ORIGINAL INVESTIGATION

Topiramate for Smoking Cessation: A Randomized, Placebo-Controlled Pilot Study

Cheryl Oncken MD, MPH¹, Albert J. Arias MD, MS², Richard Feinn PhD³, Mark Litt PhD⁴, Jonathan Covault MD, PhD⁵, Mehmet Sofuoglu MD², Henry R. Kranzler MD⁶

¹Department of Medicine and Obstetrics and Gynecology, University of Connecticut Health Center, Farmington, CT;

²Department of Psychiatry, Yale University School of Medicine, New Haven, CT; ³Department of Medical Sciences, Frank H. Netter MD School of Medicine, Quinnipiac University, Hamden, CT; ⁴Oral Health and Diagnostic Sciences and Department of Psychiatry, University of Connecticut Health Center, Farmington, CT; ⁵Department of Psychiatry, University of Connecticut Health Center, Farmington, CT; ⁶Department of Psychiatry, University of Pennsylvania Perelman School of Medicine and Philadelphia VAMC, Philadelphia, PA

Corresponding Author: Cheryl Oncken, MD, MPH, Department of Medicine and Obstetrics and Gynecology, University of Connecticut Health Center, 263 Farmington Avenue, MC 3805, Farmington, CT 06030, USA. Telephone: 860-679-3425; Fax: 860-679-1454; E-mail: oncken@nso2.uchc.edu

Received May 10, 2013; accepted July 30, 2013

ABSTRACT

Introduction: Topiramate (TOP) blocks glutamate receptors and facilitates GABA (γ -aminobutyric acid) neurotransmission, effects that may facilitate smoking cessation. We compared the effects of behavioral counseling combined with (a) TOP, (b) TOP/nicotine patch (TOP/NIC), or (c) placebo (PLC) for smoking cessation.

Methods: We conducted a 10-week randomized trial in which subjects and research personnel were blinded to TOP versus PLC but not to the TOP/NIC patch condition. In groups receiving TOP, the medication dosage was titrated gradually up to 200 mg/day. The smoking quit date (QD) was scheduled after 2 weeks of medication treatment. NIC (21 mg) was started on the QD in subjects randomized to the TOP/NIC condition. The main outcome measure was the end-of-treatment, 4-week continuous abstinence rate (CAR; biochemically confirmed).

Results: Fifty-seven subjects were randomized to treatment. The 4-week CAR was 1 of 19 (5%) in the PLC group, 5 of 19 (26%) in the TOP group, and 7 of 19 (37%) in the TOP/NIC group ($p = .056$). Pairwise comparisons showed a difference between TOP/NIC and PLC ($p = .042$) and a nonsignificant difference between TOP and PLC ($p = .18$). The PLC group gained 0.37 lb/week, the TOP group lost 0.41 lb/week, and the TOP/NIC group lost 0.07 lb/week ($p = .004$). Pairwise comparisons showed a difference between TOP and PLC ($p < .001$) and between TOP/NIC and PLC groups ($p = .035$). Paresthesia was more frequent in subjects on TOP than PLC ($p = .011$).

Conclusions: TOP, alone or in combination with the NIC, resulted in a numerically higher quit rate than PLC and decreased weight. A larger, PLC-controlled trial is needed to confirm these findings.

INTRODUCTION

Despite progress made in the pharmacological treatment of nicotine dependence, cigarette smoking continues to be a leading contributor to mortality in the United States (Mokdad, Marks, Stroup, & Gerberding, 2004, 2005). Three categories of medication (nicotine replacement therapies, bupropion, and varenicline), with varying degrees of efficacy (Fiore et al., 2008; Stead, Perera, Bullen, Mant, & Lancaster, 2008), are approved by the U.S. Food and Drug Administration (FDA) to treat tobacco dependence. None of these first-line treatments is recommended over another, and combinations of them increase efficacy compared with a single agent (Fiore et al., 2008). The optimal

treatment choice depends on the patient's preference, previous treatment response, and relevant medical contraindications.

