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A Randomized Trial Evaluating Whether Topiramate Aids Smoking Cessation and Prevents Alcohol Relapse in Recovering Alcohol-Dependent Men

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Abstract

Background—Alcohol and nicotine dependence frequently co-occur, and quitting smoking might enhance long-term alcohol abstinence. Topiramate appears to help non-alcohol-dependent individuals quit smoking, and our pilot work suggested efficacy only in men. It also prevents relapse to alcohol in recently detoxified alcoholics. We evaluated topiramate in abstinent alcohol-dependent men to assess whether this medication (i) promotes smoking cessation and (ii) prevents alcohol and other drug relapse in the context of smoking cessation treatment.

Methods—One hundred and twenty-nine alcohol-abstinent (mean ~6 months) alcohol-dependent male smokers (80% with other substance use disorders) participated in this 12-week randomized, double blind, parallel group comparison of topiramate (up to 200 mg/d) and placebo with a 24-week non-treatment follow-up period. The study was carried out sequentially at 2 academic centers in the Midwest and Southern California between March 23, 2009 and November 20, 2014. All participants received manual-guided smoking cessation counseling combined with medication-focused compliance enhancement therapy. Randomization was block designed by the research pharmacist in a 1:1 ratio. Participants, investigators, and research personnel were masked to treatment assignment. The primary smoking end point was biochemically confirmed 4-week continuous abstinence from smoking during weeks 9 to 12, while the secondary end point was relapse to any drinking or drug use during the entire 36-week evaluation period. Logistic regression was used to determine the effects of topiramate on quitting smoking and alcohol

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relapse, controlling for relevant covariates. The trial is registered at ClinicalTrials.gov (number NCT00802412) and is now closed.

Results—Only a small proportion (7.9%) of topiramate-treated participants were able to quit smoking, and this cessation rate was similar to placebo (10.6%; odds ratio = 1.60; 95% confidence interval 0.4, 6.5; $p = 0.51$). Roughly 30% of the sample had a documented relapse to drinking or drug use during the study, and these rates were similar in the topiramate (20/63; 31.8%) and placebo groups (18/66; 27.3%; $p = 0.58$). Results of a longitudinal logistic regression model examining time to any alcohol relapse revealed no medication effect.

Conclusions—Topiramate at a daily dosage of up to 200 mg per day, combined with smoking cessation and medication adherence counseling, had no effects on smoking cessation or the prevention of alcohol or drug relapse in male smokers who were in early or sustained full remission from alcohol and motivated to make a quit attempt. Alternative approaches for treating this high-risk, dually dependent population are needed.

Keywords

Smoking Cessation; Topiramate; Relapse Prevention; Nicotine; Alcohol

While rates of smoking have declined in the general population, recovering alcohol-dependent individuals continue to smoke cigarettes at alarmingly high rates, have more difficulty maintaining smoking abstinence, and are at increased risk for tobacco-related diseases and death compared with nonalcoholic smokers (Heffner et al., 2007; Prochaska et al., 2004). Controversy exists as to the best way to treat these dually dependent smokers (Joseph et al., 2004), and to date, no single medication has been found that can both aid smoking cessation and prevent relapse to alcoholism in this high-risk population.

Nicotine and ethanol act synergistically to enhance reward in the brain's mesolimbic dopamine reinforcement circuit, in part, by imbalancing excitatory glutamatergic and inhibitory GABAergic inputs on dopamine neurons in favor of excitation (Doyon et al., 2013). Preclinical studies have found that the Food and Drug Administration-approved antiepileptic medication, topiramate, reduces nicotine-induced dopamine release in the nucleus accumbens, presumably through its GABA-facilitatory and glutamate-inhibitory effects (Schiffer et al., 2001). A preliminary study conducted by some of the authors found that topiramate enhanced short-term smoking cessation rates and reduced nicotine withdrawal and postcessation weight gain in male nonalcoholic smokers (Anthenelli et al., 2008). Others have reported similar short-term effects in nonalcoholic (Oncken et al., 2014) and alcoholic smokers (Johnson et al., 2005), and there is compelling evidence that topiramate reduces heavy drinking in alcoholics (Blodgett et al., 2014), at least among those carrying a specific glutamate receptor subunit genotype (rs2832407*CC) in *GRIK1* (Kranzler et al., 2014). However, no information is available regarding whether topiramate will both (i) promote tobacco abstinence and (ii) maintain alcohol abstinence in a dually dependent, treatment-seeking population.

The primary objective of this study was to determine the extent to which topiramate aids smoking cessation in dually dependent alcoholic men motivated to quit smoking. We

hypothesized that men receiving topiramate combined with standardized smoking cessation counseling would have a higher 4-week continuous smoking abstinence rate at the end of treatment (weeks 9 to 12) compared with alcoholic smokers receiving placebo and counseling. A secondary goal was to explore whether or not topiramate reduces relapse to alcohol and drug use in patients with comorbid alcohol and nicotine dependence. We hypothesized that recovering alcoholic men receiving topiramate combined with a standardized psychosocial intervention would have reduced rates of relapse to any drinking or drug use during the trial compared with alcohol-dependent subjects receiving placebo and counseling.

Materials and Methods

Study Design

This was a phase 2, 2-site (sequential), parallel, randomized controlled study designed to assess the efficacy and safety of 12 weeks of treatment with topiramate, up to 100 mg twice daily, or placebo in a 1:1 allocation ratio for smoking cessation, with 24 weeks of nontreatment follow-up. Following a 6-week medication titration period, participants set a target quit date (TQD) on day 43 that coincided with the start of the 6-week maintenance phase of the study medication as illustrated in Fig. 1.

