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Impulsiveness as a Predictor of Topiramate Response for Cocaine Use Disorder

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Abstract

Background/Objectives: Topiramate has been studied in the treatment of substance use disorders and is often used off-label in the treatment of other disorders with impaired impulse control. We sought to determine whether impulsiveness could predict topiramate treatment response in individuals with cocaine use disorder (CUD).

Methods: In a post-hoc analysis of a 12-week, double-blind, randomized, placebo-controlled trial of topiramate for CUD, we examined the relationship between response to treatment and participants' baseline score on the Barrett Impulsiveness Scale (BIS-11). During the original trial, topiramate was titrated up to 300 mg/day over 6 weeks and maintained for 6 weeks. All participants received weekly cognitive behavioral therapy.

Results: Individuals with total BIS-11 scores above the median had 11.2% more cocaine-free days with topiramate versus placebo (Bonferroni corrected $p = 0.047$). Individuals with first-order factor scores above the median in self-control (Bonferroni corrected $p = 0.020$) and at or below the median in attention (Bonferroni corrected $p = 0.022$), and second-order factor scores at or below the median in attentional (Bonferroni corrected $p = 0.024$) and motor impulsiveness (Bonferroni corrected $p = 0.046$) were all associated with a greater improvement with topiramate.

Discussion/Conclusion: The results indicate an association between higher within-group impulsiveness and response to topiramate for CUD. The subscore findings may suggest a complex interaction between effectiveness and known cognitive side effects. The finding that trait impulsiveness is associated with treatment response is a promising discovery that may help guide treatment for CUD.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Scientific Significance: This analysis suggests a possible endophenotype based on impulsiveness that can predict treatment response to topiramate.

INTRODUCTION

Clinical trials of pharmacotherapies for the treatment of stimulant use disorders, including cocaine use disorder (CUD), have thus far resulted in no FDA-approved medications. Numerous pharmacologic agents have been tested to target dopaminergic systems (bupropion, amphetamines, methylphenidate, modafinil), serotonergic systems (selective serotonin reuptake inhibitors [SSRIs], ondansetron), GA-BAergic systems (vigabatrin, baclofen, valproic acid, tiaga-bine), and more recently targeting the immune system via vaccination to stimulate an anti-cocaine antibody response.[1] Some of these studies have resulted in statistically significant outcomes, but the question of clinical significance, and thus determination of the most important primary outcome measure to evaluate efficacy, remains.

One medication that has shown a statistically significant effect is topiramate, a glutamate receptor antagonist and gamma-aminobutyric acid (GABA) receptor agonist. The first randomized, double-blind trial of 40 outpatients receiving topiramate or placebo, in conjunction with weekly cognitive behavioral therapy (CBT), showed that the topiramate group was more likely to achieve three or more continuous weeks of abstinence (59%) compared to the placebo group (26%) ($p = 0.05$).[2] A larger, randomized, double-blind, placebo-controlled trial of 142 participants completed by our group showed that topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine-free days when the data were or were not imputed conservatively (8.9% vs. 3.7%, 95%CI for estimated mean difference, .2–10.1%, $p = .04$ or 13.3% vs 5.3%, 95%CI for the estimated mean difference, 1.4–14.6%, $p = .02$, respectively) and cocaine-free weeks (16.6% vs. 5.8%; odds ratio 3.21; 95%CI, 1.24–8.32, $p = .02$).[3] However, while statistically significant, the clinical significance remains unclear, with seemingly small absolute differences between topiramate and placebo (8% more cocaine-free days, when not imputed conservatively, and 10.8% more cocaine-free weeks).