Because there are a limited number of agents available to treat tobacco use and dependence, a need exists to develop new medications for this indication. In particular, there is a need for medications that work via novel mechanisms, and thus could be used either alone or in combination with other smoking cessation medications in refractory patients. Further, current pharmacological treatments have a limited impact on the weight gain associated with smoking cessation, a common complicating factor and sometimes a deterrent to those wishing to quit (Parsons, Shraim, Inglis, Aveyard, & Hajek, 2009). Thus, novel medications that can reduce weight gain may be of particular importance.

doi:10.1093/ntr/ntt141

Advance Access publication September 21, 2013

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One such agent could be topiramate (TOP), which may be useful to treat tobacco dependence (Anthenelli, Blom, McElroy, & Keck, 2008) and may limit weight gain (Pickrell, Lacey, Thomas, Smith, & Rees, 2013). Indeed, TOP has been shown to reduce weight and is approved in combination with phentermine for weight loss (Holes-Lewis, Malcolm, & O'Neil, 2013). TOP is a sulfamate-substituted fructopyranose derivative with complex and multifaceted mechanisms of action (Johnson, 2008; White, 2005) that is FDA approved as an anticonvulsant medication and prophylactic treatment for migraine. TOP antagonizes AMPA (α -amino-3-hydroxy-5-methyl-4 isoxazole propionic acid) and kainate-type glutamatergic receptors and inhibits sodium and L-type calcium channels. It also facilitates GABAergic neurotransmission via allosteric modulation of a nonbenzodiazepine site on the GABA-A receptor. TOP's glutamate receptor antagonist and GABA receptor agonist effects may attenuate ventral striatal dopaminergic neurotransmission in smokers, providing a possible mechanism by which TOP is useful to treat addictive disorders (Johnson, 2004). In addition, TOP has been shown to have direct effects on brain dopamine and serotonin release (Okada, Yoshida, Zhu, Hirose, & Kaneko, 2005). For example, TOP, at doses comparable to those producing therapeutic effects in humans, enhanced basal and Ca^{++} -induced dopamine levels in the prefrontal cortices of rats.

In addition to evidence of TOP's efficacy in treating alcohol dependence, the medication also appears to be efficacious for smoking cessation. A sub-group analysis of 94 alcohol-dependent smokers (~75% men), who were participating in a double-blind, placebo (PLC)-controlled study of TOP for alcohol treatment, found that recipients treated with TOP were more likely than PLC recipients to quit smoking spontaneously (odds ratio [OR] 4.46; 95% CI 1.08–18.39; $p = .04$; Johnson, Ait-Daoud, Akhtar, & Javors, 2005). Subjects in that study received 12 weeks of medication treatment with the dosage of TOP increasing from 25 to a maximum of 300 mg/day by Week 8 of treatment. Treatment effects were observed after 2 weeks of medication treatment; however, the highest quit rates were observed at Week 9 when 19.4% of TOP versus 6.9% of PLC subjects quit smoking. Quit rates after medication discontinuation were not reported. In an 11-week randomized, PLC-controlled trial specifically for smoking cessation, TOP appeared to be beneficial in men, but not women (Anthenelli et al., 2008). The study used a 6-week dosage titration (up to 200 mg/day) prior to the quit date (QD), and biochemically confirmed cigarette abstinence was assessed at Weeks 8–11. Thirty-eight men and 49 women who smoked more than 10 cigarettes/day participated in the study. Men treated with TOP were four times more likely to quit than those randomized to PLC (37.5% vs. 13.6%; OR 3.8; $p = .098$) and were 16 times more likely to quit smoking than women randomized to TOP (37.5% vs. 3.7%; OR 15.6; $p = .006$). However, women in the study had a numerically higher quit rate on PLC than TOP. No posttreatment abstinence rates were reported.

