SUPPLEMENTAL MATERIALS

Supplemental Table S1 lists the adverse events endorsed by at least 10% of topiramate-treated patients.

Supplemental Figure S1: Consort diagram showing number of patients enrolled and randomized, and the number who completed the trial by medication group.

Adverse effects

To evaluate whether the adverse effects of topiramate, particularly the changes in taste and loss of appetite, were related to treatment response, we correlated the extent of endorsement of these two adverse events with changes in drinking. The correlation between number of heavy drinking days and a sum of the severity scores for change in taste and loss of appetite were very low (taste: r=-0.04, p=0.62; appetite: r=0.04, p=0.66). Similarly, there was a very low correlation between the number of abstinent days and change in taste (r=-0.07, p=0.38) and loss of appetite (r=0.05, p=0.56). These findings argue strongly against these adverse effects contributing to the efficacy of topiramate in reducing drinking.

To test whether rs2832407 moderated the likelihood or severity of topiramate-induced adverse events, we calculated two measures of adverse events: a total number of adverse events reported and an adverse event severity score using the methods described by Ray et al. (2009). For the former, we calculated a continuous measure reflecting the mean number of the following 19 adverse effects occurring at the target dosage: dizziness, decrease in appetite, changes in vision, difficulty sleeping, weight loss, fatigue, difficulty with coordination or balance, difficulty with concentration or attention, paresthesia, word-finding difficulties, memory difficulties, tremor, constipation or diarrhea, restlessness, nervousness or anxiety, irritability, depression, confusion, and changes in sexual function. For the latter, we scored the severity of each adverse event as mild=1, moderate=2, or severe=3 and summed them across medication and genotype groups.

Analogous to Ray et al.'s analysis of data from the period during which subjects were on the maximal dosage of topiramate (which in their study was days 32-37), we examined data during the last six weeks of treatment. Also as in Ray et al., we compared the CC genotype group with the A-allele carrier group. Due to positive skew in the data, we used a Poisson model for analysis.

The mean (SD) number of adverse events reported in the placebo group was 0.70 (0.94) compared with 1.10 (1.23) in the topiramate group. Dividing the treatment groups by genotype, placebo-treated patients with the CC genotype reported 0.66 (0.77) adverse events, while for A-allele carriers it was 0.73(1.07). In the topiramate group, patients with the CC genotype reported a mean of 1.43 (1.50) adverse events, compared with 0.89 (1.01) in the A-allele carrier group. There was a significant main effect of medication group (Wald $\chi^2_{(1df)}$=6.53, p=0.011), but neither the main effect of genotype group (Wald $\chi^2_{(1df)}$=0.89, p=0.35), nor the interaction of medication group X genotype group (Wald $\chi^2_{(1df)}$=2.25, p=0.13) was significant.

The mean severity rating for adverse events was 1.05 (1.47) in the placebo group and 1.64 (1.86) in the topiramate group. Placebo-treated patients with the CC genotype reported a mean severity of 1.10 (1.45) for adverse events, while for A-allele carriers it was 1.00 (1.51). In the topiramate group, patients with the CC genotype reported a mean severity of 2.13 (2.28) for adverse events, compared with 1.34 (1.51) in the A-allele carrier group. There was a significant main effect of medication group (Wald $\chi^2_{(1df)}$=9.22, p=0.002) and a non-significant trend for a main effect of genotype group (Wald $\chi^2_{(1df)}$=3.20, p=0.074), but the interaction of medication group X genotype group (Wald $\chi^2_{(1df)}$=1.35, p=0.25) was not significant.

One possible reason for the lack of replication of the findings of Ray et al. (2009) include the fact that they studied non-treatment-seeking heavy drinkers, which contrasts with the highly motivated patients in our study (as evidenced by their high rates of study completion and medication adherence).

A second possible explanation for the non-replication was that the sample size in the study by Ray et al. was small (total n=51), which may have resulted in unreliable findings.

Integrity of the masking procedure

Using a brief questionnaire administered at the end of treatment, we asked patients to tell us whether they thought that they had received active medication or placebo and to rate the extent to which they found the medication helpful (on a scale of 0-10). We received responses from 135 of the 138 participants (97.8%). Of the 65 topiramate-treated patients for whom we had data, 56 (86.2%) identified their treatment correctly and of the 68 placebo-treated patients for whom we had data, 49 (72.5%) identified their treatment correctly; topiramate patients were significantly more likely to identify the treatment correctly ($\chi^2_{(1)}$=45.78, p<0.001). The topiramate group rated the medication as very helpful [mean=9.89 (SD=15.92)], whereas the placebo group rated it as moderately helpful [mean=6.43 (SD=16.17)], also a significant difference (Mann-Whitney U test, p<0.001). Although these findings could reflect a non-pharmacological effect of the treatment intervention, a more parsimonious explanation is that they resulted from the greater number of adverse events and the better drinking outcomes in the topiramate group than the placebo group. Further, the moderation by rs2832407 of the efficacy of topiramate is most consistent with a pharmacologic effect of topiramate to reduce heavy drinking and, importantly, it implicates the kainate receptor as a mediator of that effect.

Table S1: Adverse Events[a,b] in Descending Order of Frequency in the Topiramate Group

	Topiramate (N=67)	Placebo (N=71)	P-Value[c]
Numbness/Tingling	36 (53.7)	10 (14.1)	**<0.001**
Change in Taste	25 (37.3)	6 (8.5)	**<0.001**
Tiredness/Sleepiness	18 (26.9)	16 (22.5)	0.69
Difficulty with Memory	16 (23.9)	4 (5.6)	**0.003**
Loss of Appetite	16 (23.9)	2 (2.8)	**<0.001**
Headache	15 (22.4)	14 (19.7)	0.84
Diarrhea	14 (20.9)	10 (14.1)	0.37
Weight Loss	13 (19.4)	2 (2.8)	**0.002**
Difficulty Concentrating	12 (17.9)	4 (5.6)	**0.033**
Dry Mouth	11 (16.4)	4 (5.6)	0.056
Nausea	7 (10.4)	8 (11.3)	1.00

[a]Incidence in the topiramate group >10%
[b]Frequency (%)
[c]Exact Test

Figure S1: Consort Diagram