Use of Oral Topiramate to Promote Smoking Abstinence Among Alcohol-Dependent Smokers

A Randomized Controlled Trial

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Background: Previously, our group has shown that topiramate, a sulfamate-substituted fructopyranose derivative, is an effective treatment for alcohol dependence. Herein, we extend that proof-of-concept study by determining whether cigarette-smoking, alcohol-dependent individuals from the earlier study also experienced improved smoking outcomes.

Methods: As a subgroup analysis of a larger double-blind, randomized, controlled, 12-week study comparing topiramate vs placebo as treatment for alcohol dependence, a 12-week clinical trial compared topiramate vs placebo in 94 cigarette-smoking, alcohol-dependent individuals. Of these, 45 were assigned to receive topiramate (escalating dose from 25 to 300 mg/d) and the remaining 49 had placebo as an adjunct to weekly standardized medication compliance management. The primary outcome was smoking cessation ascertained by self-report and confirmed by the level of serum cotinine (nicotine’s major metabolite).

Results: Topiramate recipients were significantly more likely than placebo recipients to abstain from smoking (odds ratio, 4.46; 95% confidence interval, 1.08-18.39; \( P = .04 \)). Using a serum cotinine level of 28 ng/mL or lower to segregate nonsmokers from smokers, we found that the topiramate group had 4.97 times the odds of being nonsmokers (95% confidence interval, 1.1-23.4; \( P = .04 \)). Smoking cessation rates for topiramate recipients were 19.4% and 16.7% at weeks 9 and 12, respectively, compared with 6.9% at both time points for placebo recipients.

Conclusion: In this trial, topiramate (up to 300 mg/d) showed potential as a safe and promising medication for the treatment of cigarette smoking in alcohol-dependent individuals.

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Smoking is the primary cause of preventable death in the Western world.\(^1\) Studies assessing the relationship between alcohol dependence and smoking have suggested a strong connection between the two.\(^2\) In sample sizes ranging from 80 to 1142, surveys of both inpatient and outpatient treatment participants with alcohol dependence showed an 86% to 97% smoking rate among men, and 82% to 90% among women.\(^3,6\) More recently, Batel and colleagues\(^7\) noted a 92% prevalence rate of nicotine dependence among 325 outpatients attending an alcohol clinic who met Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria for both disorders. DiFranza and Guerrera,\(^8\) in a non-randomized case-control study of alcoholics who received no formal treatment for nicotine dependence, observed smoking cessation rates of 7% in the alcoholics and 49% in nonalcoholic controls. Thus, spontaneous smoking cessation is infrequent among alcohol-dependent individuals, and up to 75% of dually dependent individuals require simultaneous treatment for both dependencies.\(^9\)

Yet few alcohol treatment specialists consider smoking-cessation treatment for dually dependent patients. Despite the proposal that smoking cessation can trigger alcohol relapse among the dually dependent, contemporary studies show that smoking cessation treatment does not cause abstinent alcoholics to relapse\(^10\) and could reduce moderate to heavy drinking among those still consuming alcohol.\(^11\) Hence, treatment promoting smoking cessation among smokers within an alcohol-dependent population might decrease the likelihood of relapse to drinking.

Since individuals with co-occurring nicotine and alcohol dependence have a higher risk of mortality from smoking than
METHODS

SUBJECTS

From an original cohort of 150 men and women diagnosed as having alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, we identified 94 individuals who reported smoking 1 or more cigarettes per day at the time of enrollment. Subjects were not specifically recruited based on smoking history or a diagnosis of nicotine abuse or dependence. Subjects were 21 to 65 years old, scored 8 or higher on the Alcohol Use Disorders Identification Test14 (an assessment of personal and social harm consequent to alcohol consumption), and drank 21 or more (women) or 35 or more (men) standard alcohol drinks per week during the 90 days before enrollment. One standard drink was defined as 0.35 L of beer, 0.15 L of wine, or 0.04 L of 80-proof liquor. Subjects also had a negative urine toxicologic screen for narcotics, amphetamines, or sedative hypnotic agents at enrollment.

