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Type A/Type B Alcoholism Predicts Differential Response to Topiramate in a Smoking Cessation Trial in Dually Diagnosed Men

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ABSTRACT. Objective: Babor's A/B typology characterizes alcohol-dependence subtypes, which differ across multiple defining variables; however, differences in cigarette smoking and cessation between these subtypes have not been previously investigated. Topiramate reduces heavy drinking and has separately been found to help non–alcohol-dependent individuals quit smoking. This study tested the hypothesis that topiramate's effects on smoking would be moderated by alcohol-dependence subtype, and explored craving as a mediator of this response. **Method:** One hundred twenty-nine abstinent alcohol-dependent outpatient male smokers participated in this 12-week, randomized controlled trial comparing topiramate (maximum dosage 200 mg/day) with placebo, both with brief counseling, for smoking cessation. Participants were followed for 24 weeks following end of treatment. **Results:** Of the 125 participants with sufficient subtyping data, k-means cluster analysis categorized 52 (42%) as Type A alcoholics and 73 (58%) as Type B. Types A and B did not differ on baseline smoking characteristics, urges to smoke, or smoking consequence scores. Longitudinal mixed-effects regression indicated that the effect of treatment on smoking was moderated by the Type × Time interaction. Specifically, during the nontreatment follow-up phase, Type B's treated with topiramate had relative suppressed levels of smoking compared with placebo-treated Type B's. This moderating effect of the Type × Time interaction was mediated by intention to smoke and craving related to relief of negative affect. **Conclusions:** Type B alcoholics demonstrated suppressed levels of smoking in response to topiramate treatment as compared with placebo, but only during the nontreatment follow-up phase. This effect was mediated, in part, through intention to smoke and craving to smoke to relieve negative affect. Our findings extend other studies demonstrating a differential medication response by alcoholism subtype. (*J. Stud. Alcohol Drugs, 78,* 232–240, 2017)

CIGARETTE SMOKING IS highly co-morbid with drinking, and among treatment-seeking alcoholics, the prevalence of smoking has been estimated to be as high as 80% (Kalman et al., 2010), or four times greater than for adults in the general population (Agaku et al., 2014). Men who are heavy drinkers and smoke have an age-adjusted relative rate of all-cause mortality of 2.7 compared with nonsmoking nondrinkers (Hart et al., 2010), and continued smoking following treatment for an alcohol use disorder is associated with a greater likelihood of relapse to alcohol and other drug use (Kohn et al., 2003).

There is a great need for medications that concurrently treat alcohol and nicotine use disorders and that support ongoing abstinence from both (Van Skike et al., 2016). Use of one medication for both nicotine and alcohol dependence may reduce overall cost and "pill burden," which in turn may lead to increased medication adherence in this patient population (Erwin & Slaton, 2014).

Previous alcohol- and tobacco-cessation studies, in combination, show that topiramate may hold promise as a dual-treatment medication. Topiramate has shown effectiveness in reducing heavy drinking and promoting alcohol abstinence (Johnson et al., 2003, 2007), as well as preventing early relapse to alcoholism (Martinotti et al., 2014; Paparrigopoulos et al., 2011). Topiramate has also been investigated as an aid to smoking cessation. For example, Johnson et al. (2005) reported a fourfold increase in smoking cessation in participants treated with topiramate as part of an alcohol treatment trial. Anthenelli et al. (2008) further demonstrated topiramate's ability to reduce nicotine withdrawal and enhance short-term smoking-cessation rates. However, these benefits were limited to the male smokers in their mixed-gender, non–alcohol-dependent sample. These results were corroborated, in part, by Oncken et al. (2014), but those investigators did not find a Treatment × Sex interaction effect in the non–alcohol-dependent smokers studied.

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Alcoholism typology has been demonstrated to moderate the pharmacotherapeutic effects of several different medications on drinking outcomes (Kranzler et al., 1996; Pettinati et al., 2000). As an extension of that work, and given topiramate's potential dual effects, it is important to understand how typology might also affect smoking outcomes in dually dependent patients, which has not been previously studied. This may help to increase our understanding of whether there are shared mechanisms governing conjoint smoking and drinking or perhaps divergent pathways that may drive differential smoking and drinking responses to the same medication.

