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Topiramate decreases the salience of motivationally relevant visual cues among smokers with alcohol use disorder

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Abstract

Background: There is preliminary evidence that the anticonvulsant topiramate increases the likelihood of both smoking and alcohol abstinence among smokers with alcohol use disorder (AUD), but its therapeutic mechanism has not been determined. We used event-related potentials (ERPs) to evaluate topiramate's effect on the salience of drug-related, emotional, and neutral pictorial cues to identify whether one of its potential therapeutic mechanisms involves reduction of the salience of motivationally relevant cues.

Methods: Participants, who were enrolled in a multisite clinical trial treating smokers with AUD, were randomized to receive placebo, low-dose topiramate (up to 125 mg/day), or high-dose topiramate (up to 250 mg/day), along with brief behavioral compliance enhancement treatment. A subsample (n=101) completed ERP assessments at baseline (1 week pre-medication) and week 5 (5 weeks on medication; 1 week pre-quit). We assessed the salience of pleasant, unpleasant, cigarette-related, alcohol-related, and neutral pictorial cues using the late positive potential (LPP) ERP component, and measured self-reported substance use, reinforcement, craving, and withdrawal.

Results: Five weeks of high-dose topiramate treatment decreased LPP amplitudes to both emotional (pleasant and unpleasant) and drug-related cues (alcohol and cigarette), but not to neutral cues. However, results showed that the LPPs were not significant mediators of the

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Conflicts of Interest

Dr. Ait-Daoud Tiouririne has filed US patent applications involving topiramate. Dr. Anthenelli receives research support from Pfizer and Embera NeuroTherapeutics. Dr. Cinciripini served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on smoking cessation (2006–2008), and has received grant support from Pfizer. The other authors do not have any potential conflicts to report.

relationship between topiramate dose and post-quit measures of substance use, reinforcement, craving, or withdrawal.

Conclusions: These findings suggest that high-dose topiramate (up to 250 mg/day) decreases the motivational salience of both drug-related and emotional cues among smokers with AUD. However, the nonsignificant mediation analyses preclude any firm conclusions about whether this effect represents one of topiramate's therapeutic mechanisms of action.

Keywords

Topiramate; smoking; alcohol use disorder; event-related potentials; late positive potential; cue reactivity; mediation

INTRODUCTION

Tobacco (TUD) and alcohol use disorders (AUD), two of the greater preventable causes of disease and death in the world (Lopez et al., 2006), frequently co-occur (Grant et al., 2004), with the prevalence of past-year TUD among those with past-year AUD in the United States being 51.7% (Parker et al., 2019). Studies have found that those who quit smoking had higher rates of alcohol abstinence than did those who had not quit smoking (Campbell et al., 1995; Friend and Pagano, 2005; Sobell and Sobell, 1996), which suggests that concurrent treatment of both TUD and AUD would be beneficial. One candidate medication is the anticonvulsant topiramate, a sulfamate-substituted fructopyranose derivative with both GABAergic and glutamatergic properties, which has been found to reduce drinking among those with AUD (Johnson et al., 2007; Kranzler et al., 2014; Kranzler et al., 2021). In a post-hoc analysis extending their previously published report on topiramate's effects on reducing alcohol drinking (Johnson et al., 2003a), Johnson and colleagues (2005) found that participants given topiramate were more likely to abstain from smoking than those given placebo. A small uncontrolled open-label study suggested that the majority of the study's 13-subject sample were able to abstain or reduce their daily smoking when given topiramate (Khazaal et al., 2006). The positive effects of topiramate on smoking cessation have been replicated in two other clinical studies (Baltieri et al., 2009; Oncken et al., 2014). However, topiramate's effects on concomitant smoking and alcohol treatment have been equivocal. A recent study found that topiramate did not differ from placebo in promoting smoking cessation or in preventing relapses to drinking among male smokers with AUD in remission (Anthenelli et al., 2017), although the authors found that topiramate reduced smoking among those with a subtype of AUD during post-treatment (Isgro et al., 2017).

Given the mixed evidence for topiramate's effectiveness in treating comorbid TUD and AUD, studying its underlying therapeutic mechanisms could help to optimize topiramate treatment strategies and to develop future pharmacotherapies for these conditions. One putative mechanism could be that topiramate directly reduces the salience of motivationally relevant cues (Khazaal and Zullino, 2007). This effect could result from topiramate's known inhibitory effect on the glutamatergic system, which has downstream effects on mesolimbic dopamine (DA) release. Specifically, topiramate antagonizes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamatergic receptors (Gibbs et al., 2000), and likely antagonizes N-methyl-D-aspartate receptor (NMDA)

glutamatergic receptors (Motaghinejad et al., 2017; Rawls et al., 2009). Antagonism of one or more of these glutamatergic receptors has been found to reduce nicotine- (Kenny et al., 2009; Kosowski et al., 2004; Schilström et al., 1997; Sziráki et al., 2002), alcohol- (Xiao et al., 2009), and cocaine-induced (Moghaddam and Bolinao, 1994; Pap and Bradberry, 1995) DA release in the nucleus accumbens, an essential step for the attribution of incentive salience to cues (Berridge and Robinson, 1998). Additionally, ionotropic glutamatergic antagonists have been found to block reinstatement of cue-conditioned drug-seeking behaviors in animals (Di Ciano and Everitt, 2001). Notably, topiramate, which is a known AMPA and kainate receptor antagonist (Gibbs et al., 2000; Skradski and White, 2000), has been found to reduce nicotine-induced dopamine (DA) release in the mesocorticolimbic DA pathways (Schiffer et al., 2001), the activation of which plays a key role in reward and drug addiction (Hyman et al., 2006; Volkow et al., 2002). Recent imaging work has found that topiramate, compared to placebo, reduces DA-mediated activity in mesocorticolimbic reward-related regions of the brain (Wetherill et al., 2021). Conversely, disruption of DA-mediated activity should reduce the incentive salience of drug cues, making them less attractive and less likely to induce appetitive motivation to use the drug (Berridge and Robinson, 1998). Reduction of mesolimbic DA availability has been found to reduce self-administration of nicotine (Corrigall and Coen, 1991), alcohol (Rassnick et al., 1992), and other drugs (Bergman et al., 1990; Woolverton, 1986) in animals and to reduce cue-elicited craving in alcohol- (Modell et al., 1993) and cocaine-abusing (Berger et al., 1996) humans.

The evidence for topiramate's ability to block drug craving in humans has been mixed. On the one hand, studies have found that topiramate decreases alcohol-related tonic craving (Johnson et al., 2003a) and alcohol cue-elicited craving (Wetherill et al., 2021), but another trial failed to find an effect of topiramate on cue-induced alcohol craving (Miranda et al., 2008). With smoking cessation, one small open-label study reported that most smokers who reduced or quit smoking while taking topiramate reported decreased craving to smoke (Khazaal et al., 2006), but another small double-blind study found that, compared with placebo, low-dose topiramate had no effect on cue-induced craving to smoke (Reid et al., 2007). Thus, although it is plausible, it is unclear whether topiramate's therapeutic mechanisms of action involve a DA-mediated reduction of the salience of motivationally relevant cues.

One approach to evaluate whether topiramate directly reduces the salience of motivationally relevant cues among humans is to use event-related potentials (ERPs). ERPs, which are scalp voltage measurements reflecting postsynaptic potentials in cortical pyramidal cells, provide a direct, noninvasive, millisecond-resolution measurement of neurotransmission-related neural activity (Luck, 2005). In humans, ERPs, particularly the late positive potential (LPP) component, are sensitive measures of motivational salience when the external stimuli are emotional and drug-related visual cues. Compared with neutral cues, emotional cues elicit increased levels of LPP, which typically peaks between 400 and 800 ms after stimulus onset over central and parietal sites on the scalp (Cuthbert et al., 2000; Keil et al., 2002; Schupp et al., 2000). In terms of drug cues, several studies have consistently shown that the LPP ERP component is enhanced to cigarette-related cues (McDonough and Warren, 2001; Versace et al., 2010; Warren and McDonough, 1999), even when compared with the LPPs of former smokers (Littel and Franken, 2007; Robinson et al., 2015), suggesting

that smoking-related cues are motivationally salient to smokers. Similar effects have been observed for LPP to alcohol-related cues among those with AUD (Namkoong et al., 2004; Petit et al., 2015). The robustness of the LPP as an index of response to drug-related cues makes it a potential methodology for evaluating topiramate's impact on motivational salience.

