Experimental and Clinical Psychopharmacology
2012, Vol. 20, No. 4, 293–301

1064-1297/12/$12.00 DOI: 10.1037/a0027789

Effects of Divalproex on Smoking Cue Reactivity and Cessation Outcomes Among Smokers Achieving Initial Abstinence

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Divalproex, a GABA agonist, may be a useful agent in the treatment of tobacco dependence. Cue reactivity assessment paradigms are ideally suited to explore basic mechanisms underlying the pharmacological effects of medications that purport to have efficacy for smoking cessation. Our primary goal in the current study was to examine the effects of divalproex on in-treatment reactivity to smoking-relevant and affective cues, and to determine if these reactions were predictive of posttreatment smoking behavior. There were 120 nicotine dependent smokers enrolled in an 8-week double-blind clinical trial and randomly assigned to either divalproex or placebo conditions. Of these, 72 smokers (60% female) who achieved a minimal level of abstinence underwent an in-treatment cue reactivity assessment. Contrary to expectations, divalproex was associated with greater craving and arousal during smoking cue presentation. Divalproex also inhibited cardiovascular response to pleasant cues. Although no significant differences in cessation-related outcomes between divalproex- and placebo-treated participants were observed, cue-elicited craving to smoke predicted end-of-treatment and posttreatment smoking rates. These findings suggest that in-treatment cue reactivity assessment may proactively and dynamically inform ongoing treatment as well as provide a tool for screening potential medications for smoking cessation.

Keywords: smoking, cessation, craving, cue reactivity, divalproex

Tobacco smoking remains the single most preventable cause of death worldwide (World Health Organization, 2008). Current FDA-approved pharmacological agents for smoking cessation include five forms of nicotine replacement therapy (NRT), the antidepressant bupropion, and the partial nicotine agonist/antagonist varenicline. Each of these medications has been demonstrated to approximately double 1-year quit rates relative to placebo (Cahill, Stead, & Lancaster, 2007; Hughes, Stead, & Lancaster, 2007; Silagy, Lancaster, Stead, Mant, & Fowler, 2004). More recently, researchers have increased their efforts to identify alternative, non-nicotine based agents that may increase initial cessation and enhance long-term abstinence (Foulds, Steinberg, Williams, & Ziedonis, 2006; Siu & Tyndale, 2007). Divalproex sodium (Depakote) is one medication that has received empirical and theoretical attention as a potential pharmacological agent for smoking cessation.

Divalproex, a gamma-aminobutyric acid (GABA) agonist, has been FDA-approved for the treatment of epilepsy, migraine headaches, and bipolar disorder. Divalproex mimics the naturally occurring inhibitory neurotransmitter GABA, which generally serves to inhibit the reinforcing effects of dopamine in the brain. Nicotine has the capacity to both increase dopamine and decrease GABA, which may amplify and prolong the rewarding effects of smoking (Mansvelder, Keath, & McGehee, 2002; Mansvelder & McGehee, 2000; Markou, Paterson, & Semenova, 2004; Paterson, Froestl, & Markou, 2005). Thus, agents designed to increase GABA may limit the rewarding effects of nicotine and promote cessation.

This article was published Online First April 2, 2012.

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This study was supported by a grant from Abbott Pharmaceutical, who had no role in the study beyond financial support. All authors made substantive contributions and approved the manuscript. There are no conflicts of interest to report. We thank Cynthia Myers, Laura Juliano, Suzanne Wise, and Beth Platz for their assistance in conducting the study and preparing the manuscript.

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Despite this theoretical basis, the few preliminary studies examining other medications that impact GABA transmission have had negative findings (Hughes, Stead, & Lancaster, 2011). Further research is needed before definitive conclusions can be drawn.

Medications that purport to have efficacy for smoking cessation may do so by reducing motivation to smoke, and smoking cue reactivity assessment paradigms are ideally suited to explore this possibility. Cue reactivity methodology has been employed to investigate non-nicotine based pharmacological agents for smoking cessation (Alsene, Mahler, & de Wit, 2005; Fonder et al., 2005; Hutchison et al., 1999; Hutchison et al., 2004; Mahler & de Wit, 2005; Reid, Palamar, Raghavan, & Flammino, 2007; Rohsenow et al., 2007), and numerous studies have examined how exposure to smoking-related or affective cues may increase self-reported craving to smoke (e.g., Carter & Tiffany, 1999; Drobes, 2002; Drobes & Tiffany, 1997; Juliano & Brandon, 1998; Maude-Griffin & Tiffany, 1996; Payne, Schare, Levis, & Colletti, 1991; Sayette, Martin, Wertz, Shiffman, & Perrott, 2001; Tiffany & Drobes, 1991). Of particular relevance to the present study was the extent to which cue reactivity may predict treatment outcome.

