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Predictors of Topiramate Tolerability in Heavy Cannabis Using Adolescents and Young Adults: A Secondary Analysis of a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Purpose/Background—Cannabis is the most commonly abused illicit drug and accounts for the greatest number of adolescent substance abuse treatment admissions. Despite urgent need for effective interventions, the best available psychosocial treatment options yield only modest effects. Topiramate showed promise as an adjunctive pharmacotherapy to a psychosocial intervention for cannabis misuse among adolescents and young adults in a recent clinical trial. But it was not well tolerated. This study investigated associations between clinical characteristics and side effects and dropout among adolescents and young adults randomized to topiramate.

Methods/Procedures—This study involved secondary data analysis of a randomized placebo-controlled trial of topiramate for treating cannabis misuse (ages 15–24; 50% female). We explored the interaction effects of baseline characteristics and medication condition (topiramate vs. placebo) on treatment dropout. We also explored the relationship between side effects and dropout.

Findings/Results—Higher cannabis problems were significantly associated with reduced hazard of dropout in the topiramate group ($p = .048$), and were non-significantly associated with increased hazard of dropout in the placebo group ($p = .062$). Results also showed that memory difficulties were an overwhelming predictor of dropout in the topiramate condition; 42% of participants who dropped out experienced memory difficulties while none of those who remained in the study experienced these effects.

Implications/Conclusions—By identifying who may most benefit from and tolerate this medication, treatment for substance use disorders can become more individualized and positive outcomes may be enhanced.

Keywords

Cannabis; Topiramate; Side Effects; Tolerability; Adolescents

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Introduction

Heavy cannabis use in adolescents and young adults is associated with myriad adverse outcomes including substance use disorder, depression, anxiety, and diminished educational, professional, and social achievements.[1] Unfortunately, psychosocial interventions show modest efficacy,[2] and there are no approved pharmacotherapies for cannabis use disorder[3].

Topiramate may be a promising medication for the treatment of cannabis misuse. Although topiramate has numerous mechanisms of action, it is thought to diminish the reinforcing effects of cannabis by facilitation of gamma-aminobutyric acid (GABA) transmission and inhibition of glutamatergic transmission (for a detailed discussion, see [4]). In a recent investigation, Miranda et al. (2017) found adolescents and young adults who received motivational enhancement therapy (MET) plus topiramate or placebo showed significant increases in abstinence.[5] In addition, those randomized to MET plus topiramate, but not placebo, also showed reduced grams of cannabis smoked per use day. Given there are currently no approved medications for cannabis use disorder, let alone in adolescents, this is a noteworthy preliminary finding. Additionally, topiramate has demonstrated efficacy in reducing use of alcohol and tobacco in adults,[6–8] but less so for cocaine use disorder.[9]

Despite promising findings, topiramate is associated with potent side effects, most notably transient impairment of cognitive function, particularly in memory and word finding.[5,10–12] This side-effect profile is presumed to affect its tolerability and could lead to greater rates of treatment dropout. For instance, a recent meta-analysis of topiramate for alcohol use disorders found approximately 12% dropped out due to adverse effects (vs. 5% in placebo).[6] In the trial by Miranda et al. (2017), 52% of participants in the topiramate condition dropped out (versus 23% in the placebo condition).[5] Despite notable dropout rates, a recent meta-analysis found topiramate may be the most effective medication for managing alcohol abuse.[8] Consequently, it is important to identify factors that predict topiramate tolerability to determine who might benefit most from topiramate treatment and thus advance treatment options for individuals who struggle with addiction.

Although studies have investigated moderators of adverse events associated with topiramate treatment,[13,14] this investigation is the first to explicitly analyze predictors of dropout in a secondary analysis of a randomized controlled trial (RCT) of MET plus topiramate or placebo for cannabis use in adolescents and young adults.[5] We explored two aims pertinent to topiramate tolerability. First, we explored the interaction effects of baseline characteristics and medication condition (topiramate vs. placebo) on treatment dropout. Given the dearth of research on predictors of dropout in topiramate trials, we tested variables that are regularly implicated in addiction treatment dropout, including age, level of cannabis use, and cannabis-related problems.[15,16] Second, we explored the relationship between side effects and dropout in the topiramate group.

Materials and Methods

Study design

The enrollment procedures and study design are described elsewhere.[5] Briefly, a double blind parallel group RCT tested the efficacy of topiramate (off-label use) versus placebo in treating cannabis use in adolescents and young adults. Topiramate was titrated to 200mg over four weeks and then stabilized for two weeks. Additionally, participants in both conditions received a three-session MET intervention. The Brown University Institutional Review Board approved the study, and after procedures and potential side effects were explained, written informed consent was obtained before participation from participants ≥ 18 years and assent was obtained from minors and consent from parents of participants < 18 years.