Efforts to understand how alcoholism typology may affect response to smoking-cessation pharmacotherapy require consideration of the multiple methods of subtyping alcohol dependence—including both single-domain (e.g., age at onset of alcoholism) and multidimensional formulations. Babor et al. (1992b) used a multidimensional approach, resulting in an empirically derived Type A/Type B classification based on indicators of vulnerability and severity. Type A alcoholics were characterized as having later onset, less severe dependence, fewer childhood risk factors, and less psychopathological dysfunction. Type B alcoholics demonstrated the opposite pattern, with increased familial alcoholism, early onset of alcohol-related problems, polydrug use, a more chronic treatment history (despite their younger age), and more life stress (Babor et al., 1992b). Babor's typology has since been applied in multiple studies to evaluate its usefulness in matching patients to treatments and determining treatment outcomes (Bogenschutz et al., 2009; Kranzler et al., 1996). Although preferential pharmacological treatment outcomes by medication and type are mixed, the majority of the studies indicate that Type B alcoholics are, in general, more difficult to treat (Kampman et al., 2007).

Although Babor et al. (1992b) included benzodiazepine and illicit polydrug use as two of the typology clustering variables, differences in nicotine dependence between Type A and B alcoholics have never been characterized in the literature. Given the proclivity for substance use disorders to be co-morbid, with Type B alcoholics having higher rates of polydrug use, this subtype may be more at risk for having nicotine dependence, as well as potentially having greater severity of dependence. Understanding these potential differences in smoking characteristics would be helpful in predicting nicotine-dependence severity and subsequent best treatment options in alcoholic smokers.

Finding shared linkages between the drivers of both smoking and drinking outcomes in dually dependent individuals may further aid in the quest to find dual-treatment medications. Substance use outcome expectancies may influence dual-treatment response. "Relief drinking" in Babor's original typology clustering showed significant differentiation between Type A and B male alcoholics, with Type B's reporting higher measures of alcohol consumption to relieve withdrawal and psychological distress (Babor et al., 1992b). Whether an individual's expectancy for alcohol translates to similar expectancies for cigarette smoking is unclear. However, smoking expectancies are predictive of smoking behavior (Kelemen & Kaighobadi, 2007), and, specifically, negative reinforcement expectancies have been found to predict greater rates of smoking-cessation failure (Wetter et al., 1994). If alcoholic typologies that favor relief drinking (e.g., Type B alcoholics) also favor relief smoking, this may have predictive value in smoking-cessation outcomes with or without concurrent medication treatment.

Differences in the degree of alcohol craving between typologies may also potentially affect differential medication responses. Although craving is likely multifactorial in etiology, genetic polymorphisms involving various hormones that modulate craving may predispose some alcoholic types to increased alcohol craving, whereas gene variations in other types may give some protection (Kenna et al., 2012). Whether these genetic differences that modulate alcohol craving might also modulate craving for other substances, such as nicotine, is largely unknown. Cigarette craving intensity in response to smoking-relevant cues has been found to predict likelihood of smoking, latency to smoke, and amount smoked (Shiffman et al., 2013). If hormonally affected craving for alcohol in different subtypes were to similarly affect concomitant nicotine craving, this may have predictive value of smoking response to medication among subtypes.

To evaluate the relationship between alcoholism typology and smoking, we examined (a) whether Type A and B alcoholics differed in their tobacco smoking characteristics and (b) whether typology moderates the effects of topiramate to simultaneously treat tobacco and alcohol dependence. We hypothesized that Type B alcoholics would be heavier and more severely dependent smokers than Type A alcoholics based on their higher rates of polysubstance abuse, greater psychopathological dysfunction, increased childhood risk factors, and greater life stress, each of which have independently been shown to be positive predictors for smoking (Cui et al., 2012; Fraser et al., 2014; Lasser et al., 2000; Park, 2011) and cumulatively might suggest potential for heavier and more dependent tobacco use. Whether alcoholic typology affects smoking outcomes has not been previously evaluated. We tested the hypothesis that topiramate's effects on smoking would be moderated by alcohol-dependence subtype, such that Type A alcoholics would demonstrate a preferential drug treatment response as compared to the Type B group, based on the hypothesized differences in nicotine dependence and previous studies indicating that Type B alcoholics are more generally resistant to treatment (Kampman et al., 2007). Last, we explored differences in smoking outcome expectancies between the two typologies and whether the hypothesized subtype differences in response to topiramate were mediated by craving.