This three-arm study compared the effects of TOP alone and TOP combined with a nicotine patch (NIC) with an inactive PLC on smoking quit rates (continuous 4-week abstinence at the end of treatment was our primary outcome measurement), nicotine withdrawal symptoms, the reinforcing effects of smoking, and weight gain with smoking cessation. In a human laboratory study, TOP treatment enhanced some of the subjective pleasurable effects of intravenously administered nicotine,

suggesting that there is a synergistic interaction between TOP and nicotine (Sofuoglu, Poling, Mouratidis, & Kosten, 2006). We examined the potential efficacy and tolerability of TOP, and estimated its effects on weight during smoking cessation. We hypothesized that subjects treated with TOP would gain less weight than those randomized to PLC.

METHODS

Study Overview

In this 10-week, randomized, PLC-controlled trial, subjects received behavioral counseling and daily treatment with TOP, TOP/NIC, or PLC. Subjects and research personnel were blinded to the TOP versus PLC condition, but not to the TOP/NIC condition. The primary outcome measure was the 4-week continuous smoking cessation rate confirmed by an exhaled carbon monoxide (CO) concentration of ≤ 10 ppm at the end of medication treatment (Stookey, Katz, Olson, Drook, & Cohen, 1987). The institutional review board at the University of Connecticut Health Center approved the protocol, and subjects provided written informed consent. The study was registered on clinicaltrials.gov as study # NCT00755716.

We considered a factorial design in which subjects would receive active TOP, active NIC, both medications, or a double PLC. However, due to difficulty in obtaining a PLC patch, our limited study budget, and the established efficacy of the NIC (i.e., a meta-analysis of 32 studies yielded an OR 1.9; 95% CI 1.7–2.2; Fiore et al., 2008), we opted for a study design that addressed the following questions: (a) Does TOP increase quit rates compared with PLC? (2) Does NIC add to quit rates observed with TOP alone?

Subjects

Subjects were recruited via advertising. They were enrolled in the study if they were 18–65 years old, smoked at least 10 cigarettes/day during the past year with no period of abstinence greater than 3 months, and were medically stable (i.e., no serious or unstable medical or psychiatric condition for at least 6 months). Women were required to be postmenopausal for at least 2 years or practicing an effective method of birth control. Only one member of a household was allowed to participate in the study.

Exclusion criteria included a current major depressive episode; treatment for depression within the last 12 months; a history of a psychotic, panic, or bipolar disorders; body mass index (BMI) $< 18 \text{ kg/in}^2$; uncontrolled hypertension; clinically significant hepatic or renal impairment; history of nephrolithiasis or glaucoma; a previous serious adverse event or hypersensitivity to TOP; a significant or severe drug allergy; a last-year history of drug or alcohol abuse or dependence; investigational drug treatment within 30 days of the baseline visit; tobacco dependence treatment within the past 6 months; use of non-cigarette tobacco products; lactose intolerance; and use of a medication known to have a clinically significant interaction with TOP.

Procedures

We conducted a brief medical and psychiatric history, and performed a physical exam at the screening visit, at which time we also obtained an electrocardiogram and collected blood (for measurement of electrolytes, bicarbonate levels, and renal and

liver function tests) and urine for a drug toxicology screen (and pregnancy test if the subject was a female of childbearing age). The brief psychiatric history included questions about previous psychiatric treatment and screening questions regarding problems with anxiety or anxiety attacks, a sustained period of too high a mood or extreme irritability, recurrent thoughts that are uncontrollable, hearing voices, and suicidal thoughts or attempts. Participants completed questionnaires providing basic demographic information and smoking history, including the Fagerström Test for Nicotine Dependence (FTND; [Heatherton, Kozlowski, Frecker, & Fagerström, 1991](#)). During the study, we measured weekly exhaled CO, symptoms of nicotine withdrawal via the Minnesota Nicotine Withdrawal Scale (MNWS; [Hughes & Hatsukami, 1998](#)), measures of the subjective effects of smoking using the Modified Cigarette Evaluation Questionnaire (mCEQ; [Rose, Behm, & Westman, 1998](#)) in subjects who continued to smoke, and measures of cigarette use using the Timeline Follow Back (TLFB) method ([Sobell, Sobell, Leo, & Cancelli, 1988](#)). Blood for serum bicarbonate levels was collected after 3, 6, and 9 weeks of medication treatment.