The current study evaluated topiramate's effect on the salience of drug-related, emotional, and neutral pictorial cues to determine whether the reduction of motivationally relevant cue salience is related to topiramate's therapeutic mechanism of action. Our first aim was to identify topiramate's impact on the motivational salience of drug-related and emotional cues as measured using the LPP. We hypothesized that if topiramate's primary therapeutic mechanism is to reduce the salience of motivationally relevant cues, then topiramate should result in decreased LPP amplitudes during the presentation of all motivationally relevant (drug-related, pleasant, and unpleasant) cues but not to neutral cues. Our second aim was to determine whether the reduction of motivationally relevant cue salience potentially mediates the impact of topiramate on post-quit substance use, reinforcement, craving, and withdrawal by using tests of indirect effects to evaluate the mediating effects of LPP to cue type. This manuscript presents the primary analyses of the ERP findings.

MATERIALS AND METHODS

Study Design

We recruited participants who were enrolled in a multisite placebo-controlled clinical efficacy trial (referred to as the parent trial) treating smokers with AUD who wanted to try to quit smoking and drinking (ClinicalTrials.gov Identifier: NCT01182766). As part of the parent trial, participants were randomized to receive placebo, low-dose topiramate (TPM-Low; up to 125 mg/day), or high-dose topiramate (TPM-High; up to 250 mg/day), along with brief behavioral compliance enhancement treatment (BBCET), to promote abstinence and prevent relapse to smoking and heavy drinking. Participants for the current study were all recruited at The University of Texas MD Anderson Cancer Center site, and they completed two laboratory ERP assessments that coincided with clinical visits at baseline (1 week pre-medication; i.e., 6 weeks pre-quit) and week 5 (5 weeks on medication; i.e., 1 week pre-quit; see Figure 1). These assessments consisted of dense-array ERPs (129 sensors) recorded during the presentation of drug-related (alcohol and cigarette cues), emotional (pleasant and unpleasant), and neutral pictorial cues.

A block randomization procedure stratified drug groups based on age at onset for AUD (<25 vs. ≥25 years old), sex at birth, number of drinks (standard drinking units [SDUs]) per drinking day (<8 vs. ≥8), and number of cigarettes smoked per day (<20 vs. ≥20). As part of the parent trial, participants completed an 18-week, double-blind treatment period, during which they received topiramate along with weekly brief behavioral compliance enhancement treatment (BBCET) and a self-help manual for smoking cessation. BBCET is a medication management intervention that emphasizes brief advice, compliance, motivation, and education for the treatment of comorbid AUD and smoking behavior (Johnson et al., 2003b). Titration of high-dose (50 mg to 250 mg) and low-dose (25 mg to 125 mg) topiramate, with matching placebo pill count, occurred over the first 5 weeks of the 18-week

treatment period. The targeted quit date (TQD) was set for the beginning of the sixth week of treatment, with participants instructed to not attempt smoking or alcohol cessation before the TQD. However, participants who either quit smoking or stopped consuming alcohol before the TQD continued to receive medication and counseling to prevent relapse.

Participants

Community participants were recruited using local media in the Houston, Texas metropolitan area. Inclusion criteria for the parent trial included being at least 18 years old, weighing at least 40 kg, and meeting Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-V; American Psychiatric Association, 2013) criteria for diagnosis of mild to severe AUD. Participants must have had an expired carbon monoxide (CO) level of ≥10 ppm or a urinary cotinine level of ≥ 3 ng/ml at screening, smoked an average of ≥ 5 cigarettes per day (CPD) in the 30 days prior to randomization, and consumed at least 8 standard drink units (SDUs) per week over the past month for women and at least 15 SDUs per week over the past month for men. In addition, participants were required to have a stable residence and personal telephone number, be proficient with written and oral English, and be willing to participate in a treatment program for both AUD and TUD. Women of child-bearing potential must have been using a medically acceptable form of contraception.

Exclusion criteria included meeting criteria for any current Axis I psychiatric disorder (other than AUD or TUD), as indicated on the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997), that warranted treatment or would preclude safe participation in the protocol, or having a history of suicide attempts in the previous 5 years. Participants were also excluded if they were taking medication that may adversely interact with topiramate (e.g., psychotropics, opioids, anticonvulsants, herbal preparations that impact the central nervous system), had a history of severe adverse events to anticonvulsants, received inpatient or outpatient treatment for AUD within the last 30 days prior to screening, engaged in treatment for TUD in the last 30 days prior to screening, tested positive for illicit substance use, or had members of the same household participating in the trial. Women who were pregnant or lactating were also excluded.

All participants provided informed consent at the baseline screening session that was approved by the University of Texas MD Anderson Cancer Center Institutional Review Board prior to initiating any study-related procedures. As assessed in the parent protocol, a blood alcohol concentration breath test was administered at consent and at subsequent visits as a safety measure. Participants were required to have a breath alcohol content (BAC) of 0.000% when signing the informed consent document. At subsequent visits, BAC was required to be ≤ 0.020% to complete the visit (3.43% had blood alcohol values greater than zero but less than 0.020% at laboratory visits). Participants earned up to $510 for completing all visits, procedures, and assessments that were part of the parent trial. Those electing to participate in this add-on study could earn an additional $170.

Assessments

Eligibility assessment (administered by the parent trial)—Participants initially eligible for the parent trial, as determined by a phone screen, were scheduled for an

in-person baseline screening session where the remaining eligibility criteria were assessed, including smoking status (expired CO and urinary cotinine level), illicit substance use (urinary drug screen), pregnancy status (urine pregnancy test), health (medical history, hematology, blood chemistry, urinalysis, and physical exam), and mental health (MINI).

Baseline substance use—Alcohol-related problems were measured using the Alcohol Use Disorders Identification Test (AUDIT; Bohn et al., 1995). Nicotine dependence severity was assessed using the Fagerström Test for Cigarette Dependence (FTCD; formerly the FTND; Fagerström, 2012; Heatherton et al., 1991). AUD was determined using the MINI (Lecrubier et al., 1997). Behavioral economics measures related to alcohol and tobacco use were also collected and are described elsewhere (Cui et al., 2021).

Post-quit-date substance use, reinforcement, craving, and withdrawal—Nicotine use was assessed by calculating the average number of cigarettes per day (CPD) taken from timeline follow-back of daily use (Brown et al., 1998) collected at each visit. CPD was supplemented by expired carbon monoxide (CO) measured at each visit. The modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al., 2007), the Brief Questionnaire of Smoking Urges (QSU-Brief; Cox et al., 2001), and the Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999), assessed nicotine reinforcement, craving, and withdrawal symptoms, respectively.

Alcohol use was assessed by calculating the average number of drinks per day (DPD) from timeline follow-back of daily use collected at each visit. Alcohol reinforcement, craving, and withdrawal were assessed by the Drug Effects Questionnaire (DEQ; Kirk and deWit, 2000), the Desires for Alcohol Questionnaire (DAQ; Love et al., 1998), and the Short Alcohol Withdrawal Scale (SAWS; Gossop et al., 2002), respectively. Nicotine and alcohol prolonged abstinence rates at EOT (18 weeks of medication) were evaluated as part of exploratory analyses.