We identified five published studies that investigated associations between cue reactivity assessment and smoking-related treatment outcomes. Of these, three studies reported that pretreatment cue reactivity predicted either end-of-treatment (Abrams, Monti, Carey, Pinto, & Jacobus, 1988; Payne, Smith, Adams, & Diefenbach, 2006), or posttreatment smoking (Abrams et al., 1988; Niaura, Abrams, Demuth, Pinto, & Monti, 1989). In contrast, two studies found no evidence that pretreatment cue reactivity predicted abstinence outcomes (Niaura, Abrams, Monti, & Pedraza, 1989; Shadel et al., 1998), though one study did report that posttreatment reactivity predicted smoking status at 6-month follow-up (Niaura, Abrams, Monti, & Pedraza, 1989). Payne et al. (2006) suggested that mixed cue reactivity findings may be due to limited sensitivity to detect effects afforded by the often dichotomous nature of smoking outcomes (e.g., quit vs. relapsed), and proposed that examination of more proximal and continuous treatment process variables (e.g., reduction in number of cigarettes smoked) may provide increased statistical power and reveal important mechanisms underlying cessation outcomes.

It is notable that no prior studies examined the predictive utility of in-treatment cue reactivity. We believe there are advantages associated with assessing cue reactivity at distinct time points. Pretreatment cue reactivity assessment seems most likely to inform intervention selection, elucidate important process variables, and help identify enduring characteristics that may influence the likelihood of cessation. Posttreatment reactivity data may be particularly useful in predicting and increasing our understanding of relapse. In contrast, in-treatment cue reactivity assessments may be uniquely capable of generating data that can be applied to tailor treatment in a more dynamic and fluid fashion. For example, in-treatment cue reactivity data may indicate that an intervention should be modified, extended, or intensified by predicting who is most likely to relapse. Given the need for additional tools to evaluate the efficacy of novel therapeutics to justify full-scale clinical trials (Perkins, Stitzer & Lerman, 2006), if in-treatment cue reactivity predicts outcomes on a smoking cessation trial, such data may also be used to screen medications for therapeutic potential and optimal dosing or treatment duration.

The main goal of the current study was to determine if divalproex influenced in-treatment reactivity to smoking and affective cues (e.g., cue-elicited craving) and test its potential for predicting posttreatment smoking among those who achieved initial cessation. A second, more exploratory, goal was to conduct an initial test of divalproex for smoking cessation. In particular, we hypothesized that divalproex-treated participants who achieved brief initial abstinence would demonstrate less reactivity to smoking cues, and that reduced in-treatment cue reactivity would predict less posttreatment smoking. We also predicted that divalproex-treated participants would report smoking fewer posttreatment cigarettes per day than placebo controls.

Method

Participants

Treatment-seeking smokers ($N = 120$) were recruited from community advertisements, and randomly assigned to receive either divalproex (20 mg/kg/day, divided into three doses) or placebo for 8 weeks as part of a double-blind clinical trial conducted in 2001. All analyses for the current study are restricted to a subset of 72 participants who attended a laboratory-based cue reactivity session during the active treatment phase (see Figure 1 for study flowchart).[1] Participants were required to be between 18 and 65 years of age, smoke at least 20 cigarettes per day, and have a baseline-session expired carbon monoxide concentration of at least 10 ppm. All participants met the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV;* American Psychiatric Association, 1994) criteria for nicotine dependence on enrollment. Participants who reported use of any pharmacological agents that might impact treatment outcome were excluded. All participants were screened for psychopathology by a trained rater using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Any participants with a diagnosis of schizophrenia, bipolar disorder, current major depression, dementia, or nonalcohol drug dependence were excluded. See Table 1 for demographic characteristics by medication group.

Measures

QSU–Brief. The Questionnaire of Smoking Urges–Brief (QSU–Brief; Cox, Tiffany, & Christen, 2001) is a widely used measure of self-reported craving to smoke a cigarette. Participants indicated how strongly they agreed or disagreed with each of 10 statements using a Likert-type scale that ranged from 1 (*strongly disagree*) to 7 (*strongly agree*), with higher scores indicating greater smoking urges. The QSU–Brief demonstrated excellent internal consistency ($\alpha = .87$).

FTQ. The eight-item Fagerström Tolerance Questionnaire (FTQ; Fagerström & Schneider, 1989) is an earlier version of the Fagerström Test for Nicotine Dependence and is among the most frequently used measures of nicotine tolerance and dependence.

[1] Analyses revealed no differences in treatment outcome for participants who did (vs. did not) undergo the cue reactivity assessment, irrespective of medication group assignment. There were also no differences in demographic or baseline characteristics among participants who did (vs. did not) undergo the cue reactivity assessment.

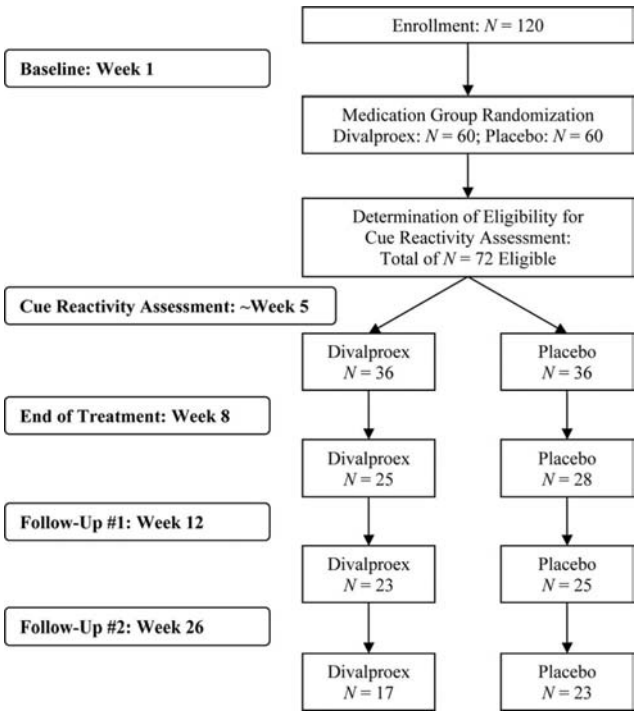

Figure 1. Study flowchart.