Assessments

We assessed vital signs, weight, adverse effects and tolerability of the medication, and exhaled CO levels at each weekly visit. We used the TLFB to assess cigarettes smoked each day during the previous week ([Sobell et al., 1988](#)). The MNWS was administered weekly, which assesses withdrawal symptoms over the last 24 hr on a 5-point scale with “0” being not at all and “4” being extreme for the following symptoms: urge to smoke, depressed mood, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, increased appetite, and insomnia. Subjects who continued to smoke were also administered the mCEQ, which assesses responses to smoking on a 7-point scale from “1,” which is not at all, to “7,” which is extremely. Specific categories included (a) satisfaction (Was smoking satisfying? Did cigarettes taste good? and Did you enjoy smoking?); (b) reward (Did smoking calm you down? Did smoking make you feel more awake? Did smoking make you feel less irritable? Did smoking help you concentrate? and Did smoking reduce your hunger for food?); (c) enjoyment (Did you enjoy the sensations in your throat and chest?); (d) relief of craving (Did smoking immediately relieve your craving for a cigarette?); (e) aversion (Did smoking make you dizzy? and Did smoking make you nauseous?).

Interventions

Study Medication

Using an urn randomization procedure to balance on sex and the FTND score, subjects were assigned with equal likelihood to one of three conditions (TOP, TOP/NIC, and PLC). The TOP tablets were over-encapsulated to match PLC tablets, which were filled with lactose powder.

Treatment with the study medication (TOP or PLC) was started at the baseline visit and the dosage was titrated up over 5 weeks (25 mg/day for 1 week, 25 mg twice daily for 1 week, 50 mg twice daily for 1 week, 75 mg twice daily for 1 week, and 100 mg twice daily for 5 weeks). A QD was set at 2 weeks after the initiation of study medication (when most subjects began a dose of 100 mg/day). The QD was based on data from [Johnson et al. \(2005\)](#) showing spontaneous cigarette abstinence during

alcohol treatment after 2 weeks of medication use. Dosing was flexible, in that the titration could be extended or the dose lowered as needed if a subject was having side effects, with the goal of maintaining the subject on a minimum of 50 mg/day of medication. During the last week of the study (Week 10), the medication was tapered by decreasing the dosage by 30% every 3 days. For subjects assigned to the TOP/NIC condition, the patch was started on the QD at 21 mg/day for 7 weeks, then reduced to 14 mg/day for 3 days then 7 mg/day for 4 days, and then stopped.

Brief Counseling/Skills Training

We provided subjects with an educational booklet “Clearing the Air: Quit Smoking Today.” At baseline and at each subsequent visit, subjects received brief, individual smoking cessation counseling (≤ 10 min) in accordance with the guidelines developed by the Agency for Health Care Research ([U.S. Department of Health and Human Services, 2004](#)). Counseling was provided by a nurse with more than 5 years of counseling experience in smoking cessation clinical trials.

Primary Endpoints

The primary efficacy endpoint was CO-confirmed cigarette abstinence during the last 4 weeks of treatment. Seven-day point prevalence abstinence was defined as the subject reporting not smoking during the previous week (not even a puff) and a clinic CO reading of ≤ 10 ppm. If a subject missed a study visit, the 7-day point prevalence was coded as not abstinent unless during the previous week, and the subsequent week, the subject reported not smoking between those visits, and the CO readings were negative. Subjects who dropped out of the study were counted as smokers. Secondary endpoints also included scores on the MNWS, mCEQ, and weight.

