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Balancing Risk and Benefit in Heavy Drinkers Treated with Topiramate: Implications for Personalized Care

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Abstract

Despite topiramate's ability to reduce heavy drinking, its adverse effects may limit its clinical utility.

Methods—To evaluate the risks and benefits of topiramate, we re-analyzed data from a completed trial of the medication in 138 heavy drinkers whose goal was to reduce their drinking to safe levels. We used no heavy drinking days during the last four weeks of treatment to calculate topiramate's number needed to treat (NNT). To balance the risks and benefits of topiramate, we adjusted the NNT using two different levels of adverse event severity: moderate or greater (NNT-AE_{mod+}) and severe or greater (NNT-AE_{sev+}). This helps to guide the clinical use of topiramate in heavy drinkers by incorporating both its beneficial and adverse effects in a single measure. Because a polymorphism (rs2832407) in the gene encoding a kainate receptor subunit appears to moderate topiramate's effects in heavy drinkers, we repeated the analyses based on rs2832407 genotype (C-homozygote vs. A-allele carrier) in the European-American (EA) subsample (n=122).

Results—Overall, the NNT for topiramate was 5.29, the NNT-AE_{mod+} 7.52, and the NNT-AE_{sev+} 6.12. Among EAs with the rs2832407*CC genotype, the NNT was 2.28, the NNT-AE_{mod+} was 2.63, and the NNT-AE_{sev+} was 2.56. In contrast, for rs2832407*A-allele carriers, the NNT was 180.00, the NNT-AE_{mod+} 322.16, and the NNT-AE_{sev+} 217.45.

Conclusions—In this sample of heavy drinkers, topiramate had a clinically important treatment effect that was most evident in EAs with the rs2832407*CC genotype. In that group, in particular, it had a robust treatment effect even when adjusted for adverse events.

Keywords

Topiramate; Alcohol Use Disorder; NNT; Adverse-Event-Adjusted; Risk-Benefit

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INTRODUCTION

Topiramate has been shown to reduce consumption of a variety of substances of abuse. It has been most widely studied in alcohol treatment and it reduces drinking in alcohol dependent individuals and heavy drinkers.¹⁻⁴ A meta-analysis showed that topiramate's efficacy in alcohol treatment is substantially greater than that of naltrexone or acamprosate,⁵ medications that are approved by the U.S. Food and Drug Administration (FDA) and most commonly prescribed for alcohol treatment. Consistent with its robust therapeutic effect the rate of topiramate prescription for alcohol treatment in the Veterans Affairs Healthcare System more than doubled from 2009 to 2012.⁶ Topiramate also increases the likelihood of cigarette abstinence among smokers.^{7,8} Some studies have also shown an effect of topiramate on abstinence from cocaine,^{9,10} though a recent study found no such effect.¹¹

In addition to its efficacy, tolerability is important in a clinician's choice of a medication to treat an alcohol use disorder (AUD) and a patient's decision to take the medication. Based on topiramate's actions in multiple neurotransmitter and enzyme systems,^{12,13} it has a variety of adverse effects, the most common of which are somnolence, fatigue, weight loss, and nervousness.¹⁴ Less common adverse effects of topiramate include cognitive difficulties (e.g., confusion, psychomotor slowing; decreased concentration, attention, and memory; speech or language problems), renal calculi, metabolic acidosis, and visual disturbances (including, rarely, secondary glaucoma).

In a study of 138 heavy drinkers whose goal was to reduce their drinking to safe levels, we found that topiramate reduced heavy drinking days (HDDs) and increased abstinent days significantly more than placebo.⁴ Further, in the subsample of European Americans (EAs; n=122), the effect was moderated by rs2832407, a single nucleotide polymorphism (SNP) in *GRIK1*, the gene that encodes the GluK1 subunit of the kainate receptor. Thus, the use of topiramate to treat heavy drinking may be most appropriate in individuals with a specific rs2832407 genotype (the frequency of which varies widely by population).