Study Participants

Adult male smokers in early or sustained full remission (abstinent 1 to 36 months) from alcohol dependence who were motivated to quit smoking and remain abstinent from alcohol and other drug use were recruited from local Veterans Affairs (VA) medical centers, recovery homes, and the general community via fliers and advertisements. After undergoing a telephone screening procedure and providing written informed consent, participants underwent a face-to-face screening and diagnostic assessment to determine their eligibility for the trial. Institutional Review Board approval was obtained from the University of Cincinnati Medical Center and Cincinnati VA Medical Center Research and Development (R&D) Committee and from the University of California, San Diego, Human Research Protections Program, and VA San Diego Healthcare System Institutional Review Board and R&D Committee. Diagnostic screening interviews were performed on 203 men between March 2009 and September 2011 in Cincinnati and between August 2012 and April 2014 in San Diego in this 2-site, randomized clinical trial.

Eligible participants were between 18 and 70 years of age, smoked an average of ≥10 cigarettes per day in the 2 months prior to randomization, were motivated to try to quit smoking based on scoring ≥ 6 on a 10-point Likert scale assessing motivation to make a quit attempt, and had a body mass index ≥18.5 kg/m^2. Participants were excluded if they had a serious and unstable medical condition within the past 6 months; if they used tobacco products other than cigarettes; or if they had made a serious quit attempt with a nicotine replacement therapy, sustained-release bupropion, varenicline, or a formal nonpharmacological therapy for smoking cessation in the 30 days before study inclusion. Other exclusion criteria were a current seizure disorder or a history of severe alcohol withdrawal; lifetime history of a psychotic disorder; and prior adverse reactions to

topiramate. Participants with positive urine toxicology screens (except for cannabis, in which case a repeat negative test prior to randomization was allowed) were excluded, as were those with a medical history (e.g., kidney stones, glaucoma) that increased the risks of topiramate or if they were taking medications (i.e., carbonic anhydrase inhibitors) that might interact with topiramate.

Procedures and Assessments

Participants completed a core battery of diagnostic assessments at the screening and randomization visits to determine their eligibility for enrollment and to obtain baseline smoking and clinical characteristics. A trained research assistant administered the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994) to characterize current and lifetime substance use and psychiatric disorders. All participants completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Current depressive symptom severity was assessed with the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), and alcohol dependence severity over the past 12 months was assessed with the Alcohol Dependence Scale (Skinner and Allen, 1982). Cravings to smoke were measured with the Questionnaire on Smoking Urges-Brief (QSU-Brief) (Cox et al., 2001). The QSU-Brief and MADRS were also administered at weeks 4, 8, and 12 postrandomization. At each weekly visit, participants underwent expired carbon monoxide (CO) breath monitoring. Participants were asked to complete a daily diary of their smoking, and to rate their symptoms of tobacco withdrawal using the modified Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986). A physical examination, electrocardiogram, and laboratory testing (complete blood count, chemistry panel, liver function tests) were also performed. As part of the safety evaluation, liver function tests and electrolytes that included serum levels of bicarbonate were obtained at weeks 4, 8, and 11 postrandomization.

At each weekly visit, participants' smoking diary cards and MNWS ratings were reviewed and CO monitoring was performed. Adherence to study medication was recorded using pill counts of the returned bottles and by reconciling those with the self-reported number of pills taken which were recorded daily on the diary cards. Volunteered, spontaneously reported, or observed treatment-emergent adverse events and concomitant medications were assessed weekly and recorded.

Interventions

Participants were randomly assigned to receive either topiramate up to 200 mg daily in divided doses or placebo orally over a 12-week period. To improve the tolerability of the medication, active drug/placebo was titrated up gradually over the course of 6 weeks, first in 25 mg increments (weeks 1 to 4), and then in 50 mg increments (weeks 5 to 6), as described in our prior work (Anthenelli et al., 2008). A 1-week titration downward period occurred after week 12 (see Fig. 1).

The TQD was set for day 43, 1 week after participants were to have achieved a steady state concentration of topiramate at a maximum dosage of 200 mg/d. Participants were not prohibited from trying to quit prior to this date, but the weekly counseling sessions prepared

the participants to try to stop smoking on the TQD. Participants who could not tolerate the maximal dosage of 200 mg/d were allowed to take lower dosages of the medication. Those discontinuing treatment prematurely were encouraged to complete all study visits or, at a minimum, to return for a closeout visit to obtain final efficacy and safety data.

All study participants received a version of *Clearing the Air: Quit Smoking Today* (U.S. Department of Health & Human Services, 2003)—the National Cancer Institute's smoking cessation self-help booklet—that had been edited by the investigators to remove advice on using other pharmacotherapies, which were prohibited during the trial. A brief (≤10-minute), manual-guided, individual counseling was provided to all study participants at each weekly visit based on the principles outlined in *Clearing the Air*. This Brief Intervention for Smoking Cessation was embellished by adding on treatment adherence counseling that used compliance enhancement therapy (Carroll et al., 1999).

Randomization and Masking

Participants were randomized to receive maximal target dosages of topiramate 100 mg twice daily or placebo in a 1:1 ratio. Study medications were dispensed in pill bottles containing masked capsules. A research pharmacist, independent from the clinical study team, prepared the computer-generated randomization schedule used to assign participants to treatment using a block size of 8 (1:1 ratio). Study product codes did not allow deciphering of randomized treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignments.

Study End Points

In keeping with guidelines implemented by the FDA and used widely in evaluating potential aids to smoking cessation, the primary efficacy end point was a minimum of 4 weeks of CO-confirmed (≤10 ppm) continuous abstinence (i.e., not even smoking a puff) for weeks 9 through 12. As recommended by the Society for Research on Nicotine and Tobacco (Hughes et al., 2003), this allowed participants a grace period following the TQD. A secondary smoking end point was 7-day point prevalence smoking abstinence from weeks 8 to 12.