Method

Study design

The present study used data obtained during a 36-week, dual-center, randomized, double-blind, parallel-group, smoking-cessation clinical trial of topiramate versus placebo in outpatient male smokers in recent recovery from alcohol dependence who were motivated to quit smoking (Anthenelli et al., 2017). The parent study was designed to include male subjects only, based on a prior study showing that topiramate aided smoking cessation in non–alcohol-dependent men but not women (Anthenelli et al., 2008). The hypotheses of the primary study were that topiramate-treated participants would have (a) higher smoking quit rates and (b) reduced rates of relapse to alcohol and other drug use compared with placebo in the context of smoking-cessation treatment. Testing moderation of topiramate's effects on smoking by alcoholism typology was an a priori secondary aim. Subjects were sequentially recruited for participation at the Cincinnati (2009–2011) and San Diego (2012–2014) study sites. The study underwent human subjects review and was approved by the institutional review boards of the University of Cincinnati, University of California at San Diego, and Veterans Affairs San Diego Healthcare System.

All subjects gave informed consent for participation in the study at the screening visit. After screening, subjects were randomized into one of two treatment arms. In the subsequent 6 weeks, the medication treatment arm received dosages of topiramate that were gradually titrated up to 200 mg or maximal tolerated dose, and the placebo arm received similar-appearing placebo capsules. Both arms received weekly, 20-minute sessions of Brief Intervention for Smoking Cessation and Compliance Enhancement Therapy (BISC-CET), which integrates problem solving and skills training for smoking cessation (based on U.S. Public Health Service Clinical Practice Guidelines; Fiore et al., 2008) and compliance enhancement therapy (Carroll et al., 1999) to promote medication adherence. Subjects' target quit day was Day 43 after randomization, at the transition from the titration period to the 6-week maintenance dosing period. At the end of the maintenance period, there was a 1-week medication taper-off period, followed by a 24-week nontreatment follow-up period.

Participants

Subjects were recruited from the Cincinnati Veterans Affairs Medical Center Substance Dependence Program and treatment programs throughout the Greater Cincinnati area, during the Cincinnati phase of the study. Subsequently, subjects in San Diego were recruited from the San Diego Veterans Affairs Medical Center Alcohol and Drug Treatment Program and the Greater San Diego community. Subject inclusion criteria were 18–70 years of age; male outpatients with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association, 2000), current nicotine dependence, and alcohol dependence in early or sustained full remission (1–36 months of abstinence); current smokers with an average of 10 or more cigarettes per day in the 2 months before the screening visit; body mass index greater than or equal to 18.5 kg/m^2; and motivated to quit smoking (≥6 on a 10-point motivation scale) and to maintain abstinence from alcohol and illicit drugs. Exclusion criteria were clinically significant laboratory abnormalities or medical problems; current or lifetime diagnosis of a psychotic disorder; known hypersensitivity to topiramate; elevated suicidal/homicidal risk in the investigator's judgment; use of smoking-cessation aids, alcohol pharmacotherapies, or any investigational drug in the prior 30 days; and a current seizure disorder or a history of severe alcohol withdrawal (alcohol withdrawal seizures, hallucinations/illusions, delirium tremens).

Study measures

Information was collected from 133 randomized participants who were assessed in multiple areas including demographic characteristics; psychiatric and substance use disorder diagnoses; family history; smoking and alcohol use/severity and craving; and depression and anxiety.

Baseline measures used for alcohol subtyping were the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II) and its Family History Assessment Module (Bucholz et al., 1994) as well as two self-report instruments: the Michigan Alcoholism Screening Test (MAST; Selzer, 1971) and the Alcohol Dependence Scale (ADS; Skinner & Allen, 1982). The Timeline Followback (TLFB; Sobell & Sobell, 1992) was used at screening and repeatedly throughout the study to assess for alcohol relapse.