Participants

Participants were 15 to 24 years old. Inclusion criteria were cannabis use at least twice weekly in the past 30 days, ≥ one symptom of cannabis abuse or dependence, and interest in receiving a psychosocial intervention combined with medication (or placebo) to reduce cannabis use. Exclusion criteria were cannabis treatment in the past 30 days, current Axis I psychopathology other than cannabis, alcohol, nicotine, or disruptive behavior disorders, active suicidal or psychotic thoughts/intentions, and medical conditions or contraindicated medications. Females were excluded if pregnant, nursing, or unwilling to use birth control.

Measures

Baseline grams per use day and percent use days were ascertained using the 90-day timeline follow-back interview.[17] Side effects were ascertained at weekly appointments by using an adapted version of the Systematic Assessment for Treatment Emergent Effects interview of side effects.[18] Cannabis-related problems were assessed via the Rutgers Marijuana Problem Index (RMPI),[19] an 18-item measure adapted from the Rutgers Alcohol Problems Index.[20] Items were rated on a 5-point scale (0 = never to 4 = more than 10 times) for the past 12 months and all items were summed to compute total scores (α = .83).

Statistical analyses

All continuous predictors (age, grams per use day, percent use days, and cannabis-related problems) were centered at the grand mean. Differences between topiramate vs. placebo groups across demographic variables were tested using chi-square (for categorical variables) or t-tests (for continuous measures). Cox proportional hazard models[21] were conducted to examine comparative survival rates between the two medication conditions and to test predictors of retention (i.e., age, grams per use day, percent use days, and cannabis-related problems). The proportional hazards assumption was tested by including an interaction term between medication condition and survival time in the model. Predictors were tested for main and interactive effects with medication condition and simultaneously included in a single model to evaluate each effect apart from other potential competing influences. Using a backward elimination regression approach, non-significant interactive effects were removed first, followed by non-significant main effects. This is a common statistical approach[22,23]

whereby multiple variables are tested simultaneously and then irrelevant variables are removed. Results indicate which of the candidate variables are the best predictors of the focal outcome (i.e., dropout). These analyses were conducted in SPSS 22.0.[24]

Associations between side effects and dropout (0 = retained, 1 = dropped out) were examined in the topiramate and the placebo group for comparison. We utilized the Fisher r-to-z transformation (i.e., standardize correlations between predictors and dropout within medication groups so that effect sizes may be compared across groups)[25–27] to verify that any side effects related to dropout in topiramate were significantly greater effect sizes than the same side effect and dropout in placebo.[25] Firth's penalized logistic regression was employed to account for instances of data separation.[28,29] In a binary response model, separation occurs when a predictor (e.g., topiramate treatment) is associated with only one outcome option. For example, in our study, all participants in the topiramate group who remained in the study did not report difficulty with memory or confusion, i.e., zero cell values in Table 2 (for other examples, see [30,31]). These analyses were run using R, version 3.3.3,[32] with the package logistf, version 1.22.[33] This approach was selected (instead of the Cox model using time to dropout) to avoid conflating side-effect reports with length of time a participant was retained in the study. Only side effects that occurred in >10% of participants in each group were retained. Of the 21 side effects collected, 19 occurred in >10% of the topiramate group, and 10 occurred in >10% of the placebo group. Due to the number of side effects tested, only those that exhibited nominal significance ($p < .05$) in individual models were entered into a combined model. Benjamini-Hochberg false discovery rate (FDR),[34] a commonly applied correction for "false positives" (i.e., type I error),[35,36] was also reported in order to identify side effect(s) with a greater degree of confidence. A FDR approach rank orders significance (p) values for each predictor and identifies only those predictors with p-values below a common critical value (in our case, $q < .05$).

Results

Two participants in the parent study[5] were excluded from this secondary data analysis because they dropped out solely for external circumstances (i.e., moving away from study location and medication contraindication). The final sample included 26 in the placebo group and 38 in the topiramate group. The sample was primarily White (56.3%) or Black (26.6%) with an equal distribution across gender (50% female), and an average age of 19.69 years (SD = 2.19). The majority were cannabis dependent (68.8%) with moderate cannabis problems (M RMPI score = 8.19; SD = 8.29), and high levels of use (M grams per use day = .67, SD = .57; M percent use days = 71.44%, SD = 27.07). The placebo group was significantly younger and smoked more grams per use day than the topiramate group (respectively: $M_{difference} = -1.48$, $t(62) = -2.81$, $p = .007$, $SE = .53$, 95%CI [−2.54, −0.42]; $M_{difference} = .34$, $t(34.26) = 2.19$, $p = .036$, $SE = .16$, 95%CI [0.02, 0.66]). There were no significant differences among the other participant characteristics.

The interaction between medication condition and survival time was not significant, indicating that the proportional hazards assumption of the Cox model was met. With placebo as the reference group (hazard ratio [HR] = 1), the HR of topiramate was 2.51 (95%CI [1.00, 6.29], $p = .050$), indicating that the estimated hazard of dropout for participants in the

topiramate condition is 2.51 times that for those in the placebo condition. The interaction term of medication condition by cannabis-related problems was significant ($p = .007$), while the other variables' main and interaction effects were not significant for percent use days, age, or grams per use day, despite the latter two variables differing by medication condition at baseline; these were excluded from the final model (see Table 1). The influence of cannabis problems on dropout was in opposite directions for treatment groups: higher cannabis problems were significantly associated with *reduced* hazard of dropout in the topiramate group ($p = .048$), and were non-significantly associated with *increased* hazard of dropout in the placebo group ($p = .062$).

