p < 0.05$), difficulty concentrating (χ^2 [2, $N = 60$] = 10.71, $p < 0.01$), and tingling in fingers and toes (χ^2 [2, $N = 60$] = 14.48, $p < 0.001$), which is similar to findings of Johnson et al. (2003). Dizziness was more frequent in the 300 mg group than the 200 mg group ($p < 0.05$). Likewise, difficulty concentrating was more frequent in the 300 mg group compared to PLA ($p < 0.05$). Tingling in fingers and toes was more frequent in the both topiramate groups compared to PLA ($p < 0.05$), but there was no difference between topiramate doses on this effect. No other differences between groups in side effects were present. At the conclusion of the study, no differences were evident across conditions in terms of dizziness and difficulty concentrating ($p > 0.20$), although the 2 topiramate groups reported residual mild tingling in fingers and toes significantly more than PLA ($p < 0.05$).

Effects of Topiramate During the Titration Period

The results of the 3 × 4 mixed ANCOVAs on the alcohol use (TLFB) and craving (OCDS subscales) variables are presented in Table 4. There was a significant topiramate × time interaction on drinks/week such that topiramate reduced drinking as dose increased (see Fig. 1). Follow-up simple effects tests indicated no significant differences between medication conditions at weeks 1 and 2, but differences were significant at weeks 3 and 4 ($p < 0.05$). At week 3, the 300 mg group reported significantly fewer drinks/week compared to the other groups ($p < 0.05$), which did not significantly differ from each other. At week 4, the 300 mg group reported significantly fewer drinks/week compared to PLA ($p < 0.01$), but not to the 200 mg group, and PLA and 200 mg were not significantly different from each other.

There was a significant main effect of topiramate and a significant topiramate × time interaction on percent heavy drinking days. Pairwise comparisons revealed that there was significantly less heavy drinking days in the 300 mg ($M = 29.83\%$, SE = 3.76%) and 200 mg ($M = 28.31\%$, SE = 3.87%) topiramate groups compared to PLA ($M = 41.80\%$, SE = 3.83%; $p < 0.05$), but there was no significant difference between active doses on this measure. The interaction effect and simple effects tests revealed no differences between groups at week 1, but significant differences emerged in weeks 2 to 4 (Fig. 1). At week 2, percent heavy drinking days for the 200 mg group were significantly lower than for both the 300 mg and PLA groups ($p < 0.05$), which
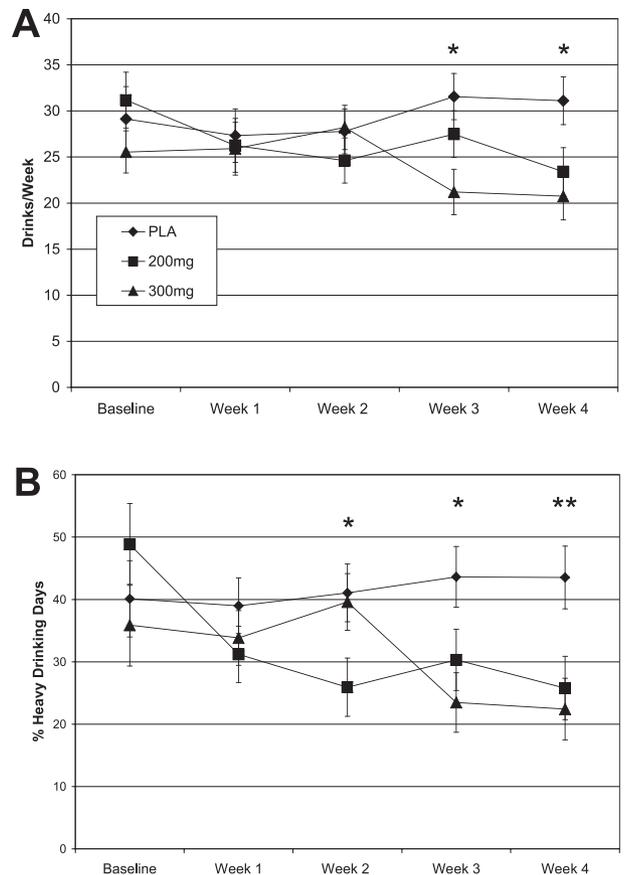
Fig. 1. Effects of topiramate on alcohol use over the course of the titration period for measures with significant interaction effects. Asterisks reflect follow-up simple effects tests; *$p < 0.05$, **$p < 0.01$. Specific comparisons between conditions at each time point are provided in the text.