Although the only serious adverse event seen in our study was in the placebo group, patients receiving topiramate reported significantly more adverse events overall [mean=5.5 (SD=3.1) than placebo patients [mean=3.0 (SD=2.5); $p<0.001$] and events of at least moderate severity [mean=1.8 (SD=1.3)] than placebo patients [mean=0.4 (SD=0.7); $p<0.001$]. Topiramate patients reported a significantly greater likelihood of numbness/tingling, change in taste, loss of appetite, weight loss, difficulty concentrating, and difficulty with memory.⁴

Despite the clinical relevance of the risk-benefit relationship, there are no published measures that jointly reflect the therapeutic and adverse effects of topiramate in treating AUD. Here, we calculated number needed to treat (NNT) and adjusted it for reported adverse events, using data from our topiramate trial.⁴ NNT is the estimated number of patients who must receive an intervention to achieve a successful outcome in one patient, relative to the effects of placebo treatment. We adjusted the NNT for two levels of adverse events: those of a moderate or greater severity (which may be most relevant to a patient's choice whether to undergo treatment) and separately those that received a severe or greater rating (which may be most relevant for a prescriber's choice as to whether to prescribe the

treatment). Finally, we repeated all of the comparisons separately by rs2832407 genotype (C-allele homozygotes vs. A-allele carriers).

We hypothesized that the adverse-event adjusted NNT for topiramate would be substantially lower than the NNTs reported in the literature for either naltrexone or acamprosate.⁵ Further, based on the prior finding that the rs2832407 genotype in *GRIK1* moderated the response to topiramate,⁴ we hypothesized that EA individuals with the rs2832407*CC genotype would have an adverse-event adjusted NNT that is lower than A-allele carriers, reflecting greater efficacy of the medication in the CC-genotype group. Further, based on a report by Ray et al.,¹⁵ in which rs2832407*C-homozygotes showed a lower risk of adverse events than A-allele carriers, we expected that the impact of adjusting NNT for adverse events would be more modest in the CC genotype patients.

METHODS

Overview

We re-analyzed data from a 12-week, double-blind, randomized, placebo-controlled trial of topiramate in a sample of 138 heavy drinkers.⁴ In that study, 67 patients (48.6%) were randomly assigned to receive topiramate and 71 patients (51.4%) received placebo. Most patients were male [placebo: n=41 (58%), topiramate: n=45 (67%)] and EA [placebo: n=66 (93%), topiramate: n=56 (84%)]. The genotype distribution among EAs was as follows: 21 topiramate-treated patients were rs2832407*C homozygotes and 30 were A-allele carriers (i.e., either heterozygotes or A-allele homozygotes) and the comparable numbers in the placebo group were 35 and 36, respectively. Additional information on the study sample is provided in Kranzler et al.⁴

Patients were seen weekly for the first six weeks to allow a gradual increase in topiramate dosage from 25 mg/day to a maximum of 200 mg/day (or a comparable number of matching placebo capsules). They were seen once every two weeks for the remaining six weeks. The Timeline Follow-back¹⁶ was administered to cover the 90-day pretreatment period and it was repeated at each treatment visit to estimate the number of HDDs since the last visit (i.e., four or more drinks in a day for women and five or more drinks in a day for men). At each visit, patients were also queried regarding the treatment-emergent occurrence of 19 adverse events that have been associated with topiramate treatment. For each adverse event endorsed, patients were asked about the nature of the adverse event and the level of functional impairment associated with it, which was categorized as mild (no impairment), moderate (some change in activities), severe (substantial limitations), life threatening/disabling, or fatal, resulting in a 5-point rating scale. Reported adverse events were followed until they resolved. Additional information on the study methods is provided in Kranzler et al.⁴

Analyses

NNT is the number of patients that needed topiramate treatment (compared with placebo) to prevent one patient from having a heavy drinking day during the last four weeks (i.e., weeks 9-12) of treatment. In this calculation, patients who withdrew prior to week 12 (15% overall)

were coded as not successfully treated. When evaluating the NNT, the lower the value, the larger the treatment effect.