Data Analysis

Based on a previous study that showed an approximate doubling of cessation rates by the third week of TOP use ([Johnson et al., 2005](#)) and clinical trial data showing a baseline treatment effect of PLC that is $\sim 13.8\%$ ([Fiore et al., 2008](#)), we estimated 4-week continuous efficacy rates with PLC to be 12%–18% and anticipated a quit rate of 24%–36% with TOP (either alone or in combination with the NIC). We recognized that the pilot study was underpowered to detect these differences, but conducted it to assess feasibility.

Baseline group comparisons on demographic and substance use history used one-way analysis of variance for continuous measures and the chi-square test (or Exact test when cell sizes were small) for categorical measures.

The comparison of the final 4-week abstinence rates between groups used the Exact test because of small cell counts. Generalized estimating equations (GEEs) with a binomial logistic probability distribution were used to model weekly abstinence rates over time. Treatment group and study week were included as factors, and the interaction between the two was used to test group differences in the change over time in abstinence rates. Because one study ([Anthenelli et al., 2008](#)) showed a large gender by treatment effect, we also ran a logistic regression on 4-week abstinence rates with treatment group and gender, and their interaction, as predictors.

The secondary outcomes of withdrawal, smoking effects, and body weight were analyzed using linear mixed models with treatment and study week as factors and the interaction between the two used to test for group differences in changes in these outcomes over time.

RESULTS

Eighty-four subjects were screened, and 57 subjects met the inclusion and exclusion criteria and were randomized to treatment. Thirty-eight subjects (66.7%) completed the 10-week study with the highest completion rate in the TOP/NIC group (16 of 19 or 84%). The rate of treatment completion in both the PLC and the TOP groups was 58% (i.e., 11 of 19 subjects in each group). The rate of completion did not differ significantly by group ($\chi^2_{(2)} = 3.95$; $p = .14$). Reasons for dropout included: adverse events (one PLC, four TOP, and one TOP/NIC), lack of efficacy (two PLC), lost to follow-up (five PLC, three TOP, and one TOP/NIC), and other (one TOP and one TOP/NIC).

Descriptive Statistics

Subject characteristics are shown in Table 1. The mean age of the sample was 47.2 ($SD = 9.6$) years, and the majority of subjects were female (60%), Caucasian (81%), married (58%), and currently employed (75%). The three groups were also comparable on average BMI, cigarettes/day, and other smoking variables.

Treatment and Medication Adherence

Medication adherence was excellent, based on pill counts at each treatment visit. The adherence rate was 93.8% ($SD = 8.0$) in the PLC group, 89.4% ($SD = 14.0$) in the TOP group, and

93.0% ($SD = 10.1$) in the TOP/NIC group. This rate did not differ by treatment group ($F_{(2,52)} = 1.03$; $p = .37$).

Smoking-Related Outcomes

Abstinence Rates

There was a near-significant group difference on the 4-week continuous abstinence rate (CAR; Exact $p = .056$). As shown in Figure 1, the PLC group had the lowest abstinence rate ($n = 1$ of 19, 5%), the TOP group had an intermediate rate ($n = 5$ of 19, 26%), and the TOP/NIC group had the highest rate ($n = 7$ of 19, 37%). Pairwise comparisons showed a significant difference between TOP/NIC and PLC ($OR\ 10.5$, 95% CI 1.14–96.57; $p = .042$), and a nonsignificant difference between TOP and PLC ($OR\ 6.43$, 95% CI –0.67 to –61.5; $p = .18$). Of note, most of the subjects who quit in the TOP ($n = 4$ of 5, 80%) and in the TOP/NIC group ($n = 4$ of 7, 57%) were women.