Smoking outcome was assessed with the Smoking TLFB (Gariti et al., 1998) administered at screening and weekly from treatment initiation through the end of the medication taper at Week 13. The TLFB was then assessed monthly through Week 36 with these data used to determine our primary outcome variable of average number of cigarettes smoked per day for each week. The baseline Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and Smoking Consequences Questionnaire–Adult (SCQ-A; Copeland et al., 1995) were used to determine whether nicotine-dependence severity and smoking outcome expectancies differed by alcoholic subtype. For the SCQ-A, we also measured three of its four factorial components—smoking expectancies for negative consequences, positive reinforcement, and negative reinforcement—to determine whether these motives differed by subtype. The Questionnaire on Smoking Urges–Brief version (QSU-Brief; Cox et al., 2001) was assessed at baseline and six time points (Weeks 4, 8, 12, 16, 24, and 36). The QSU-Brief total score

was further segregated into a two-factor structure, in which Factor 1 (QSU-Intent) reflects the anticipation of pleasure from smoking and the desire and intention to smoke, and Factor 2 (QSU-Relief) is associated with the anticipation of relief from nicotine withdrawal and negative affect. These two QSU scales were both examined as mediators of smoking outcomes.

Current depressive symptoms were assessed with the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979).

Data analysis: Subtyping

We used five clustering variables across four dimensions derived from Babor et al.'s (1992a, 1992b) original classification of Type A/B subtypes of alcoholism. Use of these five variables (lifetime severity of alcohol-related problems and abuse, alcohol-related medical problems, antisocial personality disorder symptoms, childhood behavior problems, and dependence severity) results in approximately 95% correct classification compared with Babor et al.'s (1992b) original 17 clustering variables (Brown et al., 1994). In the present study, a similar k-means clustering technique (Babor et al., 1992b) was performed for the subtyping analysis. The total scores on the MAST were used to measure lifetime severity of alcohol problems, and items from the SSAGA-II were used to derive alcohol-related medical problems. Antisocial personality disorder symptoms and childhood behavior problems were also derived from the SSAGA-II, and the ADS total score was used for current dependence severity.

Data analysis: Smoking outcomes by subtype

Differences in the demographic and clinical characteristics between the alcoholic subtypes were determined using univariate *t* tests or chi-square tests as appropriate. Longitudinal mixed-effects regression (Singer & Willett, 2003) was used to evaluate whether the effect of topiramate on cigarette smoking over time was moderated by alcohol typology. Cigarette smoking was operationalized as mean number of cigarettes per day for each week of participation. We used a modified intent-to-treat approach, such that all subjects who reported taking one or more topiramate/placebo dose ($n = 129$) were included; no assumptions were made regarding missing data. The initial model included random person-level intercepts and fixed effects of time, time^2, and time^3 terms, as well as all two- and three-way interactions between time, treatment (topiramate vs. placebo), and alcoholic subtype. Nonsignificant interaction terms were removed in a backward manner and the model was refit. Model comparisons indicated that the inclusion of both time^2, $\Delta LR\ \chi^2(1) = 575.63$, $p < .001$, and time^3, $\Delta LR\ \chi^2(1) = 322.18$, $p < .001$, main effects provided superior fit over models with simpler parameterizations of time. The final model did not include interactions between subtype or treatment with higher order time terms, as these higher order interactions did not provide superior model fit, $\Delta LR\ \chi^2(1) = 4.38$, $p = .22$. The inclusion of random slopes also did not significantly improve model fit. Significant interactions were followed by simple effects analyses that examined the effects of time, subtype, and their interactions after stratifying by treatment. Models also controlled for demographic and clinical covariates, including age, study site, baseline nicotine dependence, and baseline smoking.

We also hypothesized that the moderating effect of subtype would be mediated by cigarette craving, using the analytic framework recommended by Muller et al. (2005). The mediated effect was directly estimated with the products-of-coefficients approach, in which the mediated effect is the product of the "a path" (i.e., Predictor × Moderator effect on mediator) and the "b path" (mediator effect on outcome). For each mediator (QSU-Intent and QSU-Relief), the two path coefficients were estimated with two separate mixed-effects models using QSU data obtained at six postbaseline time points. The first model estimated the Treatment × Subtype interaction effect on QSU score, whereas the second model estimated the time-varying QSU score effect on smoking, with the Treatment × Subtype interaction controlled for. The 95% confidence interval (CI) of the mediated effect was determined with the bias-corrected bootstrap, a recommended procedure for obtaining the standard error of mediated effects (Mackinnon, 2008). Analyses were conducted in Stata version 14.0 (StataCorp LP, College Station, TX).