were not significantly different from each other. At week 3, there were fewer percent heavy drinking days in the 300 mg group than the PLA group ($p < 0.01$) and a trend toward fewer heavy drinking days in the 200 mg group compared to the PLA group ($p = 0.06$), but the 2 medication groups were not significantly different from each other. At week 4, both medication groups reported fewer heavy drinking days than the PLA group ($ps < .05$), but were nonsignificantly different from each other.

With regard to craving during the titration period, no significant main effects of medication or time were evident for any of the craving variables (i.e., OCDS- Obsessions, OCDS-Automaticity of Drinking, OCDS-Interference from Drinking, and PACS), nor were there any interaction effects.

Effects of Topiramate on Reactions to Alcohol Cues

The 3 × 3 (medication condition × cue type) mixed ANOVA revealed a significant main effect of cue type on craving (F [2, 116] = 25.26, $p < 0.001$, $\eta_p^2 = 0.30$), but no effect of medication condition (F [2, 58] = 0.04), and no medication condition × cue type interaction (F [4, 116] = 0.89). The significant main effect of cue type reflected the characteristic

increase in craving during the alcohol cue exposure trials compared to the water cue exposure trial (ps < 0.001), but no differences were evident between the 2 alcohol exposure trials. Similarly, a main effect for alcohol cues was found on the AAS (F [2, 116] = 11.03, p < 0.001, η_p^2 = 0.16), with significantly greater attention paid to the alcohol cue exposure trials compared to the water cues (p < 0.001), but no difference between the 2 alcohol cue exposure trials on the attention scale. No effect of medication or medication condition × cue type interaction effect was evident for the AAS (ps > 0.67). In terms of effects on psychophysiological arousal, a significant main effect of alcohol cues on MAP was present (F [2, 114] = 7.52, p < 0.001, η_p^2 = 0.12), but no main effect of medication (F [2, 57] = 2.22, p = 0.12) or interaction effect (F [4, 114] = 1.83, p = 0.13) was observed. The significant effect reflected greater MAP during the alcohol cue exposure trials compared to the water cue exposure trial (ps < 0.005), but no difference between the 2 alcohol trials. For BPM, neither main effects nor a medication interaction were evident (ps > 0.12).

Effects of Topiramate on Reactions to Alcohol Ingestion

Participants' BrAC following the absorption period at the estimated peak was M = 0.08 g % (SD = 0.01), with no significant differences by gender or medication. Fifteen participants required 10 to 20 minutes of additional absorption time. The ANCOVA revealed a significant medication effect on postconsumption stimulation, F (2, 55) = 3.60, p < 0.05, η_p^2 = 0.12. Pairwise comparisons indicated that the 200 mg group, but not the 300 mg group, reported significantly lower stimulation compared to PLA (p = 0.01). No significant effects of medication condition were evident on postconsumption sedation (F (2, 55) = 2.21), urge to drink (F [2, 54] = 0.10), positive affect (F [2, 55] = 0.35), or negative affect (F [2, 54] = 0.86).