Figure 2 shows the weekly abstinence rates (7-day point prevalence confirmed by an exhaled CO ≤ 10 ppm) by treatment group. At Week 3, the TOP/NIC group began to show a dramatic increase in abstinence, which peaked in Week 5 and decreased somewhat thereafter. The TOP group showed a slow, steady increase throughout the study, whereas the PLC group was consistently low on abstinence throughout the trial. The GEE analysis of weekly abstinence rates showed a significant group by week interaction effect (Wald $\chi^2 = 43.15$; $p < .001$), indicating that the change in abstinence rates differed among the three groups. Specifically, TOP differed from PLC ($p < .001$), TOP/NIC differed from PLC ($p = .019$), but TOP did not differ from TOP/NIC ($p = .15$). The results did not change with substance treatment or gender included as a covariate.

Secondary Analyses

There was a significant effect of week ($F_{(1,36,7)} = 8.36$; $p = .006$) and a nearly significant interaction between treatment and week

Table 1. Subject Characteristics^a

	Placebo	Topiramate	Topiramate/nicotine	<i>p</i> value
Gender (%)				
Female	57.9	52.6	68.4	.60
Male	42.1	47.4	31.6	
Age (years)	45.4 (7.6)	46.1 (11.1)	50.1 (9.6)	.27
Race (%)				
Caucasian	84.2	84.2	84.2	1.00
Hispanic	10.5	5.3	10.5	
Other	5.3	10.5	5.3	
Body mass index	28.7 (8.2)	29.0 (6.2)	26.7 (4.6)	.51
Marital status (%)				
Single	21.1	10.5	15.8	.66
Married	47.4	63.2	68.4	
Divorced	31.6	26.3	15.8	
Smoking history				
Age started	16.4 (4.6)	16.5 (3.8)	15.6 (2.0)	.69
Years smoked	28.6 (9.9)	27.3 (11.3)	30.7 (10.3)	.59
Cigarettes/day	22.1 (6.9)	21.1 (6.1)	20.9 (7.2)	.84
Tried quitting	94.7%	94.7%	100%	1.00
FTND (range 0–10)	6.4 (1.8)	5.1 (1.6)	6.2 (2.0)	.069
Desire to quit (range 0–100)	79.5 (19.3)	81.8 (15.7)	79.7 (14.0)	.89

Note. FTND = Fagerström Test for Nicotine Dependence.

^aResults presented as percentages or mean (SD).

Figure 1. Four-week continuous cigarette abstinence rates at the end of treatment. Abstinence rates were determined by self-report and exhaled carbon monoxide measurement.

($F_{(2,36.6)} = 2.92$; $p = .067$) on total withdrawal scores as measured by the MNWS. Overall, withdrawal scores decreased over time, with a significantly greater decrease for TOP compared with PLC ($B = -0.43$, $t_{(37.4)} = 2.41$; $p = .021$). The MNWS item on which there was the largest interaction effect was *irritability, frustration, and anger* ($F_{(2,48.8)} = 6.24$; $p = .004$): the TOP group showed a greater decline in severity of this symptom during the study period than the PLC group ($B = -0.12$, $t_{(48.9)} = 3.10$; $p = .003$).

There was a significant main effect of week on the mCEQ score ($F_{(1,31.0)} = 36.10$; $p < .001$) and a borderline significant interaction effect of treatment by week ($F_{(2,30.8)} = 2.93$; $p = .069$): mCEQ scores decreased over time and scores for the TOP group decreased significantly more than for the PLC group ($B = -1.38$, $t_{(33.2)} = 2.10$; $p = .044$). An analysis of the specific subscales of the mCEQ revealed no group differences on *satisfaction, craving, enjoyment, or aversion*. However, both the TOP ($B = -0.58$, $t_{(31.4)} = 2.08$; $p = .046$) and the TOP/NIC ($B = -0.57$, $t_{(26.8)} = 2.18$; $p = .038$) groups had a significantly greater decrease over time in *reward* than the PLC group.