Alcoholism treatment research has long focused on subtypes and their differential responses to treatment approaches, including the more traditional dyadic typology model of “type A” and “type B” alcoholism, separated by differences in age of onset, severity, family history, and psychiatric co-morbidity,[4] as well as the more recently described 5-subtype model consisting of “young adult,” “young antisocial,” “functional,” “intermediate familial,” and “chronic severe” alcoholism.[5] A pharmacologic study of ondansetron for alcohol dependence, theoretically based on evidence of serotonergic dysfunction in early-onset alcoholism, showed differential outcomes for early-onset compared to late-onset participants.[6]

The literature on cocaine dependence, conversely, is largely void of differences in outcomes based on subtypes of individuals with CUD. Two clusters, or subtypes, of cocaine dependent adults were described in a study using quantitative EEG (QEEG) showing a significant relationship between QEEG subtype and length of stay in treatment, but not on other

measures (length of exposure to cocaine, time since last cocaine use, or demographics).[7] Another study supported the validity of subtyping cocaine dependent subjects into six clusters by applying data reduction methods and empirical cluster-analytic approach, with linkage analysis showing significant genome-wide results for two clusters, but differential treatment responses were not evaluated.[8] To our knowledge, there is no published data evaluating differential pharmacologic outcomes for this population based on subtypes of CUD.

Topiramate and other anticonvulsants have been widely used off-label in psychiatric practice to target disordered impulse control. Substance use disorders, at least in part, are disorders of impulse control, making topiramate an obvious choice to target various substance use disorders. A randomized trial of 63 alcohol dependent individuals showed that topiramate reduced both alcohol consumption and improved performance on a behavioral inhibition paradigm.[9] In a large placebo-controlled clinical trial (n = 394) of binge eating disorder, another disorder with impaired impulse control, topiramate also resulted in significant improvement in multiple measures of severity of binge eating disorder, reduced weight, and also showed statistically significant reductions in the total BIS score and two of three second-order scores as a function of the treatment by time interaction.[10]

Thus, we hypothesized that individuals with CUD with higher trait impulsiveness may experience better outcome with topiramate compared to those with lower baseline impulsiveness scores. We, therefore, performed a secondary analysis of our original randomized placebo controlled clinical trial, with results supporting a statistically significant effect of topiramate over placebo on both cocaine free days and weeks, and sought to determine whether impulsiveness was a factor that could predict response to treatment with topiramate in individuals with cocaine use disorder.[3]

METHODS

Sample and Procedures

A post-hoc analysis was completed of data obtained from a previously completed double blind, randomized, placebo-controlled trial. In the original trial, research participants were recruited at the University of Virginia (Charlottesville and Richmond sites) between November 22, 2005, and July 25, 2011. The University of Virginia Institutional Review Board approved the research protocol, and all enrolled participants were provided a written informed consent.

The sample included 142 treatment-seeking individuals, aged 18 years or older, diagnosed as cocaine-dependent according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*[11] (hence-forth noted as cocaine use disorder or CUD, consistent with DSM-5 classification[12]) in a 12-week, double blind, randomized, placebo controlled clinical trial combining daily oral topiramate with weekly cognitive behavioral therapy (CBT).

Enrolled participants were in good physical health, as determined by a complete physical examination, EKG, and laboratory screening. A diagnosis of CUD was established using the

Structured Clinical Interview for *DSM-IV,* Axis I Disorders.[13] To be randomized into double-blind treatment, participants had to meet the criterion of recent history of cocaine use by providing at least one cocaine-positive urine specimen (>300 ng/ml) during the screening visit or two weeks of baseline. Exclusion criteria included physiological dependence on alcohol requiring medical detoxification, serious medical conditions, psychiatric conditions warranting treatment that would preclude safe participation, and concurrent use of psychotropic medications.

Upon review of eligibility criteria, participants were allocated at random into two treatment groups: topiramate ($n = 71$) and placebo ($n = 71$). Study medication was randomized in a 1:1 ratio of daily oral topiramate or matched placebo. Randomization was stratified to balance participants between groups on age, sex, and frequency of cocaine use (>18 vs ≤18 days' use in the past 30 days according to self-report, urine sample, or both).