We excluded individuals who (1) had a current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition axis I psychiatric diagnosis other than alcohol dependence or nicotine abuse or dependence; (2) had clinically significant alcohol withdrawal symptoms or physical abnormalities precluding safe participation, including contraindications to the use of topiramate; (3) were compelled to receive alcohol treatment; (4) had undergone alcohol treatment within 30 days of enrollment; or (5) were pregnant or lactating. Abstinence from alcohol at study entry was not an enrollment criterion but a treatment goal.

We received ethical approval for this study from the institutional review board at The University of Texas Health Science Center at San Antonio. We recruited subjects between December 29, 1998, and April 11, 2001, by newspaper or radio advertisement.

GENERAL PROCEDURES

At week 0 (baseline), after obtaining written informed consent, we established that subjects were physically healthy by taking their medical history and performing a physical examination, electrocardiogram, urinalysis, liver and renal function blood tests, and complete blood count. All women received a urine pregnancy test to confirm that they were not pregnant. Among other measures, we collected self-reported smoking and drinking data for the 90 days before enrollment using the timeline follow-back (TLFB) method,13 a technique that uses a calendar and memory aids to facilitate retrospective estimates of daily drinking over a specified period. In addition, as an objective measure of smoking cessation, we assessed the level of serum cotinine, the primary metabolite of nicotine, using a radioimmunoassay kit from Diagnostic Products Corporation (Los Angeles, Calif).16 As this study was not designed from the outset specifically to measure smoking behavior, we did not collect breath carbon monoxide level or ascertain nicotine withdrawal status, nor did we set a target quit date for smoking cessation.

Eligible subjects were enrolled at the beginning of week 1 following a review of the hematology, biochemical, and urine tests. We also assessed subjects on safety measures including vital signs, weight, adverse events,17 and concomitant medication use. The TLFB method was used to quantify self-reported smoking and drinking. From the beginning of week 1 to week 12, in a double-blind procedure, medication (placebo or 25-300 mg/d of topiramate) was dispensed according to the dose-escalation schedule summarized in Table 1 as an adjunct to weekly brief behavioral compliance enhancement treatment (BBCET).

We collected weekly self-reported smoking and drinking data using TLFB from weeks 2 to 12; serum cotinine levels at weeks 3, 6, 9, and 12; and safety and other outcome measures at scheduled intervals. Hematologic, biochemical, and urine drug screens were reevaluated at weeks 6 and 12. Physical examination was repeated at weeks 3, 7, and 11, along with an electrocardiogram at week 12. Study weeks were interspersed by a maximum of 11 days (from Monday of the previous week to Friday of the current week).

Topiramate and matching placebo tablets, supplied by Ortho-McNeil Pharmaceutical Inc (Raritan, NJ), were administered in equal numbers for each group, with the topiramate dose stabilized at the highest dose of 300 mg/d from weeks 8 to 12. Tablets were dispensed in blister packs labeled with identification, study and visit numbers, and date. The returned packs at each weekly visit, as well as the calendar-based pill-taking schedule, were used to calculate pill count and monitor compliance.13

As an aid to medication compliance, all participants received weekly BBCET, delivered as a 15- to 20-minute session emphasizing that the medication and compliance with the medication were the critical elements for changing the participant’s drinking behavior. There was no mention of smoking during BBCET sessions. While BBCET is a minimal intervention, it is clearly not a “no treatment” condition. It is a development of the clinical management condition in the National Institute of Mental Health collaborative trial on depression—essentially

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*This dose-escalation schedule is similar to that provided in the Physicians’ Desk Reference, 54th ed, 2000.
†All medications were administered as tablets; numbers in parentheses indicate the number of tablets administered. The placebo and topiramate groups received the same number of tablets; placebo tablets were inactive.

12 From alcohol-related adverse health consequences,12 an effective pharmacologic agent for treating alcoholism that also promotes smoking cessation would be of greater scientific and clinical value than a medication treating alcohol dependence alone.