Statistical Analysis

A sample size of 55 participants per group was estimated as providing 80% power for a 2-tailed χ^2 test with a 5% significance level for the comparison between topiramate and placebo. We hypothesized a 20% difference in 4-week prolonged abstinence between the groups based on hypothesized abstinence rates of 5 and 25% in the placebo and active medication groups, respectively. These hypothesized abstinence rates were based on (i) our expectation that quit rates would be uniformly lower in these alcohol- and other drug-dependent men than we observed in our preliminary study of nonsubstance abusing male smokers (Anthenelli et al., 2008); (ii) a consideration of the spontaneous quit rates observed in Johnson and colleagues (2005) secondary analysis of alcohol-dependent smokers who received topiramate for treatment of alcohol dependence; and (iii) a published meta-analysis of smoking cessation intervention in patients with substance use disorders (Prochaska et al., 2004). Finally, given the nature of this feasibility trial, there were practical cost considerations that influenced the study design and sample size.

The modified intent-to-treat (ITT) population was defined as all randomized participants who took at least 1 dose of study medication and for whom 1 postbaseline efficacy measurement was available. Members of the ITT population who did not complete the study were considered as smokers in the primary analysis. Participants who missed 1 visit during the last 4 weeks (weeks 9 to 12) of the trial were considered abstinent only if they had CO-confirmed abstinence before and after the missing visit and also had self-reported continuous abstinence during this time period.

Relapse to alcohol or other drug use was determined by participant self-report, positive urine drug testing/breathalyzer, or collateral informant report (e.g., notes documented in the electronic medical record, reports from contact persons), but missingness was not imputed as relapsed. These data were missing for 21 (16%) of participants. We used binary logistic regression to test for differences between treatment groups in terms of any relapse (i.e., to alcohol and/or drugs). Cox regression was used to evaluate treatment group differences in time to alcohol/drug relapse.

Baseline group comparisons on demographic, clinical, and smoking characteristics for categorical and continuous variables were evaluated using χ^2 tests or Fisher's exact tests and 1-way analyses of variance, respectively. CO-confirmed continuous abstinence rates (CAR) for weeks 9 through 12 were analyzed using logistic regression. Weekly point prevalence smoking abstinence rates over time from TQD through the end of follow-up (weeks 6 to 36) were analyzed via longitudinal logistic regression using generalized estimating equations (GEE). The initial GEE model included terms for time, time^2, and their interactions with treatment group. Nonsignificant terms were removed in a backward manner and the model was refit. In contrast to the primary CAR analysis, no assumptions were made about missing smoking status data in the GEE model. Attrition resulted in levels of missing data for smoking outcomes that increased over time; 37% of cases had missing smoking data at the end of treatment, and 54% were missing at the final follow-up visit. Little's test (Little and Rubin, 2002) suggested that data were missing at random. To account for the potential bias that missingness may introduce, multiple imputation of chained equations (White et al., 2011) was used to impute missing values, generating 20 data sets containing imputed values. The imputation model included all variables from the primary hypothesis tests (i.e., variables shown in Table 3), as well as time × treatment group and time^2 × treatment group. The presence of psychiatric and substance use disorder diagnoses other than alcohol and nicotine dependence, and baseline scores on the FTND were also included. Convergence was assessed by examining autocorrelation plots for each imputed variable. For all imputed variables, the correlation approached 0 (i.e., <0.05) by the 20th iteration. Both the logistic model of CAR and the GEE model of point prevalence abstinence were re-fit using these imputed data.

Potential predictors of abstinence (e.g., age, race, concomitant use of psychotropic medications, nicotine, and alcohol dependence severity score) were considered along with treatment group in a logistic regression model.

Exploratory analyses of changes from baseline through week 13 in craving, depression, and tobacco withdrawal were conducted using longitudinal mixed-effects regression. Safety data

were summarized using frequency tables, and adverse events incidence comparisons were evaluated using χ^2 tests. For these outcomes, the rates of missing data were 0% at baseline, 14% at week 6, 28% at week 10, and 34% at week 13.

Results

As illustrated in Fig. 2, of 203 men screened between March 23, 2009 and April 9, 2014, in Cincinnati ($N = 81$) and San Diego ($N = 122$), respectively, 133 completed the randomization visit. Four men did not return for their next visit and had no evidence to indicate that they had taken at least 1 dose of study medication, and thus, 129 smokers comprised the modified ITT sample. Treatment discontinuation rates and reasons for doing so were similar between the groups, with 65.9% of participants completing the 12-week active treatment phase. Overall study completion was similar across the groups, with less than half (46.5%) of study participants completing the full 9-month study.

Baseline demographics and rates of current smoking were similar between the groups; however, placebo-treated participants were more severely nicotine dependent than smokers in the topiramate group (see Table 1). Alcohol and other drug use characteristics, histories of comorbid psychiatric disorders, and use of concomitant psychotropic medications were similar between groups. In keeping with the primarily male Veteran population from which the majority (62%) of participants were drawn, rates of drug co-addiction (80%) and psychiatric comorbidity (43.4%) were high, and more than three-quarters of study participants were residing in controlled sober living environments at study entry.

Smoking Outcomes

Four-week, CO-verified, CAR during weeks 8 to 12 were generally low (9.3%) in this dually dependent population. Only 7.9% (5/63) of topiramate-treated participants were able to quit using this metric compared with 10.6% (7/66) of those on placebo. The logistic model is shown in Table 2; there was no significant difference between topiramate and placebo (odds ratio [OR] = 1.60; 95% confidence interval [CI] 0.39, 6.53; $p = 0.510$). The odds of CAR were also unrelated to site of enrollment (Cincinnati vs. San Diego), age, race, baseline smoking rate, depression score, alcohol dependence severity, or residing in a controlled sober living environment. Similarly, when the model was re-fit using imputed data, neither treatment condition (OR = 0.76 [0.06, 15.33], $p = 0.855$) nor any covariates were significantly associated with smoking abstinence.