Over the course of 6 weeks, participants were titrated from 50 mg/day up to 300 mg/day of topiramate or matching placebo. Participants who were unable to tolerate 300 mg/day were reduced to a minimum dose of 200 mg/day. The maintenance dose was continued for 6 additional weeks and participants attended the clinic three times per week for various measures, including urine testing for the primary metabolite of cocaine, benzoylecgonine. Both the active medication group and placebo group received weekly CBT throughout the 12-week trial.

Measures

At baseline, all participants completed the Barratt Impulsiveness Scale (BIS-11).[14] This is a well-validated scale that assesses the personality and behavioral construct of impulsiveness through a 30-item self-report inventory. The scale yields a total score measuring overall impulsiveness, and is composed of six first-order factors (attention, motor, perseverance, cognitive instability, self-control, and cognitive complexity), and three second-order factors including attentional (lack of focus on a task), motor (quick reactions, restlessness), and nonplanning (proclivity for the present rather than the future). These second-order factors were produced by a psychometric analysis of the six first-order factors. The attentional impulsiveness score is a combination of first-order factors attention and cognitive instability. Motor impulsiveness is a combination of motor impulsiveness and perseverance. And nonplanning impulsiveness is a combination of self-control and cognitive complexity. Participants ranked items on a scale of 1 (rarely) up to 4 (almost always/always). Eleven of the items are reverse-scored. The range of the total score is from 0 to 120, with higher scores representing greater trait impulsiveness.[15]

Analyses

All data were analyzed using the intent-to-treat principle. The primary outcome, as described in the original study,[3] was the weekly difference from baseline in the proportion of cocaine-free days. We employed a linear mixed-effects regression model, a similar analytic approach as described in our previous publication, to assess treatment response within different participants' BIS-11 scores, including both the main effects of the total BIS-11 score and the interaction between the treatment and the total BIS-11 score. For simplicity

and ease of interpretation, we dichotomized by the median BIS-11 score. Similarly, we compared the difference in percentage of cocaine-free days between the treatment groups among those with each BIS-11 first-order and second-order factor scores greater than the median compared to those at or below the median. The statistical model was also adjusted for time (in weeks), participants' weekly mean proportion of cocaine nonuse days before randomization, age at onset of cocaine use, sex, race, and frequency of self-reported cocaine use in the 30 days before informed consent as covariates. A significance level was set at $p = .05$. To control type I error due to multiple comparisons, Bonferroni multiple comparisons adjustment was used by multiplying the p-value by the number of comparisons of primary interests.

RESULTS

Baseline Characteristics

The mean and median scores for the sample for the total score (68.9 and 68, respectively), and each first-order and second-order subscore were nearly identical, indicating a close to symmetric distribution (Table 1).

BIS-11 Scores and Treatment Effect

Overall Score—While there was no significant interaction effect between the treatment and total BIS-11 score, the treatment main effect was significant ($F = 5.76$, $p = .017$). Those with BIS-11 scores above the median had a statistically significant higher percentage of cocaine-free days compared to placebo (mean difference: 11.2%, 95%CI: 1.5–20.9%, Bonferroni corrected $p = .047$). Those in the group with total scores above the median seemed to respond to topiramate better in comparison to treatment versus placebo among all participants (mean difference: 8%, 95%CI: 1.4–14.6%, $p = .020$). Those with BIS-11 scores at or below the median had no difference in treatment compared to placebo (Bonferroni corrected $p = .564$) (Table 2). The percentage of cocaine-free days did not vary by total score of impulsiveness within the topiramate group ($p = .699$).

Subscores—Among first-order factors, treatment main effects varied by first-order attention and self-control scores. Among those with attention scores at or below the median, there was an 11.4% (95%CI: 2.6–20.1%, Bonferroni corrected $p = .022$) increase in percentage of cocaine-free days for those receiving topiramate. Those with first-order self-control scores above the median had an increase of 13.6% (95%CI: 3.2–24.1%, Bonferroni corrected $p = .020$) in the percentage of cocaine-free days with topiramate versus placebo. Among those with second-order attentional and motor scores at or below the median, there was respectively an 11.9% (95%CI: 2.7–21.2%, Bonferroni corrected $p = .024$) and 10.8% (95%CI: 1.5–20.1%, Bonferroni corrected $p = .046$) increase in percentage of cocaine-free days in the topiramate group compared to placebo (Table 3). Although not reaching Bonferroni corrected significance, there was a nominally significant increase in the percentage of cocaine-free days with topiramate versus placebo among those with cognitive complexity scores at or below the median (mean difference = 8.8% 95%CI: .6–17.0%,$p = .036$), and among those with first-order perseverance scores above the median (mean difference = 11.6%, 95%CI: .4–22.9%, $p = .043$) (Table 3). Similarly, there were no

