PERSONALIZING TOPIRAMATE TREATMENT FOR ALCOHOL USE DISORDER

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Topiramate has a variety of pharmacological effects, one of which is to block kainate receptors containing GluK1 and GluK2 subunits, which are encoded by the *GRIK1* and *GRIK2* genes, respectively. Based on this pharmacology, we found an association with alcohol dependence of a single nucleotide polymorphism (SNP; rs2832407) in *GRIK1*, with the C allele overrepresented in individuals with alcohol dependence (Kranzler et al. 2009). This led us to examine the moderating effect of rs2832407 on the response to topiramate in a 12-week treatment study in 138 heavy drinkers whose goal was to reduce their drinking, followed by 3- and 6-month post-treatment follow-up visits. The rate of treatment completion and follow-ups was >80% and equal by treatment group.

During treatment, topiramate significantly reduced heavy drinking days ($p<0.001$) and increased abstinent days ($p=0.032$) compared to placebo. The topiramate group also had lower concentrations of the liver enzyme gamma-glutamyltranspeptidase and lower scores on a measure of alcohol-related problems than the placebo group. In a European-American subsample (N=122), topiramate's effect on heavy drinking days ($p=0.004$) was significantly greater than for placebo only in rs2832407 C-allele homozygotes. The number needed to treat to prevent heavy drinking in the last month of treatment, after adjustment for adverse effects, was also highly favorable for the genotype-responsive group that received topiramate.

Further, in this group, the reduction in heavy drinking days persisted for 6 months after treatment was discontinued. These findings implicate kainate receptors with the GluK1 subunit as a druggable target for the treatment of alcohol use disorder and support the use of a personalized approach to treat the disorder using topiramate.