Results

Cluster analysis

Of the 129 subjects who comprised the modified ITT sample, 125 had sufficient data to be categorized into subtypes with 52 (42%) identified as Type A alcoholics and 73 (58%) as Type B. Of the five variables used in the cluster analysis, only the SSAGA-II number of adult antisocial personality disorder symptoms ($M = 1.68$) did not significantly differ between the two groups. As demonstrated by a greater than twofold elevated ADS score, Type B alcoholics demonstrated notably greater alcohol-dependence severity ($M = 22.8$, $SD = 7.9$) compared with Type A alcoholics ($M = 9.9$, $SD = 5.2$). As depicted in Table 1, Type B alcoholics were younger than Type A alcoholics ($p < .01$) and had a significantly greater proportion of White participants ($p < .05$), but the groups were otherwise similar in educational and employment status, length of alcohol abstinence at study intake, and mood ratings.

Smoking characteristics by subtype

Baseline mean cigarettes per day did not significantly differ between Type A/B smokers, nor did the groups differ

Table 1. Demographic and clinical characteristics

Variable	Alcohol typology		
	Type A *M* (*SD*)	Type B *M* (*SD*)	Total *M* (*SD*)
Age, in years**	51.9 (7.7)	45.1 (8.5)	47.2 (9.3)
Ethnicity, % White*	45.3%	66.4%	57.9%
Years of education	12.6 (1.5)	12.6 (1.8)	12.5 (1.7)
Months worked in past year	4.2 (5.0)	4.5 (4.1)	4.1 (4.5)
Days since last drink	156.2 (158.6)	178.3 (196.7)	162.8 (172.4)
Baseline no. of cigarettes per day	18.0 (7.1)	19.7 (7.0)	19.3 (7.8)
Maximum cigarette abstinence, days	300.9 (693.9)	203.6 (370.0)	312.7 (679.3)
Baseline FTND	5.1 (1.9)	5.3 (1.9)	5.4 (1.9)
Baseline MADRS	1.4 (3.6)	1.8 (3.4)	1.6 (3.3)
QSU-Brief: Total	36.8 (13.7)	32.4 (12.6)	35.7 (14.1)
QSU-Brief: Intent	21.6 (8.1)	19.9 (7.8)	21.5 (8.3)
QSU-Brief: Relief	15.1 (6.7)	12.7 (6.0)	14.3 (7.0)
SCQ-A: Negative Consequences***	5.7 (1.2)	6.4 (0.9)	6.1 (1.2)
SCQ-A: Negative Reinforcement	5.6 (2.2)	6.2 (1.8)	6.1 (2.0)
SCQ-A: Positive Reinforcement	5.2 (1.6)	5.5 (1.5)	5.4 (1.6)

Notes: No. = number; FTND = Fagerström Test for Nicotine Dependence; MADRS = Montgomery–Asberg Depression Rating Scale; QSU-Brief = Questionnaire on Smoking Urges–Brief (Factor 1: Intent or desire to smoke; Factor 2: Relief of negative affect); SCQ-A = Smoking Consequences Questionnaire–Adult.
*$p < .05$; **$p < .01$; ***$p < .001$.

in terms of overall cigarette craving as measured throughout the study by the QSU-Brief. The percentage adherent to medication (i.e., using 80% of the prescribed maximal target dose) was similar in Type A (93%) and Type B (87%) smokers, $\chi^2(1) = 1.07$, $p = .30$, as was the mean maximum dosage achieved (Type A = 170 mg; Type B = 171 mg). Type A/B smokers also did not significantly differ on baseline nicotine-dependence scores or longest previous period of smoking abstinence. Scores on the SCQ-A indicated that Type B smokers had significantly greater expectancies for negative consequences from smoking ($p < .001$) but did not significantly differ from Type A smokers on negative or positive smoking reinforcement expectancies.