Motivational salience (ERP picture-viewing task)—The two picture-viewing ERP assessments took place at baseline (1 week pre-medication) and at week 5 (5 weeks on medication; 1 week pre-quit). As illustrated in Figure 2, the ERP assessment consisted of EEG recorded during the presentation of neutral, emotional (pleasant and unpleasant), and drug-related (cigarette and alcohol) pictorial cues for 4 s each, separated by a random inter-trial interval of 3–5 s. Pictures were selected from the International Affective Picture System (IAPS; Lang et al., 2008) and from cigarette-related picture collections previously used in our (Carter et al., 2006) and other (Gilbert and Rabinovich, 1999) laboratories. The alcohol pictures were created for this study. To reduce the possibility of ERP responses habituating to specific cues, two unique sets of pictures were created, and the presentation order of each set was randomized across participants. Each set included 5 cue types (pleasant, unpleasant, neutral, alcohol-related, and cigarette-related) with 24 cues each (total, 120 pictorial cues per set). Each session was divided into 8 equivalent blocks lasting 3.8 min each and separated by a 30-s interval, during which time participants had the opportunity to relax. The cues were presented using Psychology Tools' E-prime software (version 1.4; Pittsburgh, PA) on a plasma screen placed approximately 1.5 m from the participant's eyes. The pictures subtended approximately a 24° horizontal viewing angle. The pictorial cues were presented

twice during the session, for a total of 240 trials, and the entire cue presentation lasted approximately 36 min.

Self-reported ratings of the cues used in the picture-viewing task—As a manipulation check, at baseline the participants rated one set of the pictorial cues (n=120) using an instrument based on the self-assessment manikin (SAM; Bradley and Lang, 1994) that assessed feelings of valence (i.e., pleasantness) and arousal (i.e., intensity) evoked by each cue on a 9-point scale. We also collected ratings for craving to smoke and drink alcohol evoked by each cue on a 9-point scale. We administered the SAM and craving ratings with E-Prime software using a computer mouse and monitor. The results of the picture ratings manipulation check are reported in the Supporting Information.

Data Analyses

ERP recording and scoring—During the picture-viewing task, we recorded electroencephalograms (EEGs) using a 129-channel Geodesic Sensor Net (HydroCel GSN 128; Electrical Geodesics Inc., Eugene, OR, USA) attached to an AC-coupled high input impedance (200 MΩ) amplifier (EGI's Geodesic EEG System 200) controlled by EGI's Net Station software (v4.2.1). The voltages were sampled at 250 Hz, filtered online using 0.1 Hz high-pass and 100 Hz low-pass filters, and referenced to Cz, with scalp impedances kept below 70 kΩ, per manufacturer's recommendation. Offline, using BESA (v5.3; BESA GmbH, Gräfelfing, Germany), we visually inspected the data, used spherical splines to interpolate channels contaminated by artifacts for more than 50% of the recording, removed eye blink-related artifacts using the spatial filtering method based on artifact topographies (Ille et al., 2002), and transformed the EEG data to the average reference. Using Brain Vision Analyzer (v2.1; Brain Products GmbH, Munich, Germany), we segmented the EEG into 900-ms segments (with baseline defined as the 100-ms interval preceding the pictorial cue onset), identified and excluded segments from the subsequent processing if more than 10% of the sensors were contaminated by artifacts, and exported the averaged segmented and filtered data for random permutation analysis. Selection of the LPP (408–800 ms) component was accomplished by identifying ERP temporal and spatial regions of interest (ROIs) using a random permutation analysis approach (Keil et al., 2014), which is detailed in the Supporting Information, along with the grand-average ERP waveforms. Finally, we performed a manipulation check of the resulting ROIs at baseline, by cue type, which is also detailed in the Supporting Information.

Statistical analyses

We evaluated the distributions of all continuous variables for skewness, outliers, and normality prior to analysis. Baseline differences, by drug group, were evaluated for continuous measures using one-way ANOVA with post hoc Tukey honestly significant difference (*HSD*) tests, and for categorical measures using Fisher's Exact Test. All analyses that examined the effects of cue type, drug group, Session, and their interactions (i.e., Aim 1) on LPP response were conducted using repeated measures mixed models analyses using SAS PROC MIXED (version 9.4; SAS Institute Inc., Cary, NC, USA), with treatment adherence through week 5 (full, partial, or no topiramate dose) as a covariate and subject modeled as a random effect. For significant interactions, we conducted post hoc pairwise

tests of simple effects (Winer, 1971) on least-square means (*LSM*) to identify the sources of significant differences. The post hoc comparisons were adjusted using the Holm-Bonferroni correction to control Type I error rate (Seaman et al., 1991). To assess for parallel multiple mediation (Aim 2), we used an indirect effect bootstrapping approach (Hayes, 2018; Preacher and Hayes, 2008). The Aim 2 analyses included the baseline (1 week pre-medication) LPP of each cue type and the baseline value of each outcome questionnaire as covariates to account for potential confounding by baseline values, along with the number of days on partial or full medication dose through the EOT. We estimated effect sizes by calculating partial eta squared values for analyses involving mixed models (Tippey and Longnecker, 2016). The η_p^2 values of 0.01, 0.06, and 0.14 are considered to be small, medium, and large effects, respectively (Cohen, 1988). We calculated Cohen's d_z (within-subjects) to report effect sizes for the pairwise comparisons resulting from the mixed models, with d_z values of 0.2, 0.5, and 0.8 considered to be small, medium, and large effects, respectively (Cohen, 1988).

RESULTS

Sample characteristics

Of those 128 participants who were randomized into the parent trial at the MD Anderson site between 25 February 2013 and 10 August 2017, 101 (78.9%) agreed to participate in this add-on study. Those who elected not to participate (n=27) in this add-on study did not significantly differ from those who did enroll (n=101) on any of the reported sample characteristics. Of the 101 randomized to this study, 100 produced scorable EEG at baseline and are included in the ERP analyses. Of the 78 who attended the second sessions at week 5, 77 produced scorable EEG. Baseline demographic, smoking, and alcohol measures for the 101 randomized participants are presented, by drug group, in Table 1, along with measures of treatment adherence. The sample was largely male, White or Black, and currently employed. Those randomly assigned to the TPM-High Dose group had significantly lower AUDIT scores at baseline than those in the PLA group.

Regarding treatment adherence, we experienced a 66.3% study discontinuation rate by EOT (18 weeks of medication). Only 35.6% of participants took the topiramate or placebo medication as prescribed, at either a full or reduced dose due to adverse events, on at least 80% of the days throughout the entire 18-week treatment period. This medication adherence rate did not differ by drug group (χ^2=0.87). More importantly for our analyses, only 70.3% (n=71) took either the full or reduced dose, as prescribed, on at least 80% of the days through the first five weeks of the pharmacotherapy titration period. The proportion of participants not taking the medication as initially prescribed on at least 80% of the days through week 5 did not differ by drug group (χ^2=0.22). Treatment adherence was included as a covariate in our Aims 1 & 2 analyses, as described in the Statistical Analyses section.

Aim 1: Identify topiramate's impact on the motivational salience of drug-related and emotional cues

To evaluate Aim 1, we examined the 3-way interaction among drug group, session (baseline vs. 5 weeks on medication), and cue type on LPP. The 3-way interaction was significant

(F[8,296]=2.16, p=.0302, η_p^2= 0.02). To parse this interaction, we conducted post hoc pairwise comparisons between the two sessions for each cue type and drug group to obtain the impact of 5 weeks of medication treatment on the LPP to each cue type (see Figure 3). For TPM-High, all of the pairwise comparisons of the motivationally relevant cues significantly differed by session. LPP voltages were lower at Week 5 when compared to baseline for alcohol (LSM=0.64 vs. 1.44 μV; t[296]=3.05, p=.0025, d_z=0.35), cigarette (LSM=1.05 vs. 2.25 μV; t[296]=4.60, p<.0001, d_z=0.52), pleasant (LSM=1.90 vs. 2.57 μV; t[296]=2.58, p=.0104, d_z=0.29), and unpleasant (LSM=1.89 vs. 2.53 μV; t[296]=2.38, p=.0179, d_z=0.27) cues, but not for neutral cues (LSM=0.74 vs. 0.75 μV; t[296]=0.01, p=.99, d_z=0.00). For TPM-Low, none of the cue types differed by pairwise comparisons between time points (all p's>.11). For Placebo, only LPP to alcohol cues differed between time points (LSM=0.93 vs. 1.87 μV; t[296]=3.65, p=.0003, d_z=0.42). These findings suggest that 5 weeks of TPM-High, but not TPM-Low, exposure reduced the motivational salience of both emotional and drug-related cues.