DISCUSSION

The goals of this preliminary study were to clarify the mechanisms of topiramate's effects in reference to drinking using several approaches. The results reveal a number of findings that converge with previous clinical and preclinical reports and several novel findings. Topiramate was generally well tolerated and significantly reduced drinking and heavy drinking over the course of the medication titration period, with results generally showing the strongest effect as the dose increased. These results were consistent with previous findings that topiramate treatment decreased drinking among individuals with alcohol dependence (Johnson et al., 2003; Raguraman et al., 2005; Rubio et al., 2004). Similarly, in preclinical research, chronic administration of topiramate to mice and rats has been demonstrated to result in decreased ethanol consumption and ethanol preference (Gabriel and Cunningham, 2005; Knapp et al., 2004; Nguyen et al., 2004).

There are a number of specific aspects of topiramate's effects on drinking that were interesting in this study. Topiramate did not affect participants' frequency of drinking, but rather how much they drank during an episode, as reflected by the largest effect being on percentage of heavy drinking days, similar to the findings by Johnson et al. (2003). In addition, significant decreases were clearly evident in both medication groups by the third week of the study, suggesting that doses of topiramate as low as 100 to 175 mg may be effective in reducing heavy drinking. Interestingly, effects were evident in the 200 mg group as early as the second week (75 mg), however, this was not the case for the 300 mg group. It is not clear why this discrepancy was observed, although it is possible that either an unmeasured pharmacogenetic variable associated with greater sensitivity to topiramate was disproportionately present in the 200 mg group, or that the result is a function of random variation. Both of these interpretations must be speculative at this point.

Changes in drinking were not accompanied by changes in weekly reports of craving for alcohol using validated self-report measures. This finding is consistent with observations from the laboratory portion of the study. Exposure to alcohol cues increased urge to drink and psychophysiological reactions, indicating the validity of the cue reactivity procedure. However, topiramate did not affect the subjective or physiological responses to alcohol cues. Similarly, during the alcohol administration procedure, topiramate did not affect urge to drink alcohol during a moderately intoxicated state (mean of 0.08 g% BrAC). Thus, in contrast with Johnson et al. (2003), the present findings do not suggest that topiramate exerts its beneficial effects on drinking outcomes by attenuating craving, at least not according to the measures and experimental paradigms employed.

There are a number of possible reasons why these data diverge from the previous study showing that topiramate reduced craving (Johnson et al., 2003). One possibility, as noted above, is that Johnson et al. (2003) combined data from both abstinent and non-abstinent people at each time point, confounding the craving measure. Also, it is unclear whether topiramate may have initially reduced alcohol use via a variable other than craving, and decreased drinking could have subsequently resulted in reduced desire for alcohol. Furthermore, the previous clinical trials studied treatment-seeking alcohol dependent individuals, who are clearly different from our nontreatment-seeking heavy drinkers (of whom 60% met criteria for an alcohol use disorder). Treatment-seeking individuals may be particularly motivated to experiencing reductions in their desire for alcohol and thus may be more sensitive to the effects of medication on craving than individuals who are not seeking treatment. Alternatively, if topiramate reduced drinking via an alternative mechanism, participants may have attributed those reductions to decreased desire. Although it is unclear which of these possible factors played a role, if any, what is clear is that in this study topiramate reduced drinking and did so in the

absence of effects on craving in each of the approaches used, suggesting alternative mechanisms of action.

Interestingly, suggestive findings were evident with regard to the effect of topiramate on alcohol's subjective effects. Topiramate significantly reduced the stimulating effects of alcohol ingestion, although this was restricted to the 200 mg group compared to placebo. These findings, albeit preliminary, suggest that in the current study topiramate may have affected subjective effects of alcohol consumption by attenuating its positively reinforcing properties, but only at the lower 200 mg dose. Such relationships would be consistent with our finding that topiramate reduced drinking quantity but not frequency, and with our interpretation that this effect reflects a reduction in the reinforcing effects of alcohol once drinking has begun.