Scores ranged from 2–11, with higher scores indicating greater nicotine dependence.

Mood form. This nine-item measure (Diener & Emmons, 1984) was administered to assess negative and positive mood. Each item (four positive and five negative) was rated on a 7-point Likert-type scale that ranged from 0 (*not at all*) to 6 (*extremely*). Composite positive and negative mood scores were obtained by averaging the individual items. Excellent internal consistency was observed for both positive ($\alpha = .91$) and negative ($\alpha = .80$) mood scales.

SCL–90. The Symptom Checklist–90–R (SCL–90; Derogatis, 1977) is a 90-item measure that assesses nine major categories of symptoms (anxiety, depression, hostility, interpersonal sensitivity, obsessive–compulsive, paranoia, phobic anxiety, psychoticism, and somatization). These are then aggregated into three composite indexes: overall distress, average symptom severity, and total number of reported symptoms.

SAM. The Self Assessment Manikin (SAM; Bradley & Lang, 1994) is a nonverbal assessment of subjective emotional responses to a wide variety of stimuli. Using a joystick and computer display, participants reported affective reactions to picture cues by manipulating a cartoon figure that ranged from unhappy to happy (*valence*), wide-eyed to relaxed (*arousal*), and small to large (*dominance*), with each affective dimension scored on a 21-point scale.

Visual Analogue Scale (VAS). Using a joystick and computer display, participants made several slide-specific ratings by moving a cursor along separate 21-point visual analog scales. Participants were prompted to report how interested they were in the slide (*interest*), how much craving they experienced while viewing the slide (*craving*), how much they had wanted to smoke while viewing the slide (*approach*), and how much they had wanted to avoid smoking while viewing the slide (*avoidance*). Approach ratings were highly correlated with craving ($r > .95$, $p < .001$); therefore, only results for craving are described.

Procedure

Baseline session. Participants attended an initial session to complete baseline questionnaires and to undergo an assessment of daily smoking for the preceding 30 days. All participants were provided with brief smoking cessation counseling (in the form of a personalized message from a physician to stop smoking) and self-help materials (Glynn & Manley, 1990). Participants were then randomly assigned to either divalproex or placebo conditions (placebo pills were identical to active medication pills), medication treatment was initiated, and a quit date was scheduled. There were no baseline medication groups differences (see Table 1).

Weekly study visits. Following the baseline session, participants were scheduled to return for seven additional study visits (not including the cue reactivity session) at approximately weekly intervals. At each study visit, daily diaries of tobacco use were collected, expired carbon monoxide (CO) was measured, vital signs were obtained, and concomitant medications and adverse events were recorded, and medication compliance was evaluated via pill counts. Serum level of divalproex was also obtained at the first postbaseline study visit to assess therapeutic level. All participants received brief (~ 5 min) smoking cessation counseling at each study visit, which consisted of physician encouragement to attain or maintain abstinence.

Cue reactivity assessment. Seventy-two participants entering the double-blind treatment protocol were scheduled for a cue reactivity laboratory session. This session took place no earlier than 7 days postmedication initiation (i.e., during the second week) to ensure that therapeutic blood levels were achieved, and no later than 8t weeks following medication initiation. To avoid floor effects in cue reactivity due to acute satiation, and in keeping with the purpose of the study to examine the utility of cue reactivity in predicting smoking behavior following a quit attempt, only participants who could demonstrate their ability to achieve at least minimal success in abstaining or substantially reducing smoking were included in the cue reactivity assessment. Therefore, participants had to report three or more hours of smoking abstinence, report a 50% or greater reduction in smoking rate (for at least 1 full day), and demonstrate at least a 50% reduction from baseline CO level or have an expired CO of less than 10 ppm. Date and time of last cigarette smoked was recorded and the QSU–Brief and Mood Form was administered. The number of days between the baseline and cue reactivity sessions averaged 26.4, and did not differ between medication groups (see Table 1). Participants were compensated $25 for participating in the cue reactivity session.