Aim 2: Determine whether the reduction of motivationally relevant cue salience mediates the impact of topiramate on post-quit substance use, reinforcement, craving, and withdrawal

To evaluate Aim 2, we used tests of indirect effects to assess the relationships between drug group, the hypothesized mediators (LPP ERP), and measures of cigarette and alcohol use (CPD/CO; DPD), reinforcement (mCEQ; DEQ), craving (QSU-Brief; DAQ), and withdrawal (WSWS; SAWS). We simultaneously evaluated Week 5 (5 weeks on medication; 1 week pre-quit) values of the five LPP ERP measures to cue type (pleasant, unpleasant, cigarette-related, alcohol-related, and neutral) as mediators of the impact of drug group (placebo, TPM-Low, or TPM-High) on post-quit (weeks 6–15) measures of substance use, reinforcement, craving, and withdrawal. We calculated an average of cigarette and alcohol use (CPD/CO; DPD) over weeks 6 (1 week post-quit) through 15 (EOT; 12 weeks post-quit) and measures of reinforcement (mCEQ; DEQ), craving (QSU-Brief; DAQ), and included withdrawal (WSWS; SAWS) obtained at week 15 (the only post-quit assessment of those measures).

In terms of direct effects, increasing drug dose resulted in significantly lower CPD, expired CO, and WSWS Craving scores post-quit; all other effects were nonsignificant. To assess whether each of the 5 mediators (i.e., LPP to cue type) mediated treatment effect on post-quit substance use, reinforcement, craving, and withdrawal, we calculated a 95% bootstrap confidence interval (CI) for each using an indirect effect bootstrapping approach. We did not find any significant indirect effects of LPP ERP to cue type as mediators of the relationship between drug group and measures of post-quit cigarette or alcohol use, reinforcement, craving, or withdrawal. These findings indicated that the reduction of motivational salience of the different cues, as measured by the LPP, did not mediate the relationship between drug group and smoking outcome. The full results of the tests of direct and indirect effects on the outcome measures are reported in Table S3.

DISCUSSION

Our Aim 1 findings showed that 5 weeks of high-dose topiramate treatment (250 mg/day) decreased the motivational salience, as measured by the LPP, of both emotional (pleasant and unpleasant) and drug-related cues (alcohol and cigarette). This effect was dose dependent, as this reduction in cue salience was not found for those taking the low-dose topiramate treatment (125 mg/day). However, we did find a reduction in LPP to alcohol cues among those in the placebo group, although this effect may be less reliable because the test-retest reliability between baseline and week 5 alcohol cues was low and not statistically significant ($r = 0.19$; see Table S2). We found no evidence that the reduction in cue relevance directly mediates high-dose topiramate's effects on smoking outcomes as measured by post-quit substance use, reinforcement, craving, or withdrawal, which precludes any firm conclusions about whether this effect represents one of topiramate's therapeutic mechanisms of action.

The ERP effects suggestive of a reduction in the salience of motivationally relevant cues are consistent with topiramate's known impact on the glutamatergic and DA systems, systems which have been found to influence cue-conditioned drug-seeking behaviors in animals. Topiramate is an AMPA and kainate receptor antagonist (Gibbs et al., 2000; Skradski and White, 2000), and is likely an NMDA receptor antagonist (Motaghinejad et al., 2017; Rawls et al., 2009). Antagonists of these receptors have been found to block reinstatement of cue-conditioned drug-seeking behaviors for alcohol (Bäckström and Hyytiä, 2004), cocaine (Bäckström and Hyytiä, 2003; Di Ciano and Everitt, 2001) and for other drugs of abuse (Layer et al., 1993) in animal models. One of the mechanisms by which glutamatergic receptor antagonists are thought to block cue-conditioned drug use reinstatement is through the reduction in drug-induced DA release in the mesocorticolimbic DA pathways (Steketee, 2003). Reduced DA release in the nucleus accumbens has been associated with reduced cue-induced reinstatement of most abused substances in animals (Perry et al., 2014), and with reduced cue-elicited craving among humans with SUDs (Berger et al., 1996; Modell et al., 1993).

To our knowledge, this is the first study to observe an impact of pharmacological treatment on ERP responses to a wide array of motivationally relevant visual cues. Typically, research has used self-reports to study drug effects on drug cue reactivity. For example, other studies have found indications that pharmacological treatment can reduce drug cue reactivity measured using self-report, including varenicline for smoking cues (Brandon et al., 2011; Franklin et al., 2011) and naltrexone for alcohol cues (Rohsenow et al., 2000). Given that self-report may not be the most reliable indicator of drug effects (Baker et al., 2004), functional brain imaging (e.g., fMRI, PET) is increasingly used to examine the impact of pharmacotherapy on cue reactivity. For example, varenicline was found to reduce ventral striatum and medial orbitofrontal cortex activity to smoking cues (Franklin et al., 2011), and bupropion has been found to reduce activity of the anterior cingulate cortex (Brody et al., 2004) and other areas of the mesolimbic dopaminergic system (Weinstein et al., 2010) to smoking cues, using these techniques. However, the cost of functional brain imaging has restricted its use mainly to smaller sample sizes. ERPs, which are more affordable and easier to administer than functional brain imaging approaches, are one approach that have been

proposed as an index of treatment response among those with SUDs (Houston and Schlienz, 2018). However, few ERP studies supporting this contention has have been reported. For example, we previously found no impact of treatment by varenicline or bupropion on LPP to smoking-related or emotional cues among smokers who sought to quit smoking (Versace et al., 2019). The current study is significant in that it is among the first to show that ERPs to motivationally relevant cues can be sensitive to medication effects and reveal information about their potential mechanisms of action.

While high-dose topiramate suppressed LPP responses to motivationally relevant cues, we found no evidence that this effect mediated topiramate's effects on post-quit substance use, reinforcement, craving, or withdrawal. None of the tests of indirect effects yielded evidence of such mediation occurring through topiramate's impact on LPP to any of the picture stimulus categories on any of our outcome measures. These null findings are possibly due to the inadequate statistical power of our sample needed to detect likely indirect effect sizes (Fritz and MacKinnon, 2007), particularly given the large number of study dropouts, and thus should be considered inconclusive. Additionally, a significant proportion of participants (41.6%) did not take the medication dose as initially prescribed, either because they had temporarily or permanently stopped taking topiramate altogether, or because they were temporarily put on a reduced (i.e., half) dose. Although the drug groups did not differ in medication compliance, a reduced dose could have attenuated the impact of medication on our measures.

While we found that increasing drug dose resulted in lower CPD, expired CO, and WSWS Craving scores, we did not find an effect of topiramate dose on self-reported measures of cigarette-related reinforcement or withdrawal, or on corresponding alcohol-related measures, unlike several previous studies. Our craving findings are inconsistent with previous work that found that topiramate reduced self-reported craving to alcohol (Batki et al., 2014; Johnson et al., 2003a; Miranda et al., 2016; Wetherill et al., 2021). With regards to smoking, our lack of a drug effect on withdrawal symptoms is inconsistent with a study that found that topiramate produced lower smoking withdrawal scores over time than placebo (Anthenelli et al., 2017). However, our mCEQ findings were consistent with those of Oncken and colleagues (Oncken et al., 2014), although they did find that topiramate led to decreases in the mCEQ reward scale over time. Thus, besides reduced cigarette craving and use, it is unclear whether topiramate improves other self-reported symptoms related to AUD or TUD.