statistically significant differences within the topiramate group for any of the second-order and first-order subscores.

DISCUSSION

Impulsiveness is a well-known baseline risk factor for the development of addiction, as well as a known consequence of chronic substance use that may contribute to ongoing substance use and other impulsive behaviors.[16] Individuals with CUD have been shown to have higher self-reported trait impulsiveness as compared to healthy controls, a higher rate of discounting monetary rewards, and a higher rate of discounting cocaine rewards compared to monetary rewards.[17] Furthermore, the impact of baseline impulsiveness has been shown to be a significant predictor of both cocaine use and treatment retention.[18] Thus, impulsiveness is clearly an important characteristic of substance use disorders, including CUD, and has an impact on treatment outcomes. Topiramate appears to have a unique ability to alter impulsive behavior, and baseline impulsiveness may predict a greater treatment response. In this post hoc analysis, using overall impulsiveness as a stratification factor led to results supporting the effectiveness of topiramate in reducing cocaine use that are more robust than the original results when no stratification was used. Considering that the primary outcome of non-imputed proportion of cocaine-free days for topiramate versus placebo in the previously published data was 13.3% versus 5.3% ($p = .02$), respectively, the 11.2% estimated mean increase (Bonferroni corrected $p = .047$) in cocaine-free days for those treated with topiramate versus placebo with higher BIS-11 scores is noteworthy. The lack of statistical significance in regard to an interaction effect was anticipated, as the original study design was not powered on the interaction effects between the treatment and BIS-11 scores. Given the past evidence of the effectiveness of topiramate for numerous disorders involving impaired impulse control, we anticipated higher baseline impulsiveness would most likely benefit from treatment with topiramate. However, we considered that many individuals with CUD are enticed by the cognitively stimulating effects of cocaine, and therefore may not respond to a pharmacologic agent like topiramate with dulling effects on attention and verbal fluency.[19]

Regarding subscores for first-order and second-order factors, the results were more difficult to interpret. Among second-order factors, those with low attentional and motor impulsiveness scores had greater improvement with topiramate compared to placebo. These results appear to contradict the overall finding that higher BIS-11 scores resulted in greater improvement with topiramate. Similarly, among first-order factors, those with lower attention and cognitive complexity scores had greater improvement with topiramate compared to placebo, though only the attention score maintained significance after Bonferroni correction. More consistent with the finding of the overall BIS-11 score, those with higher first-order self-control and perseverance scores had greater improvement with topiramate than placebo, indicating that those with worse ability to engage in purposeful thoughts or action and poorer lifestyle stability and future-orientation performed better with topiramate, though again only the self-control score maintained significance after Bonferroni correction. These seemingly contradictory results from subscores could be explained by a complex interaction between the known adverse effects of topiramate worsening other aspects of cognition and the expected effect of its ability to reduce impulsiveness.

One of the limitations of this analysis is a known limitation of the BIS-11 being a self-report measure of trait impulsiveness. However, a prior study assessing correlation between BIS-11 scores and various neuropsychological testing of inhibitory control, including motor inhibition, stop signal, Stroop, and negative priming, suggested correlations with corresponding subscores on the commonly used self-report measure.[20] While a neuropsychological battery was not completed in this study, pretreatment and posttreatment testing may contribute to both the ability to predict topiramate responders based on baseline traits, and evaluate a potential effect on altering impulsiveness in this population.