Prior to undergoing the cue reactivity assessment, each participant was prepped for measurement of heart rate (HR), skin conductance (SC), facial electromyography (EMG), (corrugator [COR], zygomaticus [ZYG]), and startle response (orbicularis [ORB]) according to standard guidelines (Fowles et al., 1981; Fridlund et al., 1986). An established picture-viewing paradigm was adapted to assess subjective, behavioral, and physiological responses to 30 affective pictures (10 pleasant, 10 unpleasant, and 10 neutral) from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008), and 10 smoking-related pictures (e.g.,

Table 1
Demographic, Baseline, and Cue-Exposure Session Characteristics by Medication Group

	Placebo		Divalproex		Total	
Demographic characteristics	*n*	%	*n*	%	*n*	%
Gender						
Male	17	23.6	12	16.7	29	40.3
Female	19	26.4	24	33.3	43	59.7
Total	36	50.0	36	50.0	72	100.0
Race/ethnicity						
White	30	41.7	32	44.8	62	86.1
African American	5	6.9	4	5.6	9	12.5
Other	1	1.4	0	0.0	1	1.4
Total	36	50.0	36	50.0	72	100.0
	M	*SD*	*M*	*SD*	*M*	*SD*
Age	43.42	12.19	43.51	9.71	43.46	10.96
Years of formal education	14.78	2.37	14.72	1.92	14.75	2.14
No. of previous quit attempts	3.33	3.32	4.06	2.81	3.69	3.08
Cigarettes smoked per day	25.40	9.65	24.14	7.19	24.76	8.46
Baseline session						
Nicotine dependence score (FTQ)	6.56	1.83	6.83	1.87	6.69	1.84
Expired carbon monoxide	29.72	10.60	28.69	14.16	29.21	12.43
QSU–Brief total	34.67	10.76	30.61	14.03	32.64	12.58
SCL–90 Global Severity	0.15	0.17	0.18	0.19	0.17	0.18
SCL–90 Positive Symptom Distress	1.00	0.45	1.05	0.30	1.03	0.38
SCL–90 Positive Symptom total	11.23	11.14	13.56	12.91	12.41	12.04
Cue reactivity session						
Days since baseline session	26.83	14.24	26.03	12.86	26.43	13.48
Hours since last cigarette	33.74	59.66	14.07	24.0	23.90	46.21
Expired carbon monoxide	11.00	9.76	11.59	7.68	11.29	8.75
QSU–Brief total	29.74	12.22	32.97	12.30	31.33	12.28
Mood Form (Negative Affect scale)	4.09	4.62	4.88	5.62	4.48	5.12
Mood Form (Positive Affect scale)	12.19	5.22	12.65	5.40	12.41	5.27
Dosing and compliance						
No. 250 mg pills prescribed per week	45.5	13.54	41.2	10.15	43.48	12.10
% compliance/pre cue Rx	0.94	0.11	0.91	0.14	0.92	0.13
% compliance week of cue Rx	0.90	0.16	0.90	0.20	0.90	0.18
% compliance/total	0.93	0.13	0.90	0.14	0.92	0.13

Note. There were no significant medication group differences for any of the variables listed above (all *p*s $> .05$). FTQ = Fagerström Tolerance Questionnaire; QSU–B = Questionnaire on Smoking Urges–Brief; SCL–90 = Symptom Checklist–90.

pack of cigarettes, people smoking) from the Normative Appetitive Picture System (Breiner, Stritzke, Lang, & Patrick, 1995). Pictures were arranged in five blocks of eight, such that two pictures from each category occurred in each block. Five slide-presentation orders varied the serial position of both pictures and blocks across participants.

Participants were instructed to view each slide on a large screen located approximately 2.5 m directly in front of them, and to watch each slide for the duration of its appearance. Each picture was presented for 6 s. Standard procedures for assessing physiological reactivity to brief picture presentations were employed (e.g., Drobes, 2002; Lang, Greenwald, Bradley & Hamm, 1993). HR, SC, COR, and ZYG signals were recorded for 2 s prior to slide onset (baseline) and throughout slide presentation. Forty startle probes, consisting of a 50-ms 100-dB white noise burst with near-instantaneous rise time, were presented binaurally. Early probes (250- or 350-ms postslide onset) indexed attentional capture by images, while later probes (3,800- or 4,300-ms postslide onset) indexed incentive-motivational processing. After the slide series had been viewed once, the experimenter informed participants that they would view the same series of slides again, to view each slide for as long as they wished (maximum of 20 s), and to press a joystick button to turn off the slide before making ratings. Duration of viewing time was measured to the nearest millisecond to provide a behavioral measure of interest. Following slide offset, participants were asked to complete a VAS measure of craving, SAM ratings (i.e., valence, arousal, dominance), and VAS measures of interest, approach, and avoidance.

Follow-up sessions. Follow-up sessions took place approximately 4 weeks and 18 weeks (4.5 months) posttreatment, respectively. At each follow-up session, daily diaries of tobacco use were collected, vital signs were obtained, concomitant medications and adverse events were recorded, and expired CO was measured.

Physiological Data Processing

Physiological variables were expressed as the mean (HR) or median (SC, ZYG, COR) recorded value during each half-second interval throughout the recording duration (16 values total). The four pre-image values were averaged to form a baseline, and subsequent responses were expressed as deviations from this baseline value. HR exhibited the expected tri-phasic waveform in

response to picture onset, consisting of early and late deceleratory components, with an interceding acceleratory component (Bohlin & Kjellberg, 1979). Skin conductance was converted to log microsiemens and scored as the peak response 2 to 6 s following picture onset. ZYG and COR responses were scored as the average activity within this window. ORB was manually scored for the peak amplitude occurring within 150 ms of startle probe onset via visual inspection of the integrated waveform, using an interactive program (Cook, 1997). Results from all valid trials were used as the reference distribution for standardizing startle responding for each participant. Participants were required to have a minimum of 50% nonmissing, nonzero startles in each category to be included.