The findings of this study are tempered by several limitations, particularly the relatively small sample size and the relatively low medication adherence rates. Only 77 (76.2%) participants completed the initial five-week medication titration period, with only 71 (70.3%) taking either the full or reduced dose, as prescribed, on at least 80% of the days during this period. The small number of participants per group likely limited our ability to detect likely effect sizes when examining between-group pairwise comparisons as part of Aim 1, and the number of participants available at the week 5 time point likely reduced our ability to detect likely effect sizes as part of the tests of indirect effects (Aim 2) and of the self-reported outcome measures (exploratory aims). Additionally, our study experienced a 66.3% discontinuation rate, although this high rate appears to be consistent with other topiramate studies. For example, the 1-year discontinuation rate among those

treated for seizure disorder was found to be approximately 45% for topiramate, with adverse events being the most common reason for discontinuation (Bootsma et al., 2004; Kellett et al., 1999). While the relatively high number of adverse events likely influenced the nonadherence rates, it is likely not the only cause of study dropout, as those in the placebo group had similar rates. However, our relatively low medication adherence rates and high number of reduced doses due to adverse events suggest that use of topiramate in the alcohol-abusing smoker population will be difficult to tolerate and to evaluate in terms of clinical effectiveness.

In conclusion, by measuring the amplitude of the LPP responses to emotional, drug-related, and neutral pictorial cues, we found that topiramate resulted in reduced motivationally relevant cue salience. Moreover, we found this effect only among those treated with high-dose topiramate (up to 250 mg/day) and not for among those treated with low-dose topiramate (up to 125 mg/day), although there was some evidence that response to alcohol cues decreased over time for the placebo group. Because we were unable to find evidence that reductions in the LPP to motivationally salient cues mediated the relationship between drug group and smoking outcomes, we were unable to determine whether this mechanism represents one of topiramate's therapeutic mechanisms of action. Future studies should include larger sample sizes and determine the time course of topiramate's impact on motivational salience by examining LPPs at further time points, including post-medication. Even though more work is needed to establish the validity of this ERP approach with regards to predicting therapeutic outcomes, our findings suggest that this ERP paradigm may be sensitive to drugs' effects on motivational salience, which could be useful for evaluating other medications used for treating substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Arlington, VA.

Anthenelli RM, Heffner JL, Wong E, Tibbs J, Russell K, Isgro M, Dinh E, Wehrle C, Worley MJ, Doran N (2017) A Randomized Trial Evaluating Whether Topiramate Aids Smoking Cessation and Prevents Alcohol Relapse in Recovering Alcohol-Dependent Men. Alcohol.Clin.Exp.Res 41: 197–206. [PubMed: 28029173]

Bäckström P, Hyytiä P (2003) Attenuation of cocaine-seeking behaviour by the AMPA/kainate receptor antagonist CNQX in rats. Psychopharmacology (Berl) 166: 69–76. [PubMed: 12525959]

Bäckström P, Hyytiä P (2004) Ionotropic glutamate receptor antagonists modulate cue-induced reinstatement of ethanol-seeking behavior. Alcohol.Clin.Exp.Res 28: 558–565. [PubMed: 15100606]

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC (2004) Addiction motivation reformulated: An affective processing model of negative reinforcement. Psychol.Rev 111: 33–51. [PubMed: 14756584]

Baltieri DA, Daró FR, Ribeiro PL, Andrade AGd (2009) Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients. Drug Alcohol. Depend 105: 33–41. [PubMed: 19595518]

Batki SL, Pennington DL, Lasher B, Neylan TC, Metzler T, Waldrop A, Delucchi K, Herbst E (2014) Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: A randomized controlled pilot trial. Alcohol.Clin.Exp.Res 38: 2169–2177. [PubMed: 25092377]

Berger SP, Hall S, Mickalian JD, Reid MS, Crawford CA, Delucchi K, Carr K (1996) Haloperidol antagonism of cue-elicited cocaine craving. Lancet 347: 504–508. [PubMed: 8596268]

Bergman J, Kamien JB, Spealman RD (1990) Antagonism of cocaine self-administration by selective dopamine D(1) and D(2) antagonists. Behav Pharmacol 1: 355–363. [PubMed: 11175420]

Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? Brain Res.Rev 28: 309–369. [PubMed: 9858756]

Bohn MJ, Babor TF, Kranzler HR (1995) The Alcohol Use Disorders Identification Test (AUDIT): Validation of a screening instrument for use in medical settings. J Stud.Alcohol 56: 423–432. [PubMed: 7674678]

Bootsma HPR, Coolen F, Aldenkamp AP, Arends J, Diepman L, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, Krom M de (2004) Topiramate in clinical practice: Long-term experience in patients with refractory epilepsy referred to a tertiary epilepsy center. Epilepsy Behav 5: 380–387. [PubMed: 15145308]

Bradley MM, Lang PJ (1994) Measuring emotion: The self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 25: 49–59. [PubMed: 7962581]

Brandon TH, Drobes DJ, Unrod M, Heckman BW, Oliver JA, Roetzheim RC, Karver SB, Small BJ (2011) Varenicline effects on craving, cue reactivity, and smoking reward. Psychopharmacology (Berl) 218: 391–403. [PubMed: 21559801]

Brody AL, Mandelkern MA, Lee G, Smith E, Sadeghi M, Saxena S, Jarvik ME, London ED (2004) Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: A preliminary study. Psychiatry Res 130: 269–281. [PubMed: 15135160]

Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW (1998) Reliability and validity of a smoking timeline follow-back interview. Psychol. Addict. Behav 12: 101–112.

Campbell BK, Wander N, Stark MJ, Holbert T (1995) Treating cigarette smoking in drug-abusing clients. J Subst Abuse Treat 12: 89–94. [PubMed: 7623395]

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG (2007) Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict.Behav 32: 912–923. [PubMed: 16875787]

Carter BL, Robinson JD, Lam CY, Wetter DW, Day SX, Tsan JY, Cinciripini PM (2006) A psychometric evaluation of cigarette stimuli used in a cue reactivity study. Nicotine Tob.Res 8: 361–369. [PubMed: 16801294]

Cohen J (1988) Statistical Power Analysis for the Behavioral Sciences 2nd edn. Lawrence Earlbaum Associates, Hillsdale, NJ.

Corrigall WA, Coen KM (1991) Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology (Berl) 104: 171–176. [PubMed: 1876661]

Cox LS, Tiffany ST, Christen AG (2001) Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob.Res 3: 7–16. [PubMed: 11260806]

Cui Y, Linares Abrego P, Yoon JH, Karam-Hage M, Cinciripini PM, Ait-Daoud Tiouririne N, Anthenelli RM, Robinson JD (2021) Behavioral Economic Assessment of Alcohol and Cigarette Demand in Smokers With Alcohol Use Disorder. Front.Psychiatry 12: 1107.

Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000) Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. Biol Psychol 52: 95–111. [PubMed: 10699350]

Di Ciano P, Everitt BJ (2001) Dissociable Effects of Antagonism of NMDA and AMPA/KA Receptors in the Nucleus Accumbens Core and Shell on Cocaine-seeking Behavior. Neuropsychopharmacol 25: 341–360.

Fagerström K (2012) Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. Nicotine Tob.Res 14: 75–78. [PubMed: 22025545]

Franklin T, Wang Z, Suh JJ, Hazan R, Cruz J, Li Y, Goldman M, Detre JA, O'Brien CP, Childress AR (2011) Effects of varenicline on smoking cue–triggered neural and craving responses. Arch Gen Psychiatry 68: 516–526. [PubMed: 21199958]

Friend KB, Pagano ME (2005) Smoking cessation and alcohol consumption in individuals in treatment for alcohol use disorders. J Addict.Dis 24: 61–75.

Fritz MS, MacKinnon DP (2007) Required sample size to detect the mediated effect. Psychol Sci 18: 233–239. [PubMed: 17444920]

Gibbs JW, Sombati S, DeLorenzo RJ, Coulter DA (2000) Cellular Actions of Topiramate: Blockade of Kainate-Evoked Inward Currents in Cultured Hippocampal Neurons. Epilepsia 41: 10–16.