Previously, our group showed that up to 300 mg/d of topiramate, a sulfamate-substituted fructopyranose derivative, compared with placebo, significantly increased abstinence from alcohol among alcohol-dependent individuals.13 In the present report, as an extension of that proof-of-concept study, we examine whether topiramate, compared with placebo, significantly increased smoking abstinence among cigarette-smoking, alcohol-dependent individuals from the earlier study.
a compliance management intervention as well received as formal psychotherapies.18

**OUTCOME MEASURES**

Two outcome measures were used to quantify smoking: (1) weekly self-reported cigarette smoking (yes and amount, or no) using TLFB and (2) serum cotinine level at weeks 0, 3, 6, 9, and 12. The serum cotinine cutoff level was 28 ng/mL. Saliva, plasma, and serum levels have been shown to be interchangeable.19,20 Miller et al11 reported that the mean ± SEM cotinine level for tobacco users (294 ± 71 ng/mL) significantly differed from that of non–tobacco users (7.41 ± 2.6 ng/mL; P < .001). The range in salivary cotinine levels for the tobacco users (30.9–478 ng/mL) did not overlap that of the non–tobacco users (0.45–23.14 ng/mL). The level of 28 ng/mL falls between these 2 groups. While the Society for Research on Nicotine and Tobacco Subcommittee on Biochemical Verification19 and Sec- 

careccia et al20 have both recommended, based on large general population surveys, that a lower cutoff level of cotinine (15 ng/mL) be used for saliva, serum, or plasma samples, both reports also state that the most accurate cutoff levels may vary depending on the characteristics (including ethnic mix) of the population tested. Thus, we determined our cutoff level (1) based on the observation from this study that the maximum serum cotinine level seen in a nonsmoker was 28 ng/mL and (2) in consideration of the published reports.10–21

We also collected self-reported drinking data to calculate the weekly percentage of days abstinent (number of nondrinking days divided by the number of study days) as well as number of drinks per drinking day (total number of standard drinks divided by the number of days on which drinking occurred), a measure of drinking severity.

**STATISTICAL ANALYSIS**

Data management was conducted according to Food and Drug Administration guidelines of Good Clinical Practice. Data quality (including double-data entry) was supervised by a database coordinator and statistician. Individual subject plots were checked for unusual values and completeness. Efficacy values were validated as correct against case records. Data were analyzed using SAS software, version 8.1 (SAS Institute Inc, Cary, NC). The outcome measures analyzed were binary cotinine levels and self-reported abstinence from smoking.

We restricted all analyses to the drug intervention period and adjusted for baseline data in all models. We used logistic regression in the generalized estimating equations context to account for within-subject correlation due to repeated measures and to model the probability of nonsmoker status using cotinine levels and the probability of self-reported abstinence from smoking. We estimated odds ratios (ORs) and corresponding confidence intervals (CIs) to estimate treatment differences, and did tests of hypothesis of no treatment effect. All models were adjusted for baseline cotinine or cigarette smoking, age at problem drinking onset, sex, and body mass index (calculated as the weight in kilograms divided by the height in meters squared).

We first used main effects models adjusting for covariates for both of the outcome measures. In the main effects models for binary cotinine levels, we also adjusted for baseline percentage of heavy drinking days. We examined the relationship between abstinence from smoking and abstinence from drinking with an interaction model consisting of the longitudinal percentage of days abstinent and treatment interaction. This model estimated the difference and direction of the percentage of the change in abstinence from cigarette smoking with the percentage of the increase in abstinence from alcohol consumption.

Finally, we estimated partial correlations to investigate further the linear relationship between smoking (continuous serum cotinine levels and cigarettes per day) and alcohol abstinence (percentage of days abstinent), adjusting for baseline covariates. We also adjusted for study weeks to account for the within-subject effect.

**RESULTS**

**SUBJECTS**

Ninety-four (63%) of the 150 randomized alcohol-dependent individuals also self-reported being current smokers. Demographic and psychopathologic characteristics of cigarette-smoking, alcohol-dependent individuals were similar for both the placebo (n = 49) and topiramate (n = 45) groups (Table 2).