Results

Baseline Measures and Compliance Data

There were no significant differences between the divalproex and placebo medication groups (MG) on baseline measures of smoking rate, nicotine dependence, expired CO, or demographic characteristics (all ps $> .05$). There were also no MG differences on precue reactivity measures of mood, expired CO, self-reported urge to smoke, or number of hours since smoking the last cigarette (all ps $> .05$). Medication compliance was examined via pill counts. Participants were required to take an average of just over six pills per day, and overall rates of compliance were high (90%). Furthermore, there were no MG differences in medication compliance (all ps $> .28$). Table 1 provides baseline and precue reactivity demographic and smoking-relevant variables, as well as compliance data, by MG assignment.

Effects of Medication Group and Picture Category on Cue Reactivity Responses[2]

To determine whether medication effects interacted with picture category to influence cue reactivity, a series of 2 (MG: divalproex vs. placebo) $\times$ 4 (picture category [PC]: smoking-relevant, unpleasant, pleasant, and neutral pictures) mixed-factorial analyses of variances (ANOVAs) were conducted with MG as the between-subjects factor and PC as the within-subjects factor. To reduce the Type I error rate associated with unequal variances across the repeated measures, Greenhouse–Geisser corrected values are reported in instances in which the sphericity assumption is violated. Significant MG $\times$ PC interactions were explored via follow-up multivariate analysis of covariance (MANCOVA) to statistically control for responses to neutral slides. The alpha level for all planned comparisons underwent a modified Bonferroni correction (Sidak, 1967). Means and standard deviations for each cue reactivity variable broken down by MG and PC are presented in Tables 2 and 3.

Self-report measures. MG $\times$ PC interactions were observed for smoking-cue elicited craving, $F(3, 210) = 3.64$, $p < .05$, and arousal ratings, $F(3, 210) = 3.51$, $p = .02$. Contrary to our hypotheses, craving, $F(1, 69) = 5.76$, $p < .01$, and arousal, $F(1, 69) = 5.14$, $p = .03$ responses elicited by smoking-relevant cues were greater for participants taking divalproex relative to placebo. No other self-report MG $\times$ PC interactions were significant (all ps $> .20$). There was also no MG $\times$ PC interaction for picture viewing duration ($p = .53$).

Physiological responses.[3,4] A significant MG $\times$ PC interaction for HR, $F(3, 204) = 3.28$, $p < .05$, revealed that interceding HR acceleration in response to pleasant cues was smaller for participants taking divalproex relative to placebo, $F(1, 67) = 5.48$, $p < .05$. Linear MG $\times$ PC interactions did not reach significance for any other physiological response variables (all ps $> .18$).

In-Treatment Cue Reactivity as a Predictor of Posttreatment Smoking

Multiple regression equations, controlling for reactivity to neutral cues, baseline smoking rate, and drug condition, were employed to determine whether cue-elicited self-report and physiological responses (in which significant interactions were found) were predictive of end-of-treatment and posttreatment smoking. Of self-report responses, only cue-elicited craving was found to predict end-of-treatment smoking ($\beta = .35$, $F_{change} = 5.88$, $R^2_{change} = .091$, $p = .02$), such that participants who reported greater craving in response to the presentation of smoking cues also reported smoking more cigarettes per day once treatment ended. Smoking cue-elicited craving also predicted greater cigarette consumption at 4 weeks ($\beta = .40$, $F_{change} = 7.01$, $R^2_{change} = .119$, $p = .011$) and 18 weeks ($\beta = .40$, $F_{change} = 5.00$, $R^2_{change} = .103$, $p = .032$) posttreatment. Physiological responses did not predict posttreatment smoking (all ps $> .5$).

Initial Test of Divalproex for Smoking Cessation

Overall abstinence rates at end of treatment and each follow-up point were very low ($< 6\%$) and did not differ across medication groups (ps $> .5$). Therefore, we sought to examine medication effects on end-of-treatment and posttreatment reductions in smoking. Analyses of covariances (ANCOVAs) were conducted with MG as the fixed factor and baseline smoking rate as the covariate. Contrary to expectations, analyses revealed no MG differences for smoking reduction at end-of-treatment, $F(1, 50) = 2.67$, $p = .11$,

[2] All analyses were repeated with gender as a covariate, and separately with the number of days between baseline session and cue reactivity as a covariate. The overall pattern of findings was unchanged in these analyses. Therefore, these variables were not included as covariates in the data reported.

[3] Outliers (values larger than three standard deviations from the mean) were present for the following variables and thus excluded from analyses: HR-A1 (two participants), HR-D2 (four participants), SC (three participants), COR (four participants), ZYG (four participants). Equipment failure or other problems resulted in additional data loss for SC (19 participants), COR (three participants) and ZYG (two participants), startle response to early probes (STR-early; 47 participants) and startle response to late probes (STR-late; 38 participants).