In the logistic regression models for the placebo group, no side effects were significantly associated with dropout. For the topiramate group, four side effects were significantly associated with dropout, including: difficulty with memory, slow thinking or reactions, word finding difficulties, and confusion (see Table 2). Difficulty with memory survived a FDR correction of $q = .05$,[34] and in the combined penalized logistic regression model, backward regression revealed that only difficulty with memory was significant, suggesting that topiramate-induced memory difficulties accounted for a significant proportion of the variance in dropout from the medication condition. A Fisher r-to-z transformation identified a significant difference between placebo and topiramate ($r = -.036$, $r = .516$, respectively, $p = .024$), verifying that this effect was specific to topiramate.

Discussion

This study explored predictors of dropout and retention in a RCT of MET plus topiramate or placebo for cannabis use in adolescents and young adults.[5] The first set of analyses sought to determine if age, level of cannabis use, or cannabis problems were associated with rate of dropout in topiramate versus placebo. We found that those with higher cannabis problems were less likely to drop out while taking topiramate as compared to those receiving the placebo. The second set of analyses explored the relationship between side effects of topiramate and dropout. We found that memory difficulties were a strong predictor of dropout, with 42% of participants who dropped out and 0% of participants who did not dropout reporting difficulty with memory.

Although preliminary, these results suggest that individuals with higher cannabis problems should be prioritized for treatment with topiramate. Furthermore, despite evidence that several side effects often occur in participants taking topiramate,[10] we found that only one domain of side effects (difficulty with memory) led to dropout. All other categories of side effects were not related to dropout and were therefore presumed to be more tolerable. This indicates that medication-induced memory deficits should be closely monitored, and that titration or alternative medications should be considered in the event a patient endorses these side effects.

This study was not without its limitations. First, the study was relatively small and therefore permitted only testing for large effect sizes. Second, the sample was composed of heavy cannabis-using adolescents and young adults, and thus may not generalize to older users or other substance use. Third, this analysis did not incorporate genotyping or variation in

titration or dosage, which are all factors known to impact adverse events.[13,14,37–39] It will be important for future investigations to clarify how rates of dropout vary in relation to demographics, substance of abuse, genetic variation, dosage, and rate of titration.

Despite its limitations this study provided valuable preliminary evidence that certain variables, such as cannabis problems and memory-related side effects, are associated with retention in topiramate trials. Patient characteristics and reports of memory impairment could be important determinants of clinical decision making with regard to slowed titration, reduced dosage, or alternative approaches. By identifying who may most benefit from and most tolerate this medication, treatment for substance use disorders can become more individualized and positive outcomes could be enhanced.[13]

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Table 1

Cox proportional hazard models predicting dropout

	Hazard ratio	95% Confidence interval	*p*
Original Model			
Med	2.48	.62 – 9.99	.200
Age	1.19	.55 – 2.55	.660
GUD	3.66	.12 – 109.10	.454
PUD	1.02	.94 – 1.12	.593
RMPI	1.23	1.04 – 1.45	.016
AgexMed	.87	.56 – 1.35	.533
GUDxMed	.30	.03 – 3.36	.328
PUDxMed	.997	.95 – 1.05	.910
RMPIxMed	.86	.77 – .97	.014
Final Model			
Med	2.61	.91 – 7.49	.074
RMPI	1.22	1.06 – 1.42	.008
RMPIxMed	.87	.78 – .96	.007
Placebo Only			
RMPI	1.06	.997 – 1.12	.062
Topiramate Only			
RMPI	.917	.84 – .999	.048

Note. Med = medication condition (1 = placebo, 2 = topiramate), GUD = grams per use day, PUD = percent use days, RMPI = Rutgers Marijuana Problem Index.

Table 2

Penalized logistic regression models of side effects (SE) predicting dropout in the topiramate condition

	Dropout participants (*N* = 19) who endorsed SE	Non-dropout participants (*N* = 19) who endorsed SE	Odds ratio	95% Confidence interval	*p*
Difficulty with memory	8	0	28.79	13.10 – 3866.09	.001 *
Slow thinking or reactions	10	2	7.77	1.77 – 46.99	.006
Word finding difficulties	9	2	6.36	1.45 – 38.47	.013
Confusion	5	0	14.73	1.48 – 1998.20	.018

Note.

* Difficulty with memory was the only side effect to maintain significance in a backward regression multivariate model of all 4 nominally significant side effects. Difficulty with memory survived a FDR q = .05 (corrected for 19 side effects tested). The 15 side effects which were non-significant (ps > .05) are not included in the table.