Smoking outcomes by subtype

Overall, the main effect of topiramate on smoking reduction was not statistically significant, but analyses of smoking outcomes over the 36-week study (Table 2) revealed a significant Type × Treatment × Time interaction ($z = -5.90$, $p < .001$). As shown in Figure 1, the temporal patterns of smoking in the placebo and topiramate conditions differed for Type A and Type B groups. In the Type A group, topiramate initially led to lower smoking than placebo, but this small difference in smoking abated over time such that topiramate and placebo had similar smoking during follow-up. In contrast, in the Type B group, topiramate appeared to suppress increases in smoking over time; the placebo condition had lower smoking during treatment, but the topiramate condition had lower smoking during follow-up. When we stratified the sample by medication condition, a statistically significant Type × Time interaction effect in the placebo condition ($z = 4.86$, $p < .001$) indicated that the Type B group had greater increases in smoking over time as compared with Type A. However, the opposite pattern was observed in the topiramate condition, as a significant and negative Type × Time simple interaction effect ($z = -3.59$, $p < .001$) indicated that over time the Type A group had relative increases in smoking compared with Type B. This was likely attributable to Type A's initially having lower levels of smoking, but both groups ending at similar levels of smoking in the final month of follow-up.

Mediation analyses were conducted to assess whether the observed Treatment × Subtype × Time interaction effect could be explained by the medication's effects on cigarette craving (Figure 2). Data for these analyses were limited to the six visits in which both QSU and smoking were assessed. For QSU-Intent, the mediated effect was negative and statistically significant (*ab* = -0.41, bias-corrected 95% CI [-0.72, -0.08]), such that the Treatment × Type interaction predicted lower smoking via lower QSU-Intent scores. For QSU-Relief, the estimated indirect effect was also negative and statistically significant (*ab* = -0.35, bias-corrected 95% CI [-0.66, -0.21), such that the Treatment × Type interaction predicted lower smoking via lower QSU-Relief scores. These results indicated that topiramate reduced cigarette craving to a greater extent for the Type B versus Type A group, which mediated the differential effects of topiramate on smoking outcomes in the Type A and Type B groups.

Discussion

To our knowledge, the present study is the first to examine smoking differences in Type A/Type B alcohol-dependent individuals. Latent variable analyses in this sample produced two subgroups that generally matched the profiles of Type A/

TABLE 2. Longitudinal mixed-effects regression model: The relationship between treatment and mean number of cigarettes smoked per day from Weeks 1 to 36 was moderated by type and varied over time (see Figure 1 for graphic depiction of smoking rates over time)

Variable	Coefficient	*SE*	*z*	*p*
Intercept	24.43	1.26	19.44	<.001
Site[a]	-2.26	1.00	-2.25	<.05
Age	-0.07	0.31	0.17	.17
Baseline cigarettes/day	0.44	0.07	6.05	<.001
FTND[b]	0.02	0.31	0.95	.95
Time[c]	-2.62	0.09	-30.33	<.001
Time (quadratic)	0.13	0.01	23.02	<.001
Time (cubic)	-0.002	0.0001	-18.72	<.001
Treatment	-1.87	1.51	-1.24	.22
Type	-1.13	1.37	-0.82	.41
Treatment × Type	2.88	1.92	1.50	.14
Treatment × Time	0.13	0.03	4.55	<.001
Type × Time	0.13	0.03	5.24	<.001
Treatment × Type × Time	-0.22	0.04	-5.90	<.001

[a]0 = Cincinnati, 1 = San Diego; [b]Fagerström Test for Nicotine Dependence; [c]time coded in weeks since baseline (1–36).

Type B alcoholism described in prior research (Babor et al., 1992b). Contrary to our initial hypothesis, we did not detect any significant difference in baseline rates of smoking or nicotine-dependence severity between the two groups, and there was no difference in the longest previous period of smoking abstinence. Type B smokers were found to have greater expectancies for negative consequences from smoking. However, the "relief drinking" analog previously reported in Type B alcoholics did not translate to similar expectancies with smoking, as Type A and B groups had similar negative and positive smoking reinforcement expectancies.