Body weight remained fairly steady during the course of the study. However, after controlling for exhaled CO level, there was a significant treatment by week interaction ($F_{(2,47.3)} = 6.29$; $p = .004$). Figure 3 shows that the PLC group had a moderate increase in weight during the study (0.37 lbs/week), whereas the TOP group experienced a modest decrease (-0.41 lbs/week) and the TOP/NIC showed minimal change in weight (-0.07 lbs/week). Pairwise comparisons showed a difference between TOP and PLC ($p < .001$), TOP/NIC and PLC ($p = .035$), and a nonsignificant difference between TOP and TOP/NIC.

Safety and Tolerability

There were no serious adverse events (i.e., death, disability, hospitalization, or an important medical event that may jeopardize the subject's life or require surgical or medical intervention) during the study. Adjusting for weeks of participation, there was a significant difference in the number of total reported adverse events ($F_{(2,53)} = 3.97$; $p = .025$; PLC = 40, TOP = 62, TOP/NIC = 87), with the only significant pairwise contrast occurring between PLC and TOP/NIC ($p = .007$). About 45% of the adverse events were mild, 45% were moderate, and 10% were considered severe. Level of severity of the events was not related to treatment ($\chi^2_{(4)} = 6.47$; $p = .17$). When examining the frequency of all adverse events, only paresthesia was reported by more subjects in the TOP groups. Although no subjects in the PLC group reported paresthesia, 47% (9 of 19) of subjects in both the TOP and the TOP/NIC groups reported this adverse effect ($p = .011$). Supplementary Table 1 shows the frequency of various moderate or severe adverse events in the three treatment groups.

DISCUSSION

We found a numerically greater 4-week CAR in the groups treated with TOP or TOP/NIC than with PLC. Post-hoc analysis revealed a significant difference between the TOP/NIC and the PLC arms, and a nonsignificant advantage for the TOP group compared with PLC. These results are supported by similar findings for the analysis of the 7-day point prevalence (weekly abstinence) measure. TOP also decreased withdrawal

Figure 2. Seven-day point prevalence cigarette abstinence rates throughout the study, confirmed with exhaled carbon monoxide measurement (BL = baseline, TOP = topiramate, TOP/NIC = topiramate and nicotine patch, PLA = placebo).

symptoms and the rewarding effects of smoking. The medication was well tolerated, with no serious adverse events, suggesting that the risk/benefit ratio for TOP in smokers is favorable. A nonsignificantly larger proportion of subjects in the TOP/NIC group than the PLA group completed treatment compared with PLA, suggesting that combining the two treatments may help increase adherence to treatment.

Our findings agree with those of the only other randomized controlled trial of TOP for smoking cessation, which also showed potential efficacy of the medication. However, the efficacy in that study was limited to men (Anthenelli et al., 2008). In contrast, we found that TOP appears to be effective for smoking cessation in both sexes. Because both trials of TOP for smoking cessation involved small samples, future studies should use larger study samples to explore sex differences in relation to TOP effects on smoking cessation.

We included a TOP/NIC arm because TOP is known to produce a large number of adverse effects (Bodalía et al., 2013). Further, we were concerned that stopping smoking combined with the GABAergic and glutamatergic effects of TOP could potentially induce nicotine withdrawal, as observed in a cue reactivity study (Reid, Palamar, Raghavan, & Flammiano, 2007). The addition of the NIC to TOP could alleviate withdrawal, making the combination treatment similar to a nicotinic receptor

partial agonist. The addition of the NIC did boost initial quit rates. Although the beneficial effect does not appear to be due to a reduction in either nicotine withdrawal symptoms or the reinforcing effects of smoking, it occurred in the context of greater study retention in the group receiving the combined treatment.

It is noteworthy that Anthenelli et al. (2008) prescribed a 6-week course of TOP, titrating the dose up to 200 mg/day prior to the QD, compared with our 2-week lead-in time prior to planned smoking cessation. It is possible that the effect of TOP on 4-week CARs at the end of treatment would have been greater in our study if we had included a longer pretreatment phase prior to the QD. Such an interpretation appears to be supported by the fact that quit rates in the TOP group increased with continued use of the medication and 7-day point prevalence abstinence rates were highest during the last week of medication treatment.