Figure 3 depicts weekly point prevalence abstinence rates during the maintenance phase (weeks 6 to 12) of the trial when most participants had stabilized on the 200 mg/d dose target and the subsequent follow-up phase (weeks 13 to 36). These data were analyzed with GEE with results shown in Table 3. Consistent with the CAR results, there was no difference between the topiramate and placebo groups ($z = -0.02$, $p = 0.947$). Treatment group × time interaction terms were not significant and were omitted from the final model. As Table 3 indicates, age, race, baseline cigarettes per day, depression score, alcohol dependence severity, days since last drink, and residing in a sober living environment were not significantly associated with abstinence. There were significant effects of both time ($z = -7.79$, $p < 0.001$) and time^2 ($z = 6.96$, $p < 0.001$) indicating a reduction in smoking during

the initial weeks that returned toward baseline levels over time. Finally, participants who enrolled at the San Diego site were more likely to be abstinent compared with those who enrolled in Cincinnati ($z = -2.06$, $p = 0.039$). Refitting the model using imputed data yielded similar results in terms of treatment condition and other covariates, with the exception that greater baseline alcohol dependence severity was associated with greater odds of smoking ($z = 2.12$, $p = 0.035$).

Smoking Withdrawal and Craving

Figure 4 illustrates changes in nicotine withdrawal as measured by the total score on the MNWS through week 13. After controlling for baseline severity of nicotine dependence as measured by the FTND ($z = -3.80$, $p < 0.001$), topiramate-treated participants had lower weekly average nicotine withdrawal scores than smokers receiving placebo ($z = -18.04$, $p < 0.001$).

In contrast to these tobacco withdrawal mitigating effects, we found no significant effect of topiramate on smoking craving as measured by total scores on the QSU-Brief. However, while there was no difference between topiramate and placebo on QSU-Brief Factor 1 assessing appetitive urges to smoke, for Factor 2 (i.e., urges to smoke for negative affect relief), there was a main drug effect ($z = 3.01$, $p = 0.003$) in the opposite direction than predicted; topiramate-treated participants had consistently higher QSU-Brief Factor 2 scores than placebo.

Alcohol and Other Drug Relapse

Overall, 38 of 129 men (29.5%) relapsed to alcohol ($N = 20$), other drugs ($N = 6$), or both substances ($N = 12$) during this 36-week study. Figure 2 denotes whether these relapses occurred in the active treatment or follow-up phase of the trial. There was no difference in the proportions relapsing between the topiramate (31.8%) and placebo (27.3%) groups ($p = 0.58$).

We also examined time to alcohol relapse using a Cox regression model. The difference between topiramate and placebo participants was not significant (hazard ratio = 1.30; 95% CI = 0.66, 2.55; $p = 0.445$). Similarly, the effects of enrollment site, baseline alcohol dependence, depression, cigarettes per day, time since last drink, and residential status (controlled sober living vs. not) were not significant. Figure 5 depicts the percentage of participants who reported having at least 1 drink during the assessment period at each study visit throughout the trial.

Medication Adherence, Drug Tolerability, and Adverse Events

Overall, 74.4% of participants were able to reach the maximum target dosage of 200 mg topiramate/placebo. Topiramate-treated participants achieved a maximum average dose of 164 mg/d, while those in the placebo group averaged 169 mg/d. Using 80% of the prescribed maximal target dose as the cut off for medication adherence, there was no difference in the proportion achieving this metric between groups (placebo = 85%; topiramate = 86%; $p = 0.89$).

Discontinuations due to either medical or psychiatric adverse events were less than 10% in the placebo group and 14% in the topiramate group. Serious adverse events (SAEs) were reported in 1 topiramate-treated participant who was hospitalized after expressing suicidal ideation following a relapse to heavy alcohol and drug use. Three placebo-treated participants also had SAEs: 2 who were hospitalized following relapses and 1 due to atrial fibrillation. None of the SAEs were determined to be study drug related.

Table 4 describes the type and incidence of all adverse events occurring in at least 10% of participants in either group. There were no significant differences between the groups, and the adverse event profile was consistent with those observed in other studies using topiramate.

Discussion

To our knowledge, this is the first report evaluating topiramate's efficacy and safety as an aid to both smoking cessation and alcohol relapse prevention in dually dependent male smokers motivated to make a quit attempt. Contrary to our hypotheses, topiramate monotherapy at a dosage up to 200 mg per day neither helped recovering alcohol-dependent men quit smoking nor prevented relapse to alcohol or drug use. The medication ameliorated symptoms of nicotine withdrawal, but had no overall effect on cravings to smoke. However, there was some indication that treatment with topiramate increased a particular category of craving: urges to smoke to relieve negative affect. The medication was generally well tolerated, with the majority of participants able to reach the maximal targeted dose. The adverse events observed were consistent with those already known for this antiepileptic medication, but occurred at lower rates than those we observed previously in non-alcohol-dependent smokers.

We studied men exclusively because our pilot work in non-alcohol-dependent smokers without current psychiatric disorders demonstrated gender-specific effects on smoking cessation with men responding to the medication but not women (Anthenelli et al., 2008). The present results differ from our prior work. Oncken and colleagues (2014), who also evaluated topiramate for smoking cessation in otherwise healthy smokers, found a nonsignificant difference between topiramate and placebo capsules ($p = 0.18$), but also found that when topiramate was combined with transdermal nicotine replacement in an unblinded fashion, significantly more individuals treated with the combination quit smoking compared with those taking placebo capsules. Although Johnson and colleagues (2005) reported that actively drinking alcoholics treated with topiramate were more likely to spontaneously quit smoking compared with alcoholic smokers receiving placebo, that study used a 300 mg per day target dose, had an unorthodox smoking cessation end point (i.e., plasma cotinine levels ≤28 ng/ml), and was not designed to adequately assess the mechanisms through which topiramate might facilitate change in smoking behavior (e.g., by reducing cravings and nicotine withdrawal symptoms). Taken together, then, and in contrast to some prior studies, we conclude that topiramate monotherapy at a dosage of up to 200 mg per day is not an efficacious smoking cessation aid among men with co-occurring alcohol dependence. However, based on others' prior work, it may show some utility when combined with nicotine replacement or when used at higher dosages.