In summary, interpreting the significance of second-order and first-order subscores is complex, and perhaps less meaningful due to the limited validity of these subscores on their own, and taking into consideration that some first-order scores are a sum of the scores of only three questions. However, the significantly greater percentage of cocaine-free days in those with a higher total BIS-11 score on topiramate versus placebo was a noteworthy finding. Clinically, this indicates that the BIS-11 may serve as a good indicator for the selection of patients with CUD who are most likely to respond to topiramate. The significant difference may also indicate the need for baseline impulsiveness to be considered in randomization procedures of future clinical trials of topiramate or other agents that are thought to target impulsivity in individuals with CUD.

CONCLUSION

This post hoc analysis of a large cohort of individuals with CUD emphasizes the role of baseline trait impulsiveness as measured by the BIS-11 as a predictor of treatment response. Amongst findings of minimal or no improvement with dozens of pharmacotherapeutics for CUD, this significant clinical effect of a medication based on easily measured individual characteristics imparts hope that accounting for baseline characteristics or subtypes of individuals with CUD may improve outcomes with an already available treatment option. More research to refine the impulsiveness phenotype is needed to help maximize treatment effectiveness while minimizing adverse events.

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TABLE 1.

Descriptive statistics of BIS-11 scores

	Mean	Lower quartile	Median	Upper quartile
Overall (total) score	68.9	63	68	73
Attentional	19.8	18	20	22
Attention	13.0	11	13	15
Cognitive instability	6.8	6	7	8
Motor	26.8	24	26	29
Motor	16.8	15	17	18
Perseverance	10.1	9	10	11
Nonplanning	28.3	26	28	30
Self-control	16.2	15	16	18
Cognitive complexity	12.2	11	12	13

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TABLE 2.

Estimated mean differences in cocaine-free days between topiramate and placebo among BIS-11 total scores

	Estimated mean difference (%)	Lower 95%C.I.	Upper 95%C.I.	*p*-value	Bonferroni corrected *p*-value
> Median	11.19	1.51	20.88	**0.024**	**0.047**
≤ Median	5.20	−4,28	14.67	0.282	0.564

Bold values indicate statistical significance $p < 0.05$.

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TABLE 3.

Estimated mean differences in cocaine-free days between topiramate and placebo among BIS-11 subscores

	Estimated mean difference (%)	Lower 95% C.I.	Upper 95% C.I.	*p*-value	Bonferroni corrected *p*-value
Second-order					
Attentional					
>Median	3.32	−6.24	12.87	0.495	0.990
≤Median	11.92	2.66	21.18	**0.012**	**0.024**
Motor					
>Median	4.98	−4.76	14.72	0.316	0.632
≤Median	10.81	1.53	20.09	**0.023**	**0.046**
Nonplanning					
>Median	7.82	−2.65	18.28	0.143	0.286
≤Median	8.04	−0.62	16.71	0.069	0.138
First-order					
Attention					
>Median	3.28	−7.16	13.70	0.536	0.999
≤Median	11.37	2.62	20.12	**0.011**	**0.022**
Cognitive					
>Median	6.37	−5.52	18.27	0.293	0.586
Instability					
≤Median	7.50	−0.50	15.49	0.066	0.132
Motor					
>Median	6.45	−4.01	16.91	0.226	0.452
≤Median	8.23	−0.36	16.82	0.060	0.120
Perseverance					
>Median	11.64	0.36	22.92	**0.043**	0.086
≤Median	5.42	−2.72	13.55	0.191	0.382
Self-control					
>Median	13.64	3.22	24.05	**0.010**	**0.020**
≤Median	4.32	−4.18	12.82	0.318	0.636
Cognitive					

	Estimated mean difference (%)	Lower 95% C.I.	Upper 95% C.I.	*p*-value	Bonferroni corrected *p*-value
Complexity					
>Median	5.98	−5.08	17.03	0.288	0.576
≤Median	8.78	0.57	16.98	**0.036**	0.072

Bold values indicate statistical significance $p < 0.05$.