TOP has been shown to reduce weight (Pickrell et al., 2013) and has been studied as a treatment for obesity in persons with psychiatric comorbidities (Kirov & Tredget, 2005; McElroy et al., 2007). TOP is approved in combination with phentermine for weight loss (Holes-Lewis, Malcolm, & O'Neil, 2013). Consequently, it is not surprising that subjects in the TOP group lost significantly more weight than subjects in the PLA group (who gained weight). Subjects in the combined medication group also had a slight decrease in body weight. This finding is

Figure 3. Mean (SD) change in body weight (pounds) in the three treatment groups (TOP = topiramate, TOP/NIC = topiramate and nicotine patch, PLC = placebo).

important because the majority of smokers who quit gain weight (Fiore et al., 2008; Perkins, 1993), and fear of weight gain can hinder smoking cessation efforts (Perkins et al., 2001). Although bupropion SR and nicotine gum have been shown to delay or reduce weight gain, no pharmacotherapies have been shown to promote smoking cessation and weight loss. Consequently, TOP may be a particularly useful medication for individuals who are concerned about weight gain when they stop smoking.

It is noteworthy that TOP appeared to decrease withdrawal, in particular, it reduced scores on the *anger*, *irritability*, and *frustration* item of the MNWS. In both TOP groups, individuals who continued to smoke appeared to experience reduced rewarding effects of smoking. Further, TOP's effects on irritability in this study contrast with those reported by Anthenelli et al. (2008), who found that irritability was the most frequent adverse effect of the drug.

TOP is efficacious in the treatment of alcohol dependence, as well as showing potential efficacy for smoking cessation and weight loss. TOP may also have beneficial effects on anxiety, anger, and impulse control (Fontenelle, Oostermeijer, Harrison, Pantelis, & Yücel, 2011; Nickel et al., 2005; Riazza Bermudo-Soriano, Perez-Rodriguez, Vaquero-Lorenzo, & Baca-Garcia, 2012). Consequently, TOP may be useful in psychiatric populations with high rates of cooccurring

nicotine dependence, alcohol dependence, and problems with weight control. Indeed, there is an ongoing study evaluating the potential utility of TOP to treat tobacco dependence in persons with depression (García Campayo et al., 2008) and TOP reduced tobacco use in a study of alcohol-dependent smokers (Johnson et al., 2005).

This study is limited by the small sample size, the open-label treatment of the TOP/NIC group, lack of a NIC-only condition, and no follow-up posttreatment. Although it appears that there is an additive treatment effect of TOP and nicotine, the sample size and study design limit the conclusions that can be drawn concerning the efficacy of the combination.

Further study of the efficacy of TOP for smoking cessation is warranted. Questions remain about how long subjects should be pretreated with TOP prior to the QD and whether it should be combined with other treatments to increase subject retention and enhance efficacy. Larger double-blind, PLC-controlled studies are needed to determine the safety, efficacy, and tolerability of TOP for smoking cessation.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 can be found online at <http://www.ntr.oxfordjournals.org>.

FUNDING

This project was supported by funds from the Department of Medicine at the University of Connecticut Health Center and the General Clinical Research Center (M01RR006192). HRK's participation was funded by National Institute on Alcohol Abuse and Alcoholism (K24 AA13736).

DECLARATION OF INTERESTS

CO currently is receiving study medication (nicotine inhaler and placebo) from Pfizer Pharmaceuticals for a National Institutes of Health-funded study of nicotine inhaler for smoking cessation during pregnancy. MS has served as an expert witness on behalf of Pfizer in lawsuits related to varenicline. HRK has served as a consultant or advisory board member for Alkermes, Lilly, Lundbeck, Pfizer, and Roche and as a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, supported by AbbVie, Lilly, Lundbeck, and Pfizer.

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