Gilbert DG and Rabinovich NE (1999) The international smoking image series (with neutral counterparts), v. 1.2. Department of Psychology, Southern Illinois University, Carbondale, IL.

Gossop M, Keaney F, Stewart D, Marshall EJ, Strang J (2002) A Short Alcohol Withdrawal Scale (SAWS): Development and psychometric properties. Addict Biol 7: 37–43. [PubMed: 11900621]

Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA (2004) Nicotine dependence and psychiatric disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 61: 1107–1115. [PubMed: 15520358]

Hayes Andrew F. (2018) Introduction to mediation, moderation, and conditional process analysis: A regression-based approach The Guilford Press, New York.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991) The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. Br.J.Addiction 86: 1119–1127.

Houston RJ, Schlienz NJ (2018) Event-Related Potentials as Biomarkers of Behavior Change Mechanisms in Substance Use Disorder Treatment. Biol.Psychiatry Cogn.Neurosci.Neuroimaging 3: 30–40. [PubMed: 29397076]

Hyman SE, Malenka RC, Nestler EJ (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. Annu.Rev.Neurosci 29: 565–598. [PubMed: 16776597]

Ille N, Berg P, Scherg M (2002) Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. J Clin Neurophysiol 19: 113–124. [PubMed: 11997722]

Isgro M, Doran N, Heffner JL, Wong E, Dinh E, Tibbs J, Russell K, Bittner T, Wehrle C, Worley MJ, Anthenelli RM (2017) Type A/Type B Alcoholism Predicts Differential Response to Topiramate in a Smoking Cessation Trial in Dually Diagnosed Men. J Stud Alcohol Drugs 78: 232–240. [PubMed: 28317503]

Johnson BA, Ait-Daoud N, Akhtar FZ, Javors MA (2005) Use of oral topiramate to promote smoking abstinence among alcohol-dependent smokers: A randomized controlled trial. Arch.Intern.Med 165: 1600–1605. [PubMed: 16043677]

Johnson BA, Ait-Daoud N, Bowden CL, Diclemente CC, Roache JD, Lawson K, Javors MA, Ma JZ (2003a) Oral topiramate for treatment of alcohol dependence: A randomised controlled trial. Lancet 361: 1677–1685. [PubMed: 12767733]

Johnson BA, Diclemente CC, Ait-Daoud N, Stoks SM (2003b) Brief behavioral compliance enhancement treatment (BBCET) manual (Johnson BA, Ruiz P, Galanter M eds.), pp. 282–301. Lippincott Williams & Wilkins, Baltimore, MD.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA, Kranzler HR, Mann K, O'Malley SS, Swift RM (2007) Topiramate for treating alcohol dependence: A randomized controlled trial. JAMA 298: 1641–1651. [PubMed: 17925516]

Keil A, Bradley MM, Hauk O, Rockstroh B, Elbert T, Lang PJ (2002) Large-scale neural correlates of affective picture processing. Psychophysiology 39: 641–649. [PubMed: 12236331]

Keil A, Debener S, Gratton G, Junghofer M, Kappenman ES, Luck SJ, Luu P, Miller GA, Yee CM (2014) Committee report: Publication guidelines and recommendations for studies using

electroencephalography and magnetoencephalography. Psychophysiology 51: 1–21. [PubMed: 24147581]

Kellett MW, Smith DF, Stockton PA, Chadwick DW (1999) Topiramate in clinical practice: First year's postlicensing experience in a specialist epilepsy clinic. J Neurol Neurosurg Psychiatry 66: 759–763. [PubMed: 10329750]

Kenny PJ, Chartoff E, Roberto M, Carlezon WA, Markou A (2009) NMDA Receptors Regulate Nicotine-Enhanced Brain Reward Function and Intravenous Nicotine Self-Administration: Role of the Ventral Tegmental Area and Central Nucleus of the Amygdala. Neuropsychopharmacol 34: 266–281.

Khazaal Y, Cornuz J, Bilancioni R, Zullino DF (2006) Topiramate for smoking cessation. Psychiatry Clin Neurosci 60: 384–388. [PubMed: 16732758]

Khazaal Y, Zullino DF (2007) Topiramate-induced weight loss is possibly due to the blockade of conditioned and automatic processes. Eur.J.Clin.Pharmacol 63: 891–2; author reply 893. [PubMed: 17632711]

Kirk JM, deWit H (2000) Individual differences in the priming effect of ethanol in social drinkers. J Stud.Alcohol 61: 64–71. [PubMed: 10627098]

Kosowski AR, Cebers G, Cebere A, Swanhagen A-C, Liljequist S (2004) Nicotine-induced dopamine release in the nucleus accumbens is inhibited by the novel AMPA antagonist ZK200775 and the NMDA antagonist CGP39551. Psychopharmacology 175: 114–123. [PubMed: 15088078]

Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM (2014) Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. The American Journal of Psychiatry 171: 445–452. [PubMed: 24525690]

Kranzler HR, Morris PE, Pond T, Crist RC, Kampman KM, Hartwell EE, Lynch KG (2021) Prospective randomized pharmacogenetic study of topiramate for treating alcohol use disorder. Neuropsychopharmacol 46: 1407–1413.

Lang PJ, Bradley MM and Cuthbert BN (2008) International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8 University of Florida, Gainesville, FL.

Layer RT, Uretsky NJ, Wallace LJ (1993) Effects of the AMPA/kainate receptor antagonist DNQX in the nucleus accumbens on drug-induced conditioned place preference. Brain Res 617: 267–273. [PubMed: 8402155]

Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, Janavs J, Dunbar GC (1997) The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. Eur Psychiatry 12: 224–231.

Littel M, Franken IH (2007) The effects of prolonged abstinence on the processing of smoking cues: An ERP study among smokers, ex-smokers and never-smokers. J.Psychopharmacol 21: 873–882. [PubMed: 17984163]

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL (2006) Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. Lancet 367: 1747–1757. [PubMed: 16731270]

Love A, James D, Willner P (1998) A comparison of two alcohol craving questionnaires. Addiction 93: 1091–1102. [PubMed: 9744139]

Luck SJ (2005) An introduction to the event-related potential technique MIT Press, Cambridge, MA.

McDonough BE, Warren CA (2001) Effects of 12-h tobacco deprivation on event-related potentials elicited by visual smoking cues. Psychopharmacology (Berl) 154: 282–291. [PubMed: 11351935]

Miranda R, MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, Swift R, Ray L, McGeary J (2008) Effects of topiramate on urge to drink and the subjective effects of alcohol: A preliminary laboratory study. Alcohol.Clin.Exp.Res 32: 489–497. [PubMed: 18215213]

Miranda R, MacKillop J, Treloar H, Blanchard A, Tidey JW, Swift RM, Chun T, Rohsenow DJ, Monti PM (2016) Biobehavioral mechanisms of topiramate's effects on alcohol use: An investigation pairing laboratory and ecological momentary assessments. Addict Biol 21: 171–182. [PubMed: 25353306]

Modell JG, Mountz JM, Glaser FB, Lee JY (1993) Effect of haloperidol on measures of craving and impaired control in alcoholic subjects. Alcohol.Clin.Exp.Res 17: 234–240. [PubMed: 8488960]

Moghaddam B, Bolinao ML (1994) Glutamatergic antagonists attenuate ability of dopamine uptake blockers to increase extracellular levels of dopamine: Implications for tonic influence of glutamate on dopamine release. Synapse 18: 337–342. [PubMed: 7886626]

Motaghinejad M, Motevalian M, Fatima S, Beiranvand T, Mozaffari S (2017) Topiramate via NMDA, AMPA/kainate, GABA A and Alpha2 receptors and by modulation of CREB/BDNF and Akt/GSK3 signaling pathway exerts neuroprotective effects against methylphenidate-induced neurotoxicity in rats. J Neural Transm 124: 1369–1387. [PubMed: 28795276]