The smoking patterns observed during the trial were generally consistent with our hypothesis that Type A/Type B alcoholics would differentially respond to topiramate's effects on smoking in this dually dependent population. However, we did not expect the specific pattern that was observed. Namely, Type B alcoholics on placebo had increased levels of smoking compared with topiramate-treated Type Bs, but this difference did not emerge until the posttreatment follow-up phase. Furthermore, this difference increased in magnitude over time, with greater separation between topiramate and placebo at later time points. In contrast, during

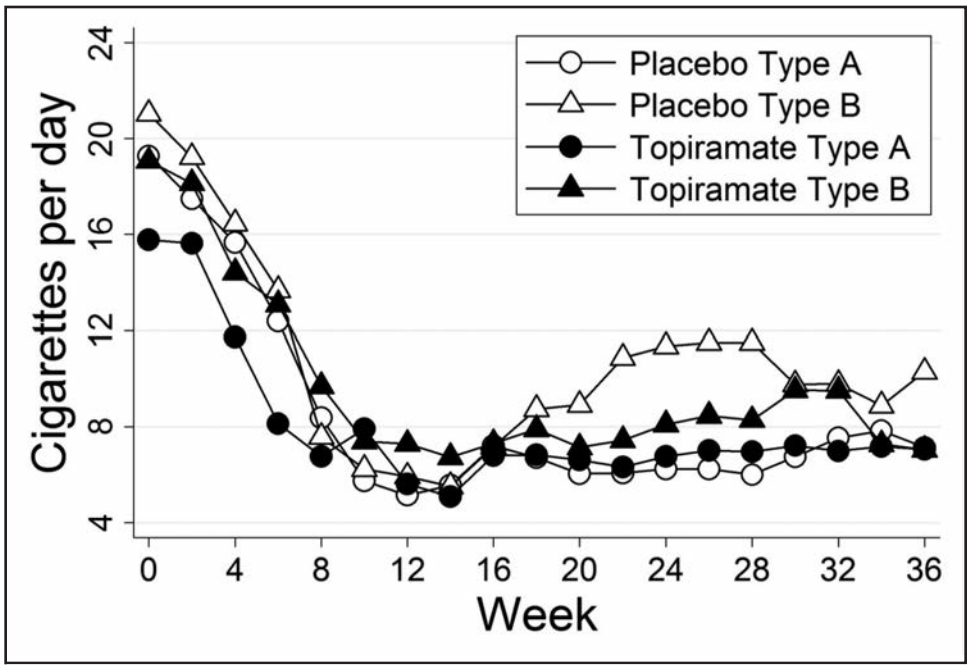

FIGURE 1. Average daily cigarette smoking rates per week in the Type A (circles) and Type B (triangles) subgroups as a function of treatment with topiramate (filled symbol) versus placebo (open symbol). Weeks 1–12 represent the active treatment phase, and Weeks 13–36 are the nontreatment follow-up phase. For clarity, only biweekly time points are illustrated.

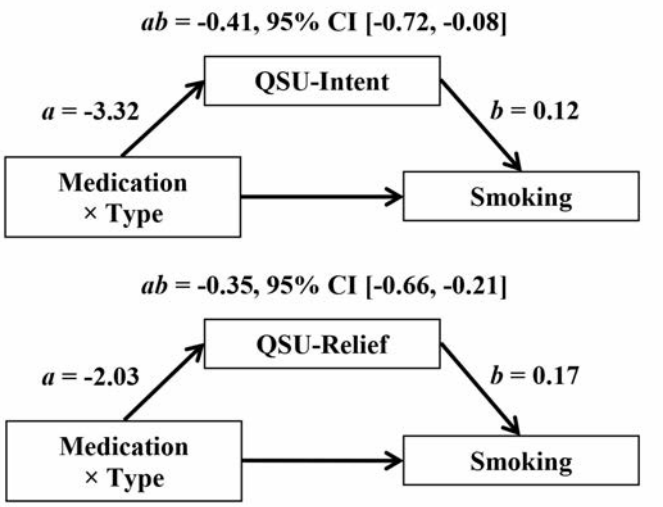

FIGURE 2. Display of analytic model for mediated moderation analyses and estimation of mediated effect with the Topiramate × Subtype interaction predicting smoking outcomes indirectly via scores on the Questionnaire of Smoking Urges (QSU)–Brief subscales (Intention and Relief). CI = confidence interval.

follow-up, Type A alcoholics had similar levels of smoking in the topiramate and placebo conditions. Taken together, one interpretation of these results is that Type B smokers might have derived more benefit from the combination of topiramate and counseling than did Type A smokers.