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**Table 2. Demographic and Psychopathologic Characteristics of Cigarette-Smoking, Alcohol-Dependent Individuals***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Topiramate (n = 45)</th>
<th>Placebo (n = 49)</th>
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<td>14 (29)</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

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*Where no units are indicated, data are reported as number (percentage) of subjects; for specified units, mean (SE) values are given.
†Defined by Hollingshead and Redlich.22
‡Baseline nicotine days is the number of days on which cigarettes were smoked in the past 90 days.
§Calculated as the weight in kilograms divided by the height in meters squared.
OUTCOME MEASURES

Main effects repeated-measures analyses restricted to the drug intervention period revealed that the OR for achieving self-reported abstinence from smoking in the topiramate vs placebo group was 4.46 (95% CI, 1.08-18.39; P=.04). The Figure displays the percentage of nonsmokers in the topiramate and placebo groups across the trial period. Based on dichotomized serum cotinine level, individuals in the topiramate group, compared with those in the placebo group, had 4.97 times the odds of being categorized as nonsmokers (95% CI, 1.1-23.4; P=.04).

The interaction model examining the relationship between smoking and drinking showed a significant treatment differential in the slopes of the percentage of drinking abstinence and smoking abstinence. We estimated that a 1% increase in drinking abstinence leads to an increase of 4% in the odds of smoking abstinence in the topiramate group compared with the placebo group (OR, 1.04; 95% CI, 1.01-1.06; P=.02).

For those who received topiramate, the partial correlations were as follows: (1) between cigarettes per day and percentage of days abstinent, −0.24 (P=.01); (2) between serum cotinine and percentage of days abstinent, −0.29 (P=.004); and (3) between cigarettes per day and serum cotinine, +0.62 (P<.001). In contrast, placebo recipients had the following partial correlations: (1) between cigarettes per day and percentage of days abstinent, +0.28 (P=.003); (2) between serum cotinine and percentage of days abstinent, +0.2 (P=.04); and (3) between cigarettes per day and serum cotinine, +0.2 (P=.04).

With respect to medication compliance, the mean (SE) percentages of pills taken (ratio of number of pills taken to the number of pills given in a study week) were similar for the topiramate and placebo groups: 91.4 (1.0) and 91.7 (0.8), respectively. Mean topiramate dose at week 12 was 279.2 mg.

Adverse events were typically rated as mild or moderate, and all resolved without specific medical intervention. No serious adverse events occurred. The 5 adverse events reported more frequently in the topiramate group than in the placebo group were: (1) dizziness, 9 (20%) vs 5 (10%) (P=.25); (2) paresthesia, 29 (64%) vs 9 (18%) (P<.001); (3) psychomotor slowing, 10 (22%) vs 7 (14%) (P=.42); (4) memory and/or concentration impairment, 7 (16%) vs 2 (4%) (P=.08); and (5) weight loss, 20 (44%) vs 9 (18%) (P=.008).

The mean study completion rate was 62.9% for both groups, with no significant difference between them. Reasons for discontinuation also did not differ between groups and were related to being lost to follow-up (19.1%), patient choice (10.6%), adverse events (5.3%), and non-compliance (2.1%). The average weight change at week 12 from baseline was −4.75 kg and +0.24 kg (mean difference, −5.00 kg; P=.02) in the topiramate and placebo groups, respectively.

COMMENT

The reinforcing effects of nicotine and alcohol associated with abuse liability are mediated principally through corticomesolimbic dopamine pathways. Topiramate might antagonize these reinforcing effects by modulation of corticomesolimbic dopamine function. As members of our group have proposed, topiramate might exert this antideropaminergic action by simultaneously facilitating the actions of the inhibitory neurotransmitter γ-aminobutyric acid through a nonbenzodiazepine receptor site and antagonizing the excitatory effects of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate glutamate receptors on A10 dopaminergic neurons at the cell body and nucleus accumbens. Topiramate might, therefore, be a promising agent for the treatment of both nicotine and alcohol dependence.