Namkoong K, Lee E, Lee CH, Lee BO, An SK (2004) Increased P3 amplitudes induced by alcohol-related pictures in patients with alcohol dependence. Alcohol.Clin.Exp.Res 28: 1317–1323. [PubMed: 15365301]

Oncken C, Arias AJ, Feinn R, Litt M, Covault J, Sofuoglu M, Kranzler HR (2014) Topiramate for smoking cessation: A randomized, placebo-controlled pilot study. Nicotine Tob.Res 16: 288–296. [PubMed: 24057996]

Pap A, Bradberry CW (1995) Excitatory amino acid antagonists attenuate the effects of cocaine on extracellular dopamine in the nucleus accumbens. J Pharmacol Exp Ther 274: 127–133. [PubMed: 7616389]

Parker MA, Sigmon SC, Villanti AC (2019) Higher smoking prevalence among United States adults with co-occurring affective and drug use diagnoses. Addict.Behav 99: 106112. [PubMed: 31476691]

Perry CJ, Zbukvic I, Kim JH, Lawrence AJ (2014) Role of cues and contexts on drug-seeking behaviour. Br J Pharmacol 171: 4636–4672. [PubMed: 24749941]

Petit G, Cimochowska A, Cevallos C, Cheron G, Kornreich C, Hanak C, Schroder E, Verbanck P, Campanella S (2015) Reduced processing of alcohol cues predicts abstinence in recently detoxified alcoholic patients in a three-month follow up period: An ERP study. Behav Brain Res 282: 84–94. [PubMed: 25576964]

Preacher KJ, Hayes AF (2008) Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 40: 879–891. [PubMed: 18697684]

Rassnick S, Pulvirenti L, Koob GF (1992) Oral ethanol self-administration in rats is reduced by the administration of dopamine and glutamate receptor antagonists into the nucleus accumbens. Psychopharmacology (Berl) 109: 92–98. [PubMed: 1365677]

Rawls SM, Thomas T, Adeola M, Patil T, Raymondi N, Poles A, Loo M, Raffa RB (2009) Topiramate antagonizes NMDA- and AMPA-induced seizure-like activity in planarians. Pharmacol.Biochem.Behav 93: 363–367. [PubMed: 19447129]

Reid MS, Palamar J, Raghavan S, Flammino F (2007) Effects of topiramate on cue-induced cigarette craving and the response to a smoked cigarette in briefly abstinent smokers. Psychopharmacology (Berl) 192: 147–158. [PubMed: 17345064]

Robinson JD, Versace F, Engelmann JM, Cui Y, Slapin A, Oum R, Cinciripini PM (2015) The motivational salience of cigarette-related stimuli among former never and current smokers. Exp Clin Psychopharmacol 23: 37–48. [PubMed: 25436840]

Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, Colby SM, Kaplan GB (2000) Naltrexone's effects on reactivity to alcohol cues among alcoholic men. J. Abnorm. Psychol 109: 738–742. [PubMed: 11195999]

Schiffer WK, Gerasimov MR, Marsteller DA, Geiger J, Barnett C, Alexoff DL, Dewey SL (2001) Topiramate selectively attenuates nicotine-induced increases in monoamine release. Synapse 42: 196–198. [PubMed: 11746717]

Schilström B, Nomikos GG, Nisell M, Hertel P, Svensson TH (1997) N-methyl-d-aspartate receptor antagonism in the ventral tegmental area diminishes the systemic nicotine-induced dopamine release in the nucleus accumbens. Neuroscience 82: 781–789.

Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ (2000) Affective picture processing: The late positive potential is modulated by motivational relevance. Psychophysiology 37: 257–261. [PubMed: 10731776]

Seaman MA, Levin JR, Serlin RC (1991) New developments in pairwise multiple comparisons: Some powerful and practicable procedures. Psychol Bull 110: 577–586.

Skradski S, White HS (2000) Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia 41 Suppl 1: S45–7. [PubMed: 10963478]

Sobell LC, Sobell MB (1996) Alcohol Abuse and Smoking: Dual Recoveries. Alcohol Health Res World 20: 124–127. [PubMed: 31798042]

Steketee J (2003) Neurotransmitter systems of the medial prefrontal cortex: Potential role in sensitization to psychostimulants. Brain Res.Rev 41: 203–228. [PubMed: 12663081]

Sziráki I, Sershen H, Hashim A, Lajtha A (2002) Receptors in the ventral tegmental area mediating nicotine-induced dopamine release in the nucleus accumbens. Neurochem.Res 27: 253–261. [PubMed: 11958525]

Tippey KG and Longnecker MT An Ad Hoc Method for Computing Pseudo-Effect Size for Mixed Models 2016. Available at: http://www.scsug.org/wp-content/uploads/2016/11/Ad-Hoc-Method-for-Computing-Effect-Size-for-Mixed-Models_PROCEEDINGS-UPDATE-1.pdf.

Versace F, Robinson JD, Lam CY, Minnix JA, Brown VL, Carter BL, Wetter DW, Cinciripini PM (2010) Cigarette cues capture smokers' attention: Evidence from event-related potentials. Psychophysiology 47: 435–441. [PubMed: 20070579]

Versace F, Stevens EM, Robinson JD, Cui Y, Deweese MM, Engelmann JM, Green CE, Karam-Hage M, Lam CY, Minnix JA, Wetter DW, Cinciripini PM (2019) Brain Responses to Cigarette-Related and Emotional Images in Smokers During Smoking Cessation: No Effect of Varenicline or Bupropion on the Late Positive Potential. Nicotine Tob.Res 21: 234–240. [PubMed: 29220524]

Volkow ND, Fowler J, Wang G-J (2002) Role of dopamine in drug reinforcement and addiction in humans: Results from imaging studies. Behav Pharmacol 13: 355–366. [PubMed: 12394411]

Warren CA, McDonough BE (1999) Event-related brain potentials as indicators of smoking cue-reactivity. Clin Neurophysiol 110: 1570–1584. [PubMed: 10479024]

Weinstein A, Greif J, Yemini Z, Lerman H, Weizman A, Even-Sapir E (2010) Attenuation of cue-induced smoking urges and brain reward activity in smokers treated successfully with bupropion. J.Psychopharmacol 24: 829–838. [PubMed: 19648219]

Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB (1999) Development and validation of the Wisconsin Smoking Withdrawal Scale. Exp Clin Psychopharmacol 7: 354–361. [PubMed: 10609970]

Wetherill RR, Spilka N, Jagannathan K, Morris P, Romer D, Pond T, Lynch KG, Franklin TR, Kranzler HR (2021) Effects of topiramate on neural responses to alcohol cues in treatment-seeking individuals with alcohol use disorder: Preliminary findings from a randomized, placebo-controlled trial. Neuropsychopharmacol 46: 1414–1420.

Winer BJ (1971) Statistical Principles in Experimental Design McGraw-Hill, New York.

Woolverton WL (1986) Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol.Biochem.Behav 24: 531–535. [PubMed: 2871561]

Xiao C, Shao XM, Olive MF, Griffin WC, Li K-Y, Krnjević K, Zhou C, Ye J-H (2009) Ethanol facilitates glutamatergic transmission to dopamine neurons in the ventral tegmental area. Neuropsychopharmacol 34: 307–318.

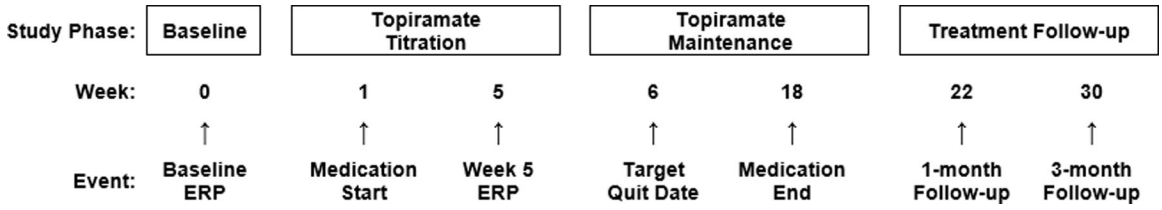

Figure 1.