In addition, although there was no significant difference in overall or factor-based craving between the Type A/B typologies as measured by the QSU-Brief, we observed that the intention to smoke and craving to smoke to relieve negative affect mediated the differential response to topiramate. Specifically, the impact of topiramate on cigarette craving was greater for the Type B group, which at least partially explains its enhanced efficacy on smoking over time in this subtype. A similar mediated moderation was demonstrated in a study by Kranzler et al. (2014), in which mean daily self-efficacy to resist heavy drinking mediated the Topiramate × Genotype interaction. Although our data did not support an expected baseline difference between typology groups in negative reinforcement smoking expectancies, the mediated moderation results suggest that stronger effects of topiramate on relief-related craving for the Type B group were implicated in suppressing their long-term increases in smoking. Consistent with prior literature on alcohol use (Kampman et al., 2007), these data support the goal of targeting negative reinforcement mechanisms of smoking in Type B alcoholic smokers.

Recent work comparing alcoholic typologies by Kranzler et al. (2012) has suggested that early age at onset of alcoholism (e.g., <25 years old) may be an equally significant moderator of alcohol treatment response and easier to apply than cluster-derived typology groups. We conducted additional analyses comparing early age at onset in our sample, and although early age at onset was more common in the Type B group than Type A (56% vs. 44%), this was not a statistically significant difference, $\chi^2(1) = 0.51$, $p = 48$. Furthermore, age at onset did not predict smoking reduction and did not moderate medication effects on smoking outcomes.

In prior research, the effects of topiramate on drinking outcomes did not vary significantly by age at onset (Johnson et al., 2003), and to our knowledge no prior study examined differential drinking responses to topiramate using Babor's typological classification. Our study did not find Type A/B group differences in relapse to alcohol; the study also was not designed to test this outcome, given that the sample comprised alcohol-dependent smokers in relatively stable recovery from drinking. Future research may be needed to continue exploring the relevance of the Type A/B distinction for pharmacotherapy response, given that personalizing treatment is an important next step toward further improving treatment outcomes for substance use and smoking.

A limitation of our study is that the cluster analysis characterization of Type A/B groups was done post hoc; therefore, stratified randomization to topiramate versus placebo for each group was not done. Other studies have done similar post hoc subtyping (Dundon et al., 2004; Kranzler et al., 1996; Roache et al., 2008) and have had replicable results. A second limitation stems from the differences among studies in the methods used to characterize Type A/B groups. However, high levels of concordance with Babor's original characterizations have been found by using measurements that represent the four main dimensions of the Babor typology (Dundon et al., 2004). Although our ability to compare smoking outcomes using two separate methods of alcoholic subtyping is a strength in our study, it would be beneficial in future studies to include genotyping as a less subjectively derived typological method. Third, all of our participants were male and the majority were veterans, thus limiting the generalizability to the population at large. Last, our sample size is relatively small; thus, we were likely underpowered to adequately assess whether Type A/Type B individuals differ on the relief-smoking construct.

In conclusion, these findings lend further support to the hypothesis that alcoholism subtypes differentially affect medication treatment responses and extend that observation to smoking outcomes. We also present data supporting the idea that craving may partially mediate this differential response. There is an ongoing need to clarify underlying mechanisms and find linkages between drivers of outcomes for those individuals who are both alcohol and nicotine dependent, both to aid in treatment strategies and, ultimately, to facilitate the prevention of the development of these disorders.

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Conflict of Interest Statement

Robert M. Anthenelli provides consulting and/or advisory board services to Pfizer, Inc., Arena Pharmaceuticals, and Cerecor. The views expressed in this manuscript are the authors' own and do not necessarily reflect the views of the Department of Veterans Affairs or the University of California.

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