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.