Study flow diagram. Participants were titrated for high-dose (50 mg to 250 mg) or low-dose (25 mg to 125 mg) topiramate, or received a placebo matched on pill count, over the first 5 weeks. The drug maintenance phase occurred from weeks 6 to 18. ERP = event-related potential.

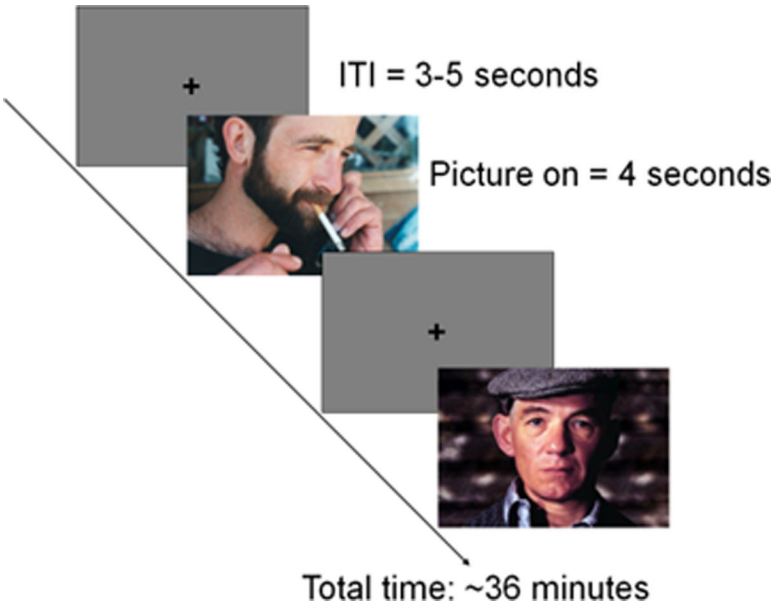

Figure 2.

The picture-viewing task: Schematic representation of the stimulus presentation procedure. Pleasant, unpleasant, neutral, alcohol-related, and cigarette-related pictures were presented while electroencephalograms were was recorded. During the slide presentation, pictures were presented in pseudo-random sequences with no more than two pictures of the same category presented consecutively. Each picture was presented for 4 seconds, and followed by a random inter-trial interval (ITI) of 3–5 s, during which a fixation cross was presented at the center of the screen.

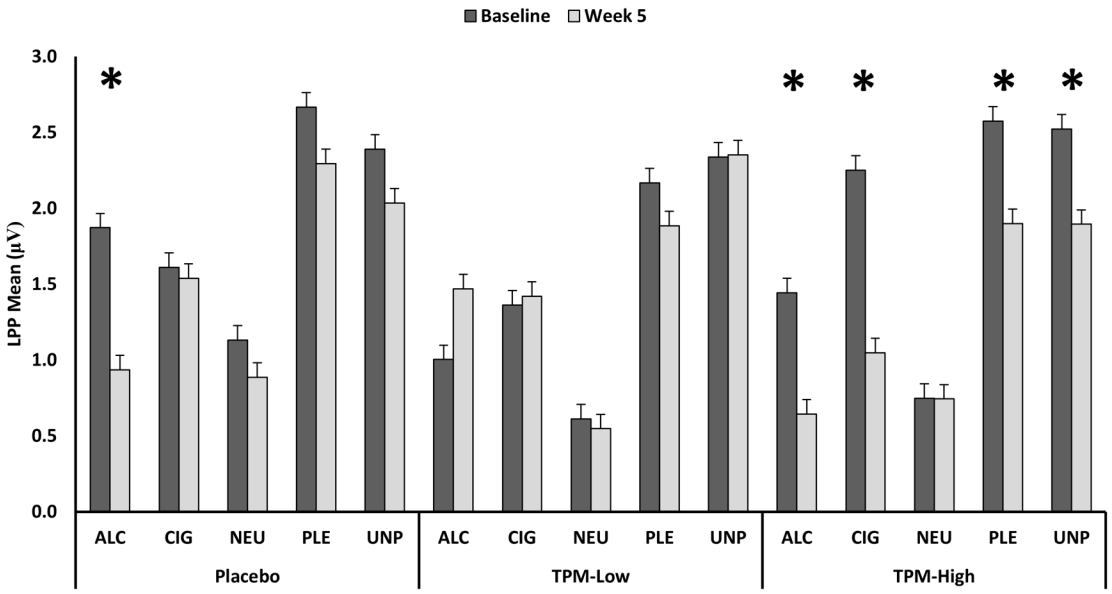

Figure 3.

The significant drug group x session x cue type 3-way interaction on mean (standard error) voltages for the late positive potential (LPP) component (408–800 ms). High-dose topiramate significantly reduced the LPPs to both the emotional (pleasant and unpleasant) and drug-related cues (alcohol and cigarette) after five weeks of drug exposure. Cue types: ALC=alcohol-related, CIG=cigarette-related, NEU=neutral, PLE=pleasant, and UNP=unpleasant. Drugs: TPM-Low=low-dose topiramate (up to 125 mg/day) and TPM-High=high-dose topiramate (up to 250 mg/day). Note: * = significant pairwise comparison, after Holm-Bonferroni correction.

Table 1.

Baseline demographic, smoking, and alcohol measures means and frequencies, by drug group, along with measures of treatment adherence.

Measure	Placebo	TPM-Low	TPM-High	Overall
	n (%)	*n* (%)	*n* (%)	*n* (%)
Sample Size	36 (35.6%)	29 (28.7%)	36 (35.6%)	101
Gender, Male	26 (72.2%)	19 (65.5%)	25 (69.4%)	70 (69.3%)
Race, White	18 (50.0%)	12 (41.4%)	22 (61.1%)	52 (51.5%)
Race, Black	13 (36.1%)	14 (48.3%)	12 (33.3%)	39 (38.6%)
Race, Other	5 (13.9%)	2 (6.9%)	1 (2.8%)	8 (7.9%)
Employed[a]	24 (66.7%)	17 (58.6%)	22 (61.1%)	63 (62.4%)
Completed Treatment[b]	11 (30.6%)	9 (31.0%)	14 (38.9%)	34 (33.7%)
Medication Adherence (week 18)[c]	12 (33.3%)	10 (34.5%)	14 (38.9%)	36 (35.6%)
Completed 5-week Titration[d]	29 (80.6%)	22 (75.9%)	26 (72.2%)	77 (76.2%)
Medication Adherence (week 5)[e]	29 (80.6%)	18 (62.1%)	24 (66.7%)	71 (70.3%)
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Age	46.9 (9.7)	46.4 (10.7)	47.1 (11.9)	46.8 (10.7)
FTCD	5.4 (2.2)	5.7 (2.5)	5.7 (2.0)	5.6 (2.2)
CPD	18.6 (8.6)	18.1 (9.5)	19.8 (8.0)	18.9 (8.6)
AUDIT	22.0 (7.0)	19.7 (7.3)	17.9 (5.8)*	19.9 (6.9)
DPD	7.8 (5.1)	9.2 (6.7)	8.5 (5.7)	8.5 (5.7)

Note:

[a]Full or part-time employed;

[b]Completed the full 18 weeks of treatment;

[c]Took either the full or reduced medication dose, as prescribed, on at least 80% of the days through week 18;

[d]Completed the initial 5 weeks of treatment and produced scoreable electroencephalography data;

[e]Took either the full or reduced medication dose, as prescribed, on at least 80% of the days through the first five weeks of pharmacotherapy;

TPM-Low = low-dose topiramate; TPM-High = high-dose topiramate; FTCD = Fagerström Test for Cigarette Dependence; CPD = cigarettes per day; AUDIT = Alcohol Use Disorders Identification Test; DPD = drinks per day.

* = significantly different from the Placebo group, Tukey's honest significance test (*HSD*) $p<.05$.