It is important to note that the dually dependent smokers in the present study differed from the samples of smokers studied previously in other topiramate trials. For example, only 5 to 6% of the participants were married, 80% of the current participants had a lifetime history of other substance use disorders, 43.4% had a history of a comorbid, independent (e.g., nonsubstance-induced) psychiatric disorder, and roughly a third were taking other psychotropic medications while enrolled in the study. While this heterogeneous population captures the real-world characteristics of Veterans and other severely dependent individuals seeking treatment in substance abuse programs in the Midwest and in Southern California, our study population oversampled treatment refractory individuals who, presumably, would have the greatest difficulty quitting smoking and sustaining alcohol/drug abstinence. The low smoking quit rate achieved (9.3%) and relatively high rates of alcohol/drug relapse (30%) observed despite recruiting a majority of participants residing in a controlled sober living environment most likely reflects the cumulative negative predictive effects each of these co-occurring disorders have on smoking outcomes.

That most of the participants in our sample were living in recovery homes where tobacco smoking was condoned may also have influenced the results. Findings from the International Tobacco Control Four Country Survey indicate that smokers who reside in social contexts where smoking is allowed have greater difficulty quitting smoking (Hitchman et al., 2014b), and that younger, male smokers of lower socioeconomic status were particularly prone to having such social networks (Hitchman et al., 2014a). Indeed, the decade-long effort to integrate tobacco dependence treatment into addiction treatment (Foulds et al., 2006; Ziedonis et al., 2006) has met with variable success throughout the United States despite compelling evidence that staff who smoke, lack of smoking cessation training among providers, and tobacco permissive campuses are all barriers to successful treatment (Guydish et al., 2007; Knudsen and Studts, 2010; Knudsen et al., 2010). To our knowledge, none of the controlled sober living environments in the 2 states from which we recruited and followed participants was tobacco-free and many of the counselors at these programs were current smokers. Thus, the development and testing of any smoking cessation pharmacotherapies or behavioral interventions in these challenging environments may prove to be a daunting task.

Consistent with our preliminary results (Anthenelli et al., 2008) and those of Oncken and colleagues (2014), we found that treatment with topiramate ameliorated nicotine withdrawal. However, also consistent with our preliminary study (unpublished results), we found that topiramate had no overall effect on cigarette craving as measured by the QSU-Brief. Of potential mechanistic importance, we found that topiramate-treated smokers reported higher levels of craving on Factor 2 of the QSU-Brief, measuring urges to smoke to relieve negative affect. Deficits in one's perceived ability to cope with negative emotions have been found to predict smoking relapse (Yong et al., 2010), so if topiramate's GABA-facilitatory and glutamate-inhibitory effects increase the negative reinforcing value of smoking, monotherapy with this agent would be ineffective. This hypothesis was first put forth by Reid and colleagues (2007) who conducted a laboratory study of topiramate's effects during a period of brief smoking abstinence and found that the medication had no effect on cue-induced craving and actually enhanced withdrawal. In contrast, each of the first-line smoking cessation aids has been found to have anticraving effects (Kotlyar et al., 2011;

Ravva et al., 2015; Shiffman, 2008) with bupropion and varenicline also mitigating withdrawal-related negative affect (Cinciripini et al., 2013; Foulds et al., 2013).

We found no evidence that topiramate prevented relapse to alcohol or drug use in the context of smoking cessation. This was an exploratory aim, and our study was not adequately powered to formally test this hypothesis, but it is noteworthy that roughly 30% of participants had documented lapses to drinking and/or drug use over the 36-week study period. This figure likely underestimates the full scope of relapses occurring in this dually diagnosed sample because 30% of participants were lost-to-follow-up and some of these were likely to be relapse events. While the vast majority of studies (Prochaska et al., 2004; Tsoh et al., 2011) have found that smoking cessation enhances alcohol abstinence, at least 1 study using nicotine replacement therapy found high rates of alcohol relapse among alcohol-dependent smokers who received concurrent or delayed smoking cessation treatment (Joseph et al., 2004). Thus, clinicians should monitor alcohol and other drug abstinence in dually dependent smokers making a quit attempt. Topiramate might also have beneficial effects reducing use of psychostimulants such as methamphetamine (Elkashef et al., 2012) or cocaine (Kampman et al., 2013)—a hypothesis not tested in the present study design.

Our study has several important limitations. First, our study sample was comprised of dually dependent male smokers with high rates of other drug co-addiction and psychiatric comorbidity (except for psychotic disorders, which were exclusionary). These smokers are likely to have a difficult time quitting smoking by virtue of having multiple negative predictors (e.g., smoking concentrated within their social milieu) of abstinence. Thus, our study results may not generalize to less severe patient populations, women, smokers with only current, active substance use disorders, or smokers with psychotic disorders. Second, we studied only 1 dose of topiramate that was lower than the 300 mg maximal dosage found to spontaneously curtail smoking in actively drinking alcoholics. Third, we did not address whether the single nucleotide polymorphism in the gene encoding a kainate receptor subunit which has been found to moderate topiramate's effects on drinking (Kranzler et al., 2014) also influenced the medication's effects on smoking. Fourth, attrition occurred across both treatment groups and missing data could have affected point estimates of smoking cessation and relapse to alcohol and drug use. However, missing data did not differ by treatment arm, so comparisons of treatment effects remain valid. Finally, the very high reported rates of adherence and lack of statistically significant differences between the topiramate and placebo groups on adverse events may indicate overreporting of adherence or the fact that we did not solicit adverse events using a structured interview. Because of budgetary limitations, we relied on low-cost, indirect measures of adherence to study medication—patient diaries and pill counts. The addition of biochemical methods of verifying self-reported adherence (e.g., plasma drug concentrations) would increase confidence in the conclusion that adherence problems did not contribute to topiramate's lack of effect on smoking cessation or alcohol and drug relapse.