There are, however, several reasons to be cautious about these results. As noted, the effect on stimulation only reflected a significant effect for the 200 mg group. In addition, the observed effects were of relatively small magnitude, suggesting that these findings per se are insufficient to fully explain the effects on drinking. Furthermore, topiramate's effect was only studied at estimated peak BrAC after 1 dose of alcohol. It is possible that topiramate has more pronounced effects at lower or higher blood-alcohol levels and it is also possible that focusing on topiramate's effects during the ascending or descending limb of the blood-alcohol curve may more precisely capture the medication's effects on experiential intoxication (Ray & Hutchison, in press; Ray et al., 2007). As such, the current findings are suggestive that topiramate may exert its impact via effects on the subjective effects of alcohol, but should be considered preliminary and supportive of the need for more fine-grained and extensive examinations of its effects on subjective intoxication.

This study had a number of limitations that should be considered. As a preliminary study, the sample size was relatively small, which resulted in statistical power to only detect moderate-to-large effect size effects. In addition, although the study sought to study topiramate's mechanisms more clearly than in previous clinical trials, its scope was nonetheless limited to 2 laboratory paradigms. As such, future studies would be well served to examine topiramate using alternative methodological approaches. Recent alcoholism pharmacotherapy studies have found that behavioral economic paradigms for assessing alcohol reinforcement (e.g., alcohol self-administration under conditions of cost) have proven to be very useful for understanding medication effects (e.g., Drobes et al., 2003; O'Malley et al., 2002). Importantly, behavioral economic measures of motivation objectively assess drug motivation but have only modest-to-moderate correlations with subjective craving (e.g., MacKillop et al., 2007; O'Malley et al., 2002; Sayette et al., 2001). Thus, such paradigms may be more sensitive to medication effects that are independent of subjective craving. In addition, because topiramate does not appear to have an acute effect on alcohol use at low doses but

more gradually reduces drinking (Johnson et al., 2003; Raguraman et al., 2005; Rubio et al., 2004), as was evident in this study, it would be informative to have fine-grained assessment of the processes that take place in initiating and sustaining those changes in future studies. Ecological momentary assessment, or close to real-time assessment in individuals daily life using structured or electronic daily diaries, has been profitably used in understanding the mechanisms of naltrexone (e.g., Armeli et al., 2006; Kranzler et al., 2004; Tidey et al., in press) and could be a promising approach for studying topiramate. Taken together, future studies that use larger sample sizes, additional experimental paradigms, and higher resolution assessment appear to be warranted.

A final consideration that is worthy of note pertains to the actual levels of drinking observed in the 2 topiramate groups. Although both groups exhibited significant decreases on multiple drinking variables, absolute drinking remained high (e.g., > 20 drinks/week). Indeed, clinically speaking, these individuals were still drinking at problematic levels. This underscores the essential role of motivation in changing excessive alcohol use. In its absence, although topiramate reduces alcohol use, its effects were not so robust as to reach healthy drinking levels. Recognizing this, it is likely that topiramate will best fit into a multifaceted clinical approach, where motivated individuals receive both psychosocial and pharmacological treatment.

Despite the various considerations of the methods and findings, the present findings are significant as the first human laboratory study to examine the biobehavioral mechanisms of topiramate's effects on drinking. The present findings suggest that while topiramate may not reduce the likelihood that an individual will drink, it may hold promise for reducing the likelihood that he or she will drink heavily. In this respect, the clinical praxis of topiramate pharmacotherapy may be similar to naltrexone (e.g., O'Malley et al., 1996; Rohsenow, 2004). Furthermore, the present findings do not support the notion that the effects of topiramate on drinking were a function of its effects on craving in the paradigms used. Rather, topiramate may exert its beneficial effects by altering the subjective experiences of alcohol ingestion, although this hypothesis requires further examination. Considerable further research is clearly necessary to understand the mechanisms underlying topiramate's effects on drinking.

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REFERENCES

American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision. American Psychiatric Association, Washington, D.C.

Anton RF, Moak DH, Latham P (1995) The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res 19:92–99.

Armeli S, Feinn R, Tennen H, Kranzler HR (2006) The effects of naltrexone on alcohol consumption and affect reactivity to daily interpersonal events among heavy drinkers. Exp Clin Psychopharmacol 14:199–208.