We calculated the proportion of patients in each treatment group that reported at least one adverse event and the average severity rating of reported events (absent=0, mild=1, moderate=2, severe=3, and life threatening/disabling=4). We adjusted the NNT separately using two levels of adverse event severity: at least one adverse event rated as moderate or greater in severity and at least one adverse event rated as severe or greater. These categories were chosen, despite being overlapping, to address patient concerns (i.e., adverse events of moderate or greater severity), which are more likely to center on comfort and safety, and prescriber concerns (i.e., adverse events that are severe or greater), which are more likely to center on safety as counterweights to efficacy.

The NNT was calculated by taking the inverse of the absolute risk reduction, the difference in event rates between the topiramate and placebo groups during the 12 weeks of treatment. We calculated 95% confidence intervals (95% CIs) for NNT using the method of Wilson.¹⁷ We adjusted the NNT by the severity of reported AEs.¹⁸ We also performed a subgroup analysis by genotype (CC vs. A-allele carrier) within EAs (n=122) to evaluate the impact on clinical utility of the moderator effect of rs2832407. Although values of NNT are often rounded up to the nearest whole number to provide a readily interpretable estimate,¹⁹ we present the values carried out to two decimal places to allow comparisons with adverse-event-adjusted NNTs and with NNTs from comprehensive reviews of naltrexone²⁰ and acamprosate.²¹

RESULTS

Full Sample (n=138)

Efficacy—Table 1 shows the proportion of patients experiencing no HDDs during the last month of treatment. As reported in Kranzler et al.⁴ in the full sample, 36% of patients treated with topiramate reported no HDDs during the last month of treatment compared to 17% in the placebo group, an NNT of 5.29.

Adverse Events—The vast majority of patients reported at least one adverse event, including 96% of the topiramate group and 86% of the placebo group, a non-significant difference ($\chi^2(1df)=3.73$, $p=0.053$). Although most adverse events were rated as mild, the mean severity rating was significantly greater in the topiramate group [1.3 (SD=0.4)] than in the placebo group [1.1 (SD=0.5)] ($F_{1,136}=8.86$, $p=0.003$). Among topiramate patients, 78% reported at least one adverse event of moderate or greater severity compared to 48% for placebo. Taking into account the presence of moderate or greater adverse events yielded an adverse-event-adjusted NNT (NNT-AE_{mod+}) of 7.52. The percentage of patients reporting a severe or greater adverse event was 16% for topiramate and 3% for placebo, yielding an adverse-event-adjusted NNT (NNT-AE_{sev+}) of 6.12.

European-American Subgroup (n=122)

The last two columns of Table 1 show the response and adverse event rates for EA patients by treatment and genotype group.

Efficacy—As previously reported,⁴ rs2832407 moderated the effect of topiramate in EAs. Among rs2832407*C-homozygotes, 57% of those treated with topiramate had no HDDs during the last month of treatment, compared to 13% of placebo patients, an NNT of 2.28. In contrast, among A-allele carriers, there was a very small difference in the likelihood of no HDDs during the last month of treatment (20% of topiramate patients and 19% of placebo patients), an NNT of 180.00. The 95% CI for this NNT (5.22 to −5.57) shows that the conditions were equivalent, i.e., topiramate had no discernible effect on the risk of HDDs in the last month of treatment.