[4] HR acceleration, SC, and ZYG all exhibited small, but notable deviations from normality (skew and kurtosis < 6). Although the analytic approach used is robust to departure from normality, various transformations were applied in an attempt to normalize the distributions. In all cases, when the overall model was run on transformed variables the general pattern of results was unchanged. For simplicity, results from analyses of untransformed variables are reported. Due to concerns about the large number of zero-magnitude trials resulting in exclusion of participants, startle amplitude (i.e. excluding zero-values) was also analyzed. Results were comparable across both metrics.

Table 2
Means and Standard Errors for Self-Report/Behavioral Measures by Medication Group and Picture Category

Craving	(a) Smoking*	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total*
Placebo	5.32 (0.99)	2.74 (0.73)	1.92 (0.64)	1.59 (0.57)	2.89 (0.63)
Divalproex	9.65 (0.99)	4.53 (0.73)	4.33 (0.64)	3.15 (0.57)	5.41 (0.63)
Total	7.48 (0.70)$_{b,c,d}$	3.63 (0.52)$_{a,d}$	3.12 (0.45)$_{a,d}$	2.37 (0.41)$_{a,b,c}$	4.15 (0.45)
Avoidance	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	8.45 (1.11)	7.61 (1.07)	9.22 (1.12)	7.03 (1.13)	8.08 (1.04)
Divalproex	7.65 (1.11)	7.26 (1.07)	8.43 (1.12)	6.85 (1.13)	7.55 (1.04)
Total	8.05 (0.78)	7.43 (0.76)$_{c}$	8.83 (0.79)$_{b,d}$	6.94 (0.80)$_{c}$	7.81 (0.74)
Arousal	(a) Smoking*	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	8.77 (0.63)	12.19 (0.65)	13.51 (0.70)	6.04 (0.60)	10.13 (0.50)
Divalproex	10.48 (0.63)	12.98 (0.65)	12.12 (0.70)	6.04 (0.60)	10.42 (0.50)
Total	9.62 (0.48)$_{b,c,d}$	12.58 (0.46)$_{a,d}$	12.85 (0.50)$_{a,d}$	6.04 (0.42)$_{a,b,c}$	10.27 (0.35)
Interest	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	3.53 (0.61)	8.54 (0.78)	11.93 (0.71)	2.08 (0.42)	6.52 (0.43)
Divalproex	4.27 (0.61)	9.13 (0.78)	13.18 (0.72)	2.34 (0.42)	7.23 (0.43)
Total	3.90 (0.43)$_{b,c,d}$	8.83 (0.55)$_{a,c,d}$	12.55 (0.51)$_{a,b,d}$	2.21 (0.30)$_{a,b,c}$	6.87 (0.30)
Valence	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	10.50 (0.42)	5.32 (0.48)	14.78 (0.46)	10.62 (0.24)	10.31 (0.19)
Divalproex	9.60 (0.42)	5.13 (0.48)	14.77 (0.46)	11.34 (0.24)	10.21 (0.19)
Total	10.05 (0.30)$_{b,c,d}$	5.23 (0.34)$_{a,c,d}$	14.77 (0.33)$_{a,b,d}$	10.98 (0.17)$_{a,b,c}$	10.26 (0.13)
Dominance	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	11.04 (0.68)	8.32 (0.59)	12.49 (0.55)	11.64 (0.50)	10.87 (0.43)
Divalproex	9.17 (0.68)	7.81 (0.59)	11.87 (0.55)	11.72 (0.50)	10.14 (0.43)
Total	10.10 (0.48)$_{b,c,d}$	8.07 (0.42)$_{a,c,d}$	12.18 (0.39)$_{a,b}$	11.68 (0.35)$_{a,b}$	10.51 (0.30)
Duration	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	2.89 (0.33)	4.35 (0.49)	4.22 (0.38)	2.61 (0.23)	3.68 (0.22)
Divalproex	3.58 (0.32)	4.45 (0.49)	4.52 (0.38)	2.84 (0.23)	2.73 (0.16)
Total	3.24 (0.23)$_{b,c,d}$	4.40 (0.38)$_{a,d}$	4.37 (0.27)$_{a,d}$	2.73 (0.16)$_{a,b,c}$	3.68 (0.22)

Note. Standard errors are in parentheses. Duration of viewing time reported in seconds. Asterisks indicate medication group differences for specified picture category after controlling for neutral cues, or the overall main effect for total ($p < .05$). Subscript letters indicate differences for pairwise comparisons of picture category total ($p < .05$).

or at either follow-up point: 4-weeks posttreatment, $F(1, 48) = 3.21$, $p = .08$; 18 weeks posttreatment, $F(1, 48) = 3.21$, $p = .08$. However, examination of the covariate-adjusted means reveals surprising trend-level findings that divalproex participants tended to smoke more cigarettes per day than those receiving placebo at the end of treatment ($M = 9.01$, $SE = 1.10$ vs. 6.60, 1.04] and at both posttreatment follow-up points: 4 weeks, $M = 9.41$ ($SE = 1.16$) versus 6.53 (1.11); 18 weeks, $M = 13.48$ ($SE = 1.82$) versus 9.89 (1.57). This observation is consistent with our finding that in-treatment cue-elicited craving to smoke was greater among those randomized to receive divalproex (relative to placebo).