Beck AT, Steer RA, Brown GK (1996) Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX.

Bohn MJ, Barton BA, Barron KE (1996) Psychometric properties and validity of the obsessive-compulsive drinking scale. Alcohol Clin Exp Res 20:817–823.

Bohn MJ, Krahn DD, Staehler BA (1995) Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcohol Clin Exp Res 19:600–606.

Carter BL, Tiffany ST (1999) Meta-analysis of cue-reactivity in addiction research. Addiction 94:327–340.

Davidson D, Palfai T, Bird C, Swift R (1999) Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol Clin Exp Res 23:195–203.

Dodd PR, Beckmann AM, Davidson MS, Wilce PA (2000) Glutamate-mediated transmission, alcohol, and alcoholism. Neurochem Int 37:509–533.

Drobes DJ, Anton RF, Thomas SE, Voronin K (2003) A clinical laboratory paradigm for evaluating medication effects on alcohol consumption: naltrexone and nalmefene. Neuropsychopharmacology 28:755–764.

Drobes D, Anton R, Thomas SE, Voronin K (2004) Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res 28:1362–1370.

First MB, Gibbon M, Spitzer RL, Williams JBW (1995) User's guide for the Structured Clinical Interview for. DSM-IV Axis I Disorders (SCID-I, Version 2.0.). New York State Psychiatric Institute, Biometrics Research Department, New York.

Flannery BA, Allen JP, Pettinati HM, Rohsenow DJ, Cisler RA, Litten RZ (2002) Using acquired knowledge and new technologies in alcoholism treatment trials. Alcohol Clin Exp Res 26:423–429.

Flannery BA, Volpicelli JR, Pettinati HM (1999) Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res 23:1289–1295.

Gabriel KI, Cunningham CL (2005) Effect of topiramate on ethanol and saccharin consumption and preferences in C57BL/6J mice. Alcohol Clin Exp Res 29:75–80.

Hyman SE, Malenka RC (2001) Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2:695–703.

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roche JD, Lawson K, Javors MA, Ma JZ (2003) Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. Lancet 361:1677–1685.

Johnson BA, Ait-Daoud N, Roache JD (2005) The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field. J Stud Alcohol 15:157–167.

Johnson BA, Swift RM, Ait-Daoud N, DiClemente CC, Javors MA, Malcolm RJ (2004) Development of novel pharmacotherapies for the treatment of alcohol dependence: focus on antiepileptics. Alcohol Clin Exp Res 28:295–301.

King AC, Volpicelli JR, Frazer A, O'Brien CP (1997) Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. Psychopharmacology 129:15–22.

Knapp CM, Markley L, Ciraulo DA, Kometsky C (2004) Topiramate and zonisamide reduce the consumption of an ethanol-sucrose solution in the rat. Alcohol Clin Exp Res 28:59.

Kranzler HR, Armeli S, Feinn R, Tennen H (2004) Targeted naltrexone treatment moderates the relations between mood and drinking behavior among problem drinkers. J Consult Clin Psychol 72:317–327.

Levine J, Schooler N (1986) SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 22:343–381.

MacKillop J (2006) Factor structure of the alcohol urge questionnaire under neutral conditions and during a cue-elicited urge state. Alcohol Clin Exp Res 30:1315–1321.

MacKillop J, Menges DP, McGeary JE, Lisman SA (2007) Influences of craving and DRD4 VNTR genotype on the relative value of alcohol. Behav Brain Funct, 3: doi:10.1186/1744-9081-3-11.

Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM (1993) Development and validation of the Biphasic Alcohol Effects Scale. Alcohol Clin Exp Res 17:140–146.

McGeary JE, Monti PM, Rohsenow DJ, Tidey J, Swift R, Miranda R Jr (2006) Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res 30:1288–1296.

Monti PM, Binkoff JA, Zwick WR, Abrams DB, Nirenberg TD, Liepman MR (1987) Reactivity of alcoholics and nonalcoholics to drinking cues. J Abnorm Psychol 96:122–126.