Adverse Events—Nearly all individuals (i.e., 92%) in both rs2832407 genotype groups experienced one or more adverse events ($\chi^2(1df)=0.02$, $p=0.90$). Among rs2832407*C-homozygotes, topiramate-treated patients reported a mean adverse event severity of 1.3 (SD=0.3), compared with 1.1 (SD=0.5) in the placebo group, a non-significant difference ($F_{1,49}=3.31$, $p=0.075$). Among A-allele carriers treated with topiramate the mean adverse event severity was 1.5 (SD=0.3), compared with 1.1 (SD=0.6) in the placebo group, a highly significant difference ($F_{1,69}=11.51$, $p=0.001$). The interaction of medication group X genotype group on this severity measure was not significant ($F_{1,118}=0.83$, $p=0.37$).

A majority of rs2832407*C-homozygotes reported an adverse event that was moderate or greater in severity, including 67% of topiramate patients and 53% of placebo patients, a non-significant difference ($\chi^2(1df)=0.91$, $p=0.34$). NNT-AE_{mod+} was 2.63 (i.e., when adjusted for adverse events that were moderate or greater in severity). Fourteen percent of topiramate patients and 3% of placebo patients experienced a severe adverse event, yielding an NNT-AE_{sev+} of 2.56.

Among rs2832407*A-allele carriers, 89% of topiramate patients and 44% of placebo patients experienced a moderate or greater adverse event. This yielded an NNT-AE_{mod+} of 322.16. Twenty percent of topiramate patients and 3% of placebo patients experienced a severe adverse event, an NNT-AE_{sev+} of 217.45.

Accounting for the rate of treatment completion did not change the results substantially (data not shown), consistent with the high rate of completion in both medication groups (topiramate: 82.1%; placebo: 87.3%).

DISCUSSION

Topiramate, although more efficacious in treating alcohol dependence than either naltrexone or acamprosate,⁵ produces a number of adverse effects that can limit its use. We found that a SNP (rs2832407) in *GRIK1* moderated topiramate's effect in reducing HDDs,⁴ identifying a highly responsive subgroup of heavy drinkers among EAs. To capture both the beneficial and adverse effects of topiramate from that study, we calculated the NNT to reduce heavy drinking and adjusted it using two levels of adverse event severity. Overall, we found that the NNT for topiramate was 5.29, a robust treatment effect when compared with the unadjusted NNTs that have been reported for both naltrexone in preventing a relapse to heavy drinking (NNT=9.09)²⁰ and acamprosate in reducing the risk of returning to any drinking after detoxification (NNT=9.09).²¹ The NNT for topiramate, when adjusted for adverse effects of

the medication was 7.52 (when considering moderate or greater adverse events) or 6.12 (when considering only severe adverse events). Thus, as hypothesized, even after adjusting for adverse events, topiramate yielded a more robust alcohol treatment effect than either naltrexone or acamprosate. Reducing the risk of HDDs is clinically important, as serious medical and psychiatric adverse outcomes²² and elevated mortality risk²³ are associated with this pattern of drinking. Thus, the use of topiramate to treat heavy drinking appears to be clinically useful. These estimates also compare favorably with the effects of medications that are efficacious in the treatment of treat major depression, including both tricyclic antidepressants, which unadjusted for adverse events had a median NNT of 9, and selective serotonin reuptake inhibitors, which unadjusted had a median NNT of 7.²⁴

We found that topiramate had a much more robust effect in promoting no HDDs in individuals with the rs2832407*CC genotype. In this group, the NNT was 2.28 unadjusted and about 2.6 adjusted for either of two severity levels of adverse effects. In striking contrast, among patients with an rs2832407*A allele, the NNT adjusted for moderate or severe adverse effects was 322.16 and for severe adverse effects was 217.45. These findings argue strongly against the use of topiramate to treat heavy drinking in patients with the rs2832407*A allele, as the benefit relative to placebo is extremely small, particularly when accounting for the adverse effects of the medication.

The finding that the impact of adjusting for adverse effects was much smaller among EAs with the rs2832407*CC genotype than those with one or two A alleles at this locus is consistent with the findings reported by Ray et al.¹⁵ They found a greater mean level of adverse effects among topiramate-treated patients who were rs2832407*A-allele carriers than those who were homozygous for the C-allele. However, we did not find an effect of genotype on the mean severity of topiramate-induced adverse effects. Thus, although topiramate's efficacy in reducing heavy drinking is greater in patients with the rs2832407*CC genotype than in A-allele carriers, the question of whether the CC-genotype group also tolerates the medication better than do A-allele carriers remains to be answered.