Discussion

The primary goals of the current study were to test our hypothesis that divalproex-treated participants would demonstrate less reactivity to smoking-relevant cues, and that individual differences in cue reactivity would predict treatment outcome. We found it surprising that divalproex-treated smokers reported greater smoking cue-elicited craving and arousal than placebo-treated smokers. Although contrary to our expectations, similar divalproex-related findings have been observed in other studies. For example, Haney et al. (2004) reported that marijuana dependent participants taking divalproex reported worse mood (e.g., irritability, edginess, anxiety), poor sleep, impaired psychomotor performance, increased caloric consumption, and weight gain. These symptoms are highly representative of the nicotine withdrawal syndrome, and are often implicated in the process of relapse (e.g., Brandon, Tiffany, Obremski, & Baker, 1990; Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Marlatt & Gordon, 1985). Thus, one possibility is that divalproex amplified some symptoms of nicotine withdrawal, including craving to smoke. Despite the unexpected effects of divalproex on smoking cue reactivity, the medication did appear to blunt the acceleratory component of the HR response to pleasant cues. Given the well-documented efficacy of divalproex for treatment of mania (Bowden, 2009), this effect may warrant further study as a potential mechanism for its mood stabilization effects.

Despite the surprising findings for divalproex effects on cue reactivity, results indicated that participants who reported greater in-treatment craving in response to the presentation of smoking-relevant cues also reported smoking more cigarettes per day at the end-of-treatment, 4-weeks posttreatment, and 18-weeks posttreatment. That our data were predictive of behavioral smoking outcomes up to 4.5-months posttreatment provides initial support for the clinical utility of assessing cue reactivity during a quit attempt.

Table 3
Means and Standard Errors for Physiological Measures by Medication Group and Picture Category

HR–D1	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	–2.60 (0.25)	–3.75 (0.36)	–2.93 (0.31)	–2.73 (0.29)	–3.00 (0.27)
Divalproex	–2.59 (0.25)	–3.76 (0.36)	–3.35 (0.31)	–3.06 (0.29)	–3.19 (0.27)
Total	$-2.60\ (0.18)_{b,c}$	$-3.75\ (0.25)_{a,c,d}$	$-3.14\ (0.22)_{a,b}$	$-2.90\ (0.21)_{b}$	–3.10 (0.19)
HR–A1	(a) Smoking	(b) Unpleasant	(c) Pleasant*	(d) Neutral	Total
Placebo	4.91 (0.43)	4.39 (0.34)	5.02 (0.42)	4.63 (0.38)	4.74 (0.47)
Divalproex	4.56 (0.44)	4.45 (0.35)	4.21 (0.44)	4.44 (0.39)	4.42 (0.38)
Total	4.47 (0.31)	4.42 (0.24)	4.62 (0.30)	4.53 (0.27)	4.58 (0.27)
HR–D2	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	–4.06 (0.33)	–3.87 (0.32)	–4.17 (0.33)	–4.22 (0.36)	–4.03 (0.31)
Divalproex	–4.26 (0.33)	–4.10 (0.32)	–3.89 (0.33)	–3.84 (0.36)	–4.02 (0.31)
Total	–4.16 (0.25)	–3.98 (0.23)	–4.03 (0.23)	–3.93 (0.23)	–4.02 (0.22)
SC	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	2.99 (1.02)	10.00 (2.52)	6.35 (1.50)	2.66 (1.12)	5.50 (1.22)
Divalproex	4.60 (0.94)	7.56 (2.33)	5.04 (1.38)	4.06 (1.04)	5.31 (1.13)
Total	$3.80\ (0.69)_{b}$	$8.78\ (1.72)_{a,d}$	5.70 (1.02)	$3.36\ (0.76)_{b}$	5.41 (0.83)
COR	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	1.70 (1.21)	15.87 (3.99)	0.10 (1.55)	1.14 (1.86)	4.70 (1.44)
Divalproex	2.59 (1.23)	17.97 (4.05)	–0.82 (1.57)	3.92 (1.89)	5.92 (1.50)
Total	$2.14(0.86)_{b}$	$16.92\ (2.84)_{a,c,d}$	$-0.36\ (1.10)_{b}$	$2.53\ (1.33)_{b}$	5.31 (1.02)
ZYG	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Placebo	–0.18 (0.82)	–0.76 (0.90)	–1.18 (1.14)	–0.94 (0.84)	–0.77 (0.52)
Divalproex	–0.21 (0.82)	0.42 (0.90)	–0.30 (1.14)	–0.98 (0.84)	–0.27 (0.52)
Total	–0.20 (0.58)	–0.17 (0.64)	–0.74 (0.81)	–0.96 (0.59)	–0.52 (0.37)
ORB	(a) Smoking	(b) Unpleasant	(c) Pleasant	(d) Neutral	Total
Early					
Placebo	44.92 (1.29)	44.69 (1.27)	48.60 (1.44)	48.17 (1.33)	46.60 (0.81)
Divalproex	51.19 (1.24)	48.11 (1.22)	48.22 (1.39)	49.22 (1.27)	49.18 (0.78)
Total	48.06 (0.90)	46.40 (0.88)	48.41 (1.00)	48.70 (0.92)	47.89 (0.56)
Late					
Placebo	51.56 (1.32)	54.43 (1.48)	49.81 (1.18)	50.83 (1.21)	51.66 (0.65)
Divalproex	48.99 (1.27)	54.02 (1.42)	49.48 (1.13))	49.91 (1.17)	50.60 (0.62)
Total	$50.27\ (0.91)_{b}$	$54.22\ (1.02)_{a,c}$	$49.64\ (0.82)_{b}$	50.37 (0.84)	51.13 (0.45)