Our results show that topiramate is significantly superior to placebo at improving the smoking outcomes of cigarette-smoking, alcohol-dependent individuals. The robustness of topiramate’s treatment efficacy is exemplified by the fact that smoking cessation was not a goal of the present study, and no specific measures, advice and/or counseling, or targets were provided to help the participants quit smoking; thus, the improvements in smoking rate represent a naturalistic change in behavior. Self-reported smoking abstinence rates were also corroborated independently by biochemical measurement of serum cotinine level.

We considered the possibility that the observed antismoking effects were simply a reflection of decreased drinking rather than an independent effect of topiramate on smoking. While the drinking reductions probably contributed to the antismoking effects, there are 5 reasons why this phenomenon cannot entirely explain these findings. First, the magnitude of the averaged treatment response for topiramate on smoking was about the same as that observed for drinking. This magnitude of effect of topiramate on smoking, if replicated, would approach or surpass that of other currently available pharmacologic agents.

Second, while cigarette consumption and serum cotinine levels lessened as individuals became more abstinent in the topiramate group, in contrast, increasing ab-
stinentence from alcohol was associated with greater consumption of cigarettes and higher serum cotinine levels for the placebo group. These findings, although we did not test this directly, would support the premise that topiramate recipients experienced a specific antismoking effect for topiramate, whereas placebo recipients might have compensated for drinking less by smoking more.

Third, in clinical trials among smokers who are dependent on alcohol, using compounds found to be effective pharmacotherapy for alcohol dependence (eg, naltrexone and acamprosate), little evidence has emerged either for significant reductions in smoking or for drinking reductions to be paralleled by diminutions in smoking.26,29

Fourth, no effective pharmacotherapy for alcohol dependence (including naltrexone) has been established as an effective smoking cessation aid among those dependent solely on nicotine.30 Thus, it is unique for an effective pharmacotherapy for alcohol dependence also to have a strong antismoking effect.

Finally, there is intriguing evidence that the use of an effective smoking-cessation agent—eg, the nicotine patch—significantly improves smoking cessation rate, regardless of comorbid alcohol dependence. However, among smokers who also were dependent on alcohol, increased sobriety did not affect smoking outcomes or response to nicotine replacement.10 Hence, the antismoking potential of an effective pharmacotherapy might be more dependent on its direct antismoking pharmacologic effects than on an associated reduction in smoking to parallel a reduction in drinking.

There are, however, 6 limitations that should be considered when appraising the results of this study. First, because we did not plan at the outset of the trial to study smoking behavior formally, some assessment measures that would have enabled fuller characterization of the population on smoking history and outcome (eg, breath carbon monoxide level or nicotine withdrawal) were not included in the design. Indeed, our ability to determine cotinine level was only possible because we had additional serum available. Serum cotinine was, therefore, examined as a dichotomous variable to categorize smoker vs nonsmoker status (>28 vs ≤28 ng/mL, respectively). Hence, it remains to be elucidated what type of alcohol-dependent smoker responds to topiramate and whether topiramate ameliorates nicotine withdrawal.

Second, we could only include cigarette smokers because this was the only validated measure of nicotine consumption that could be collected using TLFB. Thus, topiramate’s effects on those consuming nicotine through means other than cigarettes in an alcohol-dependent population remain unknown.

Third, because we did not have a follow-up period, the extent to which topiramate’s antismoking effects were maintained following treatment could not be determined.

Fourth, because this study specifically excluded individuals with comorbid axis I psychiatric disorders, the results might not generalize to this population.

Fifth, because of our relatively small sample size, we had to be conservative in deciding which inferential tests to perform to conserve statistical power. In addition, because of the relatively small cohort compared with the overall trial sample,13 many of the differences in the frequency of adverse events between the topiramate and placebo groups did not achieve statistical significance.

Finally, it could be argued that our 12-week trial period was relatively short; thus, longer-term testing is warranted to replicate our findings.

In summary, these results demonstrate topiramate’s potential as a safe and promising medication for treating alcohol-dependent cigarette smokers. This finding should garner scientific interest because no medication has been established as an effective treatment for comorbid alcohol and nicotine dependence.

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REFERENCES