In conclusion, our findings do not support the use of topiramate at a dose of 200 mg as a single medication to curb both smoking and drinking in dually dependent men. More intensive interventions including combinations of the FDA-approved first-line smoking cessation aids and antirelapse medications are warranted along with concomitant, novel

behavioral interventions. Of course, no combination of treatments may work if delivered in environments where smoking is allowed in the social context.

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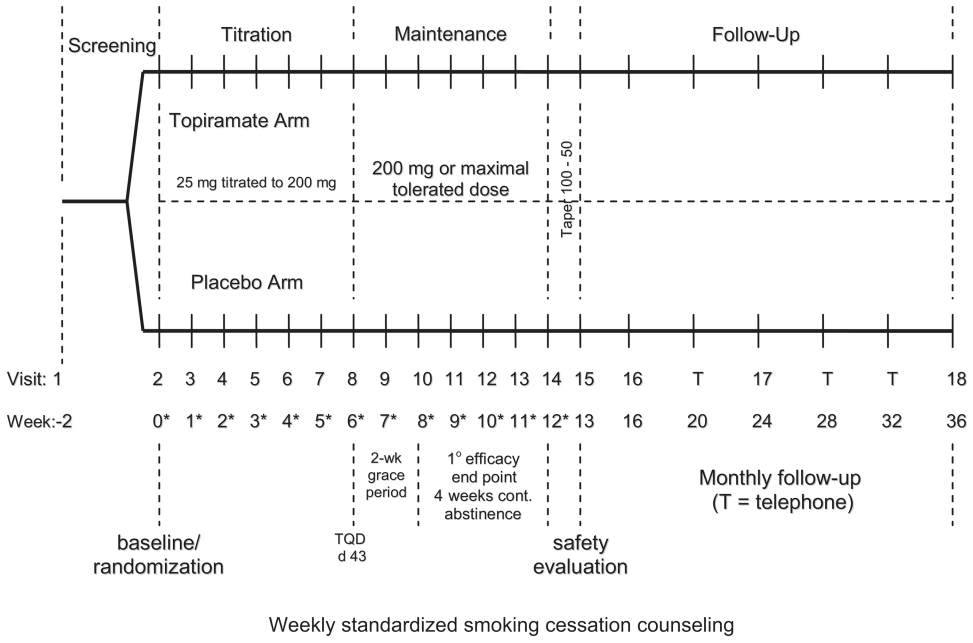

Fig. 1.

Study design. TQD, target quit date.

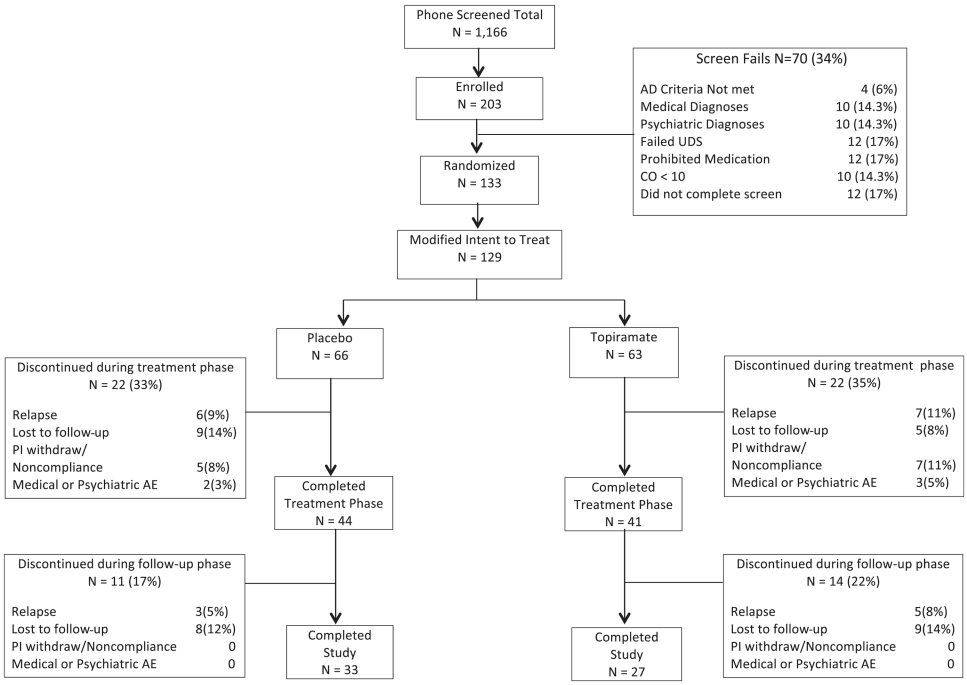

Fig. 2.

CONSORT flow diagram. AD, alcohol dependence; UDS, urine drug screen; CO, carbon monoxide; Relapse = any use of alcohol or other drugs. PI, Primary Investigator; AE, adverse event. Treatment phase was weeks O (baseline) through week 12. Follow-up phase was weeks 13 to 36.