Note. Standard errors in parentheses. Asterisk indicates drug group differences after controlling for neutral cues (HR–A1; $p < .05$) or drug group difference within timing category averaged across all picture categories (ORB; $p < .05$). Subscript letters indicate differences for pairwise comparisons of picture category total ($p < .05$). HR = heart rate; SC = skin conductance; COR = corrugator; ZYG = zygomaticus; ORB = orbicularis.

To our knowledge, this is the first study to demonstrate that in-treatment reactivity responses are prospectively related to post-treatment tobacco use. Previous studies have conducted assessments at either pretreatment or posttreatment time points. Although there are potential benefits associated with all three approaches, in-treatment cue reactivity may provide unique information that can be used to dynamically inform ongoing treatment considerations in "real-time." The association between in-treatment cue reactivity and cessation outcomes raises the possibility that cue reactivity procedures may be useful for screening potential smoking cessation medications. To elucidate the relative importance of in-treatment cue reactivity, future research should directly compare the predictive utility of each assessment time point. If in-treatment cue reactivity remains predictive, future research should incorporate cue reactivity into a battery of measures designed to predict cessation outcomes among treatment-seeking smokers. These batteries may have utility for treatment tailoring by determining who is most likely to benefit from a more intensive treatment approach.

A more exploratory aim of the current study was to conduct an initial test of a potentially new pharmacological agent for smoking cessation. Our hypothesis that participants randomized to receive divalproex would report smoking fewer posttreatment cigarettes per day relative to placebo controls was not supported. In fact, trend-level findings revealed that divalproex-treated participants tended to smoke more posttreatment cigarettes per day than placebo-treated participants. Although this study was not fully powered to test the efficacy of divalproex for smoking cessation, these results do call into question the utility of divalproex in the treatment of tobacco dependence. This fits with negative findings that have been reported for other GABA medications (Hughes et al., 2011), and strengthens the argument against a significant role for GABAergic agents in the treatment of smoking cessation. Similar poor outcomes have been reported among studies that examined divalproex for the treatment of alcohol and marijuana dependence (e.g., Brady, Myrick, Henderson, & Coffey, 2002; Haney et al., 2004; Levin et al., 2004). Although pharmacological agents that increase GABA (e.g., divalproex) are hypothesized to

aid smoking cessation by inhibiting the reinforcing effects of nicotine, there is some evidence that these medications may also exacerbate symptoms that are characteristic of nicotine withdrawal. Indeed, among individuals undergoing treatment for marijuana withdrawal, divalproex administration (relative to placebo) was shown to worsen mood, impair sleep, and cognitive performance, and increase food intake and body weight (Haney et al., 2004; Levin et al., 2004).

Several study limitations should be considered. First, although in-treatment cue reactivity may generate data that has the potential to inform ongoing treatment, we did not systematically vary when cue reactivity assessments were conducted. Therefore, the question of when cue reactivity may be most predictive of treatment outcome remains unanswered. Second, only participants who met minimal abstinence and smoking reduction criteria were included in the cue reactivity assessment. Although consistent with our goal to examine the utility of cue reactivity in predicting smoking behavior following a quit attempt, these criteria may serve to constrain generalizability. Third, the lack of reported blood levels of divalproex reduces our ability to draw definitive conclusions about the role of divalproex in the effects observed, and more extensive clinical trials should obtain such data. Nonetheless, information derived from pill counts indicated that participants were largely compliant with medication dosing. Fourth, missing psychophysiological data (due to equipment failure) limits the conclusions that can be drawn about the effects of divalproex on physiological responses to cues.

Finally, the current study was not powered to draw definitive conclusions regarding the efficacy of divalproex for smoking cessation, and we observed considerable attrition following the cue reactivity assessment (see Figure 1). Although the results of several studies have cast doubt on the potential for divalproex in the treatment of addiction, some promising preliminary findings for divalproex in the treatment of alcohol withdrawal have been reported (Myrick, Brady, & Malcolm, 2000). It is also important to note that participants in the current study (regardless of medication group) did not demonstrate particularly impressive cessation-related outcomes. The minimal counseling in the current study (i.e., weekly physician encouragement to stop smoking) may have been insufficient for optimizing cessation outcomes (Fiore et al., 2008).

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Received June 6, 2011
Revision received January 27, 2012
Accepted January 27, 2012 ■