Monti PM, Rohsenow DJ, Hutchison KE (2000) Toward bridging the gap between biological, psychobiological, and psychosocial models of alcohol craving. Addiction 95:S229–S236.

Monti PM, Rohsenow DJ, Rubonis AV, Niaura RS, Sirota AD, Colby SM, Abrams DV (1993) Alcohol cue reactivity: effects of detoxification and extended exposure. J Stud Alcohol 54:235–249.

Nguyen SA, DeLeon CP, Middaugh LD (2004) Topiramate effects on ethanol consumption by C57BL/6 mice. Alcohol Clin Exp Res 28:16A.

O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, Rounsaville B (1996) Six month follow-up of naltrexone and psychotherapy for alcohol. Arch Gen Psychiatry 53:217–224.

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ (2002) Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortial axis. Psychopharmacology 160:19–29.

Raguraman J, Priyadharshini KR, Chandrasekaran R (2005) Effects of topiramate in alcohol dependence. Aust N Z J Psychiatry 39:736–737.

Ray LA, Hutchison KE (2007) Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: A double-blind placebo-controlled study. Arch Gen Psychiatry 64:1069–1077.

Ray LA, Hutchison KE, MacKillop J, Miranda R Jr, Audette A, Swift R, Monti PM (2008) The effects of naltrexone during the descending limb of the blood alcohol curve. Amer J Addict, in press.

Rohsenow DJ (2004) What place does naltrexone have in the treatment of alcoholism?. CNS Drugs 18:547–560.

Rohsenow DJ, Howland J, Minsky SJ, Arnedt JT (2006) Effects of heavy drinking by maritime academy cadets on hangover, perceived sleep, and next-day ship power plant operation. J Stud Alcohol 67:406–415.

Rohsenow DJ, Monti PM, Abrams DB, Rubonis AV, Niaura RS, Sirota AD, Colby SM (1992) Cue elicited urge to drink and salivation in alcoholics: Relationship to individual differences. Adv Behav Re Ther 14:195–210.

Rohsenow DJ, Monti PM, Hutchison KE (2000) Naltrexone's effects on reactivity to alcohol cues among alcoholic men. J Abnorm Psychol 109:738–742.

Rubio G, Ponce G, Jimenez-Arriero MA, Palomo T, Manzanares J, Ferre F (2004) Effects of topiramate in the treatment of alcohol dependence. Pharmacopsychiatry 37:37–40.

Sayette MA, Martin CS, Wertz JM, Shiffman S, Perrott MA (2001) A multidimensional analysis of cue-elicited craving in heavy smokers and tobacco chippers. Addiction 96:1419–1432.

Sobell LC, Maisto SA, Sobell MB, Cooper AM (1979) Reliability of alcohol abusers' self-reports of drinking behavior. Behav Res Ther 17:157–160.

Staiger PK, White JM (1991) Cue reactivity in alcohol abusers: stimulus specificity and extinction of the responses. Addict Behav 16:211–221.

Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H (1994) Naltrexone-induced alternations in human ethanol intoxication. Am J Psychiatry 151:1463–1467.

Tidey JW, Monti PM, Rohsenow DJ, Gwaltney CJ, Miranda R Jr, McGeary JE, MacKillop J, Swift RM, Abrams DB, Shiffman S, Paty JA (2007) Moderators of naltrexone's effects on drinking, urge and alcohol effects in the natural environment. Alcohol Clin Exp Res 32:1–9.

Watson D, Clark LA, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 54:1063–1070.

Weiss F, Lorang MT, Bloom FE, Koob GF (1993) Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. J Pharmacol Exp Ther 267:250–258.

Weiss F, Porrino LJ (2002) Behavioral neurobiology of alcohol addiction: Recent advances and challenges. J Neurosci 22:3332–3337.

Wertz JM, Sayette MA (2001) A review of the effects of perceived drug use opportunity on self-reported urge. Exp Clin Psychopharmacol 9:3–13.