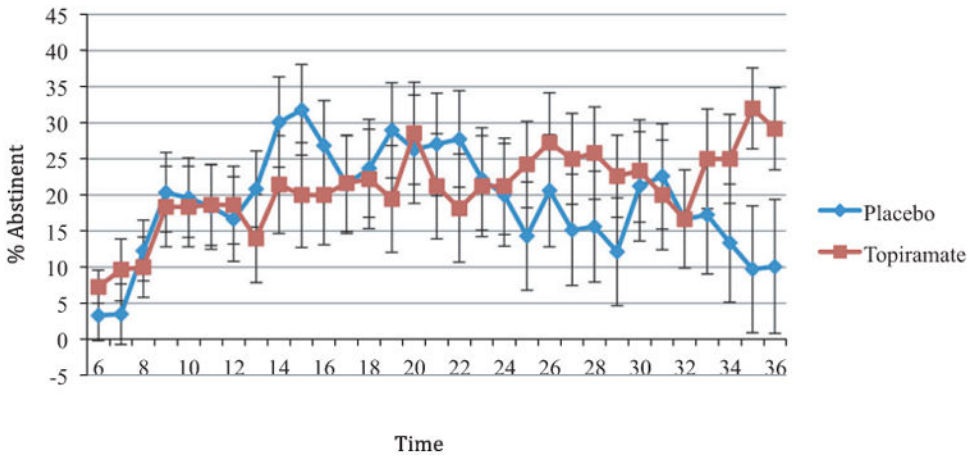

Fig. 3.

Weekly point prevalence of smoking abstinence. Seven-day point prevalence abstinence rates during treatment (weeks 6 to 12) and follow-up (weeks 13 to 36). Target quit day was day 43. Vertical bars show standard error mean (SEM).

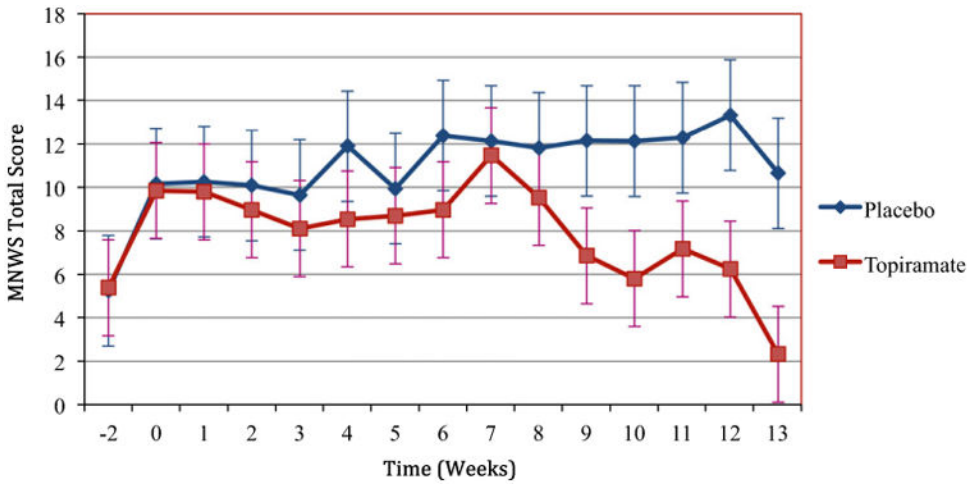

Fig. 4.

Change in tobacco withdrawal. Total scores on the Minnesota Nicotine Withdrawal Scale (MNWS) obtained at screening (–2 weeks), randomization (week 0), during active treatment (weeks 1 to 12), and following a 1-week medication taper (week 13). Vertical bars show standard error mean (SEM).

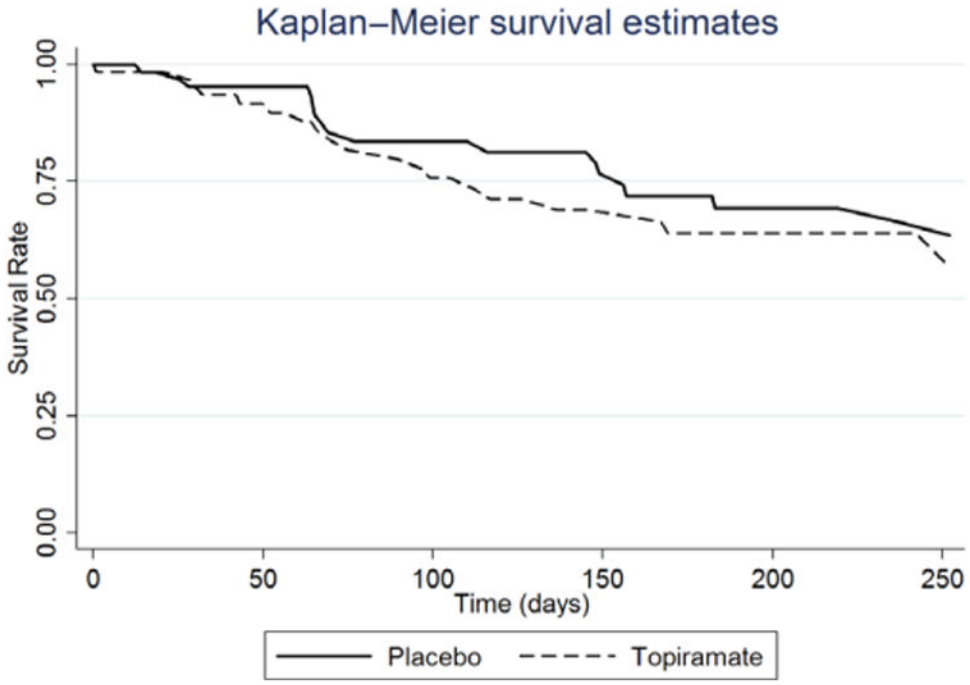

Fig. 5.

Kaplan–Meier survival estimates for relapse to alcohol/drug use. Time to event analysis illustrating relapse to any alcohol or illicit drug use as a function of time.

