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Topiramate reduces heavy drinking in patients seeking to cut down on alcohol consumption

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Heavy drinking is common in the United States and takes a personal and societal toll, with an annual estimated cost of $223.5 billion due to losses in workplace productivity, health care and criminal justice expenses. Data shows that 23 percent of individuals age 12 or older reported drinking five or more drinks on one occasion in the previous month, and almost seven percent reported doing so on at least five days per month. Despite this, few heavy drinkers seek out treatment—especially those who do not meet the clinical criteria for an alcohol use disorder, but whose drinking causes substantial damage to individuals, their families and the community.

Researchers at Penn Medicine have shown that the anticonvulsant medication, topiramate, previously shown to reduce drinking in patients committed to abstinence from alcohol, can also be helpful in treating problem drinkers whose aim is to curb their alcohol consumption – particularly among a specific group of patients whose genetic makeup appears to be linked to the efficacy of the therapy. Their findings are published in the current issue of the *American Journal of Psychiatry*.

"This study represents an important next step in understanding and treating problem drinking," says Henry R. Kranzler, MD, professor of Psychiatry, director of Penn's Center for Studies of Addiction and lead author on the study. "Our study is the first we are aware of in which topiramate was evaluated as a treatment option for patients who want to

limit their drinking to safe levels, rather than stop drinking altogether."

The randomized double-blind trial included a total of 138 heavy drinkers, approximately half of whom received 12 weeks of treatment with topiramate at a maximal dosage of 200 mg/day and half of whom received a placebo. Both groups underwent brief counseling to reduce drinking and increase abstinent days. The study was initiated at the University of Connecticut Health Center and completed at the Center for Studies of Addiction at the University of Pennsylvania.

The study had three phases: a one-week pre-treatment assessment period, a 12-week treatment period and a nine-day medication taper period.

Patients were seen weekly during the first six weeks of treatment, followed by three biweekly visits in which their breath alcohol concentration, weight and vital signs were measured and concurrent medications, the occurrence of adverse events and protocol adherence monitored. Patients were also interviewed at each visit on their drinking and medication use since the last visit.

The results showed that the patients who received topiramate had fewer heavy drinking days than those in the placebo group. By the end of treatment, the odds of experiencing a heavy drinking day in the placebo group was five times more than that of the topiramate group; and the number of patients who experienced no heavy drinking days on the last four weeks of treatment in the topirmate group was more than double that of the placebo group. In addition, topiramate patients reported more abstinent days than placebo patients.

The study has important implications for the personalized treatment of heavy drinking. Analysis showed that only individuals with a specific genotype found in 40 percent of European-Americans benefitted from

treatment with topiramate. The genotype involves two copies of a variant in the gene encoding a subunit of the receptor for an excitatory amino acid neurotransmitter, glutamate. This study, by virtue of showing that only individuals with a certain form of the kainate (glutamate) receptor reduced drinking with topiramate treatment, indicates that this receptor plays a key role in topiramate's effects on drinking. Because topiramate interacts with multiple neurotransmitter and enzyme systems, this provides a specific target for the development of medications to reduce heavy drinking. Targeting this receptor could yield the greatest therapeutic effect in heavy drinkers, while reducing topiramate's common side effects, which include fatigue, dizziness, and memory problems.

Kranzler is optimistic about the potential for the personalized treatment of heavy drinking. "Our hope is that the study will result in additional research on how best to help patients who have struggled with heavy drinking and the problems it causes, but who are unable or unwilling to abstain from alcohol altogether. These findings may allow us to predict, in advance, who may benefit from topiramate treatment, thereby avoiding the unnecessary use of the medication."

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