Although we adjusted the NNT to account for adverse effects, we did not ascertain the relative importance of the beneficial and adverse effects of the medication to the patients participating in the study. This can be partially overcome by having the patients rate the utility value of each outcome,²⁵ which could then be incorporated in the risk-benefit analysis. Moreover, the severity rating may not fully capture the clinical impact of different adverse events. For example, despite a similar rating, paresthesia and visual changes may be of different importance to the patient. Another study limitation is that the sample was not very large (n=138), particularly in the subgroup analyses (CC genotype n=56, A-allele carriers n=66).

The findings reported here have a number of clinical implications. First, the NNT for topiramate (5.29) compares favorably to that of antidepressants for the treatment of depression (median of 7-9) and is superior to that of the two medications approved to treat alcohol dependence: naltrexone and acamprosate (9.09 for both; though it should be noted that the criteria on which these NNTs are based differ across the three medications, limiting direct comparisons among them). Adjusting for adverse events does not substantially alter

those findings. However, the NNT for topiramate in rs2832407*C homozygotes (2.28) was substantially lower than for the overall sample or for A-allele carriers (180.00), suggesting that topiramate should be prescribed only to individuals with the CC genotype, though efforts to replicate the findings are needed. Ultimately, the clinical utility of this approach will depend on the widespread availability of SNP genotyping for use in clinical decision making.

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Clinical Points

- Heavy drinking is prevalent in the population and commonly associated with a variety of adverse medical and social effects. There are comparatively few treatments with more than modest efficacy to reduce heavy drinking. Topiramate was effective in reducing heavy drinking among individuals with alcohol dependence, especially those homozygous for the *GRIK1* rs2832407*C allele.
- Because topiramate has a variety of pharmacological effects, it is associated with adverse effects that limit its clinical use. A risk/benefit analysis that used no heavy drinking as a criterion for treatment success and adjusted for adverse events showed that topiramate compared favorably to other currently used alcohol treatment medications, with the greatest benefit seen among rs2832407*C allele homozygotes.

Table 1

Rate of Heavy Drinking, Adverse Events, Number Needed to Treat and Adverse-Event-Adjusted Number Needed to Treat by Treatment Group and Genotype Group

Measure	Full Sample (n=138)		European-American Subsample (n=122)			
	Placebo (n=71; 51.4%)	Topiramate (n=67; 48.6%)	<i>rs2832407</i> *C-allele Homozygotes (n=51; 41.8%)		<i>rs2832407</i> *A-allele Carriers (n=71; 58.2%)	
No HDDs	17%	36%	Placebo (n=30; 58.8%)	Topiramate (n=21; 41.2%)	Placebo (n=36; 50.7%)	Topiramate (n=35; 49.3%)
AE _{Mod+}	48%	78%	13%	57%	19%	20%
AE _{Sev+}	3%	16%	53%	67%	44%	89%
NNT (95% CI)	5.29 (3.05, 23.67)		3%	14%	3%	20%
NNT-AE _{mod+}	7.52		2.28 (1.57, 5.71)		180.00 (5.22, -5.57)	
NNT-AE _{sev+}	6.12		2.63		322.16	
			2.56		217.45	

n=number of patients, HDDs=heavy drinking days, AE=adverse event; subscripts Mod+ refers to the occurrence of an AE or moderate or greater severity and Sev+ to the occurrence of an AE that was severe or greater; NNT=number needed to treat; 95% CI=95% confidence interval; NNT-AE_{mod+}=NNT adjusted for moderate or greater AEs; NNT-AE_{sev+}=NNT adjusted for severe or greater AEs