Table 1
Demographic and Clinical Characteristics

Variable	Placebo (*N* = 66)	Topiramate (*N* = 63)
Site (San Diego)	36 (54.5%)	34 (54%)
Age (years)	46.9 (9.8)	47.2 (9.0)
Race (Caucasian)	40 (60.6%)	32 (50.8%)
Veteran Status	39 (59%)	41 (65.1%)
Education (years)	12.5 (1.7)	12.7 (1.9)
Marital status	30 (45.5%)	20 (31.8%)
	never	never
	32 (48.5%)	40 (63.5%)
	div/sep/widower	div/sep/widower
Baseline CPD	21.2 (7.4)	19.7 (7.0)
FTND *	6.1 (1.6)	5.4 (2.0)
Days since last drink	178.7 (170.1)	177.9 (198.4)
ADS	22.1 (27.4)	21.9 (38.4)
Sober living residence	50 (75.8%)	50 (79.4%)
MADRS	1.4 (3.6)	1.8 (3.2)
Substance use disorders (%)		
Any use disorder	54 (81.3)	49 (77.4)
Cannabis use disorder	37 (56.1)	37 (58.7)
Stimulant use disorder	44 (66.7)	41 (65.1)
Opioid use disorder	16 (24.2)	13 (20.6)
Other substance use disorders	13 (19.7)	10 (15.9)
Psychiatric disorders (%)		
Any independent psychiatric disorder	24 (36.4)	32 (50.8)
Mood disorders	7 (10.6)	8 (12.7)
Anxiety disorders	9 (13.6)	12 (19.1)
Substance-induced disorders	34 (51.5)	24 (38.1)
CD/ASPD/ADHD	16 (24.2)	23 (36.5)
Other disorders	2 (3.0)	2 (3.2)
Psychotropic medications (%)		
Mood stabilizers	5 (7.6)	1 (1.6)
Antidepressants	19 (28.8)	13 (20.6)
Anxiolytics	4 (6.1)	1 (1.6)
Antipsychotics	4 (6.1)	2 (3.2)

CPD, cigarettes per day; FTND, Fagerström Test for Nicotine Dependence; ADS, Alcohol Dependence Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CD, conduct disorder; ASPD, antisocial personality disorder; ADHD, attention deficit hyperactivity disorder.
All participants met DSM-IV-TR criteria for alcohol and nicotine dependence.
Results presented as number (percentage) or mean (SD).

* $p < 0.05$.

Table 2

Logistic Regression Model of the Effect of Treatment Assignment on Continuous Abstinence

Effect	Coefficient	Standard error	Odds ratio (95% CI)	*p*-Value
Enrollment site	−0.16	0.76	0.85 (0.19, 3.73)	0.829
Age	0.02	0.04	0.98 (0.90, 1.06)	0.590
Race	−0.14	0.35	0.87 (0.44, 1.72)	0.683
Alcohol Dependence Scale (ADS)	−0.01	0.01	0.99 (0.97, 1.01)	0.264
Baseline cigarettes per day	−0.04	0.04	0.97 (0.89, 1.04)	0.264
MADRS	0.18	0.19	1.20 (0.83, 1.73)	0.342
Days since last drink	−0.01	0.01	1.00 (1.00, 1.01)	0.953
Sober living	−0.01	0.92	0.99 (0.16, 6.02)	0.987
Treatment	0.47	0.72	1.60 (0.39, 6.53)	0.510
Concomitant psychotropic medication use	−1.16	0.75	0.31 (0.07, 1.37)	0.123

Key for dummy variables entered in the model—site: 0 = Cincinnati, 1 = San Diego; Race: 1 = Asian American, 2 = African American, 3 = Non-Hispanic Caucasian, 4 = Hispanic/Latino, 5 = Other or Multiple Backgrounds; Sober Living: 0 = No, 1 = Yes; Treatment: 0 = Placebo; 1 = Topiramate.

Table 3
GEE Model of Weekly Point Prevalence Smoking Status, Weeks 6 to 36

Effect	Coefficient	Standard error	*z*-Score	*p*-Value
Enrollment site	−0.12	0.06	−2.06	0.039
Age	0.01	0.01	0.11	0.916
Race	−0.02	0.02	−0.65	0.517
ADS	−0.01	0.01	−1.78	0.074
Baseline cigarettes per day	0.01	0.01	0.53	0.596
MADRS	0.02	0.01	1.64	0.098
Days since last drink	0.01	0.01	0.30	0.767
Sober living	−0.01	0.07	−0.09	0.931
Time	−0.02	0.01	−7.79	<0.001
Time^2	0.01	0.01	6.96	<0.001
Treatment	−0.01	0.05	−0.02	0.947
Concomitant psychotropic medication use	−0.07	0.07	−0.96	0.337

Key for dummy variables entered in the model—site: 0 = Cincinnati, 1 = San Diego; Race: 1 = Asian American, 2 = African American, 3 = Non-Hispanic Caucasian, 4 = Hispanic/Latino, 5 = Other or Multiple Backgrounds; Sober Living: 0 = No, 1 = Yes; Treatment: 0 = Placebo; 1 = Topiramate.

Table 4
Adverse Events Observed in ≥10% of Participants

Preferred term of adverse event	Placebo (*n* = 66) (%)	Topiramate (*n* = 63) (%)	*p*-Value
Upper respiratory infection	13 (20)	7 (11)	0.18
Headache	8 (12)	12 (19)	0.28
Paresthesia	6 (9)	12 (19)	0.10
Appetite—loss	4 (6)	9 (14)	0.12
Concentration span reduced	6 (9)	8 (13)	0.51
Dysgeusia	6 (9)	7 (11)	0.70
Dizziness	7 (11)	4 (6)	0.39
Back pain	7 (11)	2 (3)	0.10
Somnolence	5 (8)	6 (10)	0.69
Depression	3 (5)	6 (10)	0.27