Drug that curbs heavy drinking is more effective in patients with specific genotype

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The drug topiramate (Topamax) is effective at helping alcohol-dependent individuals and heavy drinkers avoid heavy drinking, but many patients and clinicians have shied away from using the drug due to its reputation for side effects, such as drowsiness and cognitive difficulties. A new risk-benefit analysis from psychiatrists in the Perelman School of Medicine at the University of Pennsylvania, shows that topiramate is both highly effective and seems to cause fewer side effects in drinkers who carry a specific genotype for the gene GRIK1. The findings appear this week in the *Journal of Clinical Psychiatry*.

GRIK1 encodes a certain neurotransmitter receptor subunit on brain cells, known as kainate receptors. A team led by Penn's Henry R. Kranzler, MD, a professor of Psychiatry and director of the Center for Studies of Addiction, were the first, in 2009, to show that that people with a C variant in the DNA sequence in the GRIK1 genewere significantly more likely to be alcohol dependent.

Then, in a landmark 2014 trial, Kranzler and colleagues found evidence that topiramate's effectiveness was largely limited to a subset of people who had two copies of the C allele in that location in GRIK1 (one copy inherited from each parent).

"In our new study, we've gone a step further with that data and mapped the incidence of side effects in those with the C variant and those without," Kranzler said, noting that complaints from patients' about sleepiness and memory difficulties, especially early in treatment, have been common among those taking the drug.

The team, including lead author Richard Feinn, PhD, an assistant professor of medical sciences at Quinnipiac University; and Brenda Curtis, PhD, a research associate in the department of Psychiatry at Penn Medicine, started with an effectiveness measure known as Number Needed to Treat (NNT), which indicates how many patients need to be treated, on average, for one patient to have a successful outcome that would not occur with placebo treatment. The NNT for topiramate turned out to be 5.29 for their full sample of 138 patients. For comparison, the published NNT figures for other standard alcoholism treatment drugs, such as naltrexone and acamprosate, are about nine. Adjusting the topiramate NNT for adverse events such as numbness/tingling in the extremities, change in taste, loss of appetite and weight, and difficulty concentrating, and with memory, that figure rose to about 7.5. This means that about eight patients would need to be treated with topiramate to produce a successful outcome without causing any additional moderate or worse adverse events during the entire 12-week treatment period.

However, the most striking finding came when the analysis was restricted to the 122 patients of European ancestry, in whom the GRIK1 C variant is relatively common. Among the 51 patients who had two copies of the C variant of GRIK1, topiramate's NNT was 2.28—signifying strong efficacy—whereas in the remaining 71 patients, who had only one copy of the C variant or two copies of another variant, the NNT was 180, indicating almost no efficacy.

When adjusted for adverse events, the NNT for the "CC-genotype" group remained essentially the same. "The drug appears to be very effective in heavy drinkers with this genotype, even when we factor in the occurrence of adverse events," Kranzler the new study's senior author, explained.

By contrast, the NNT in the non-CC group went from bad to worse: it was 322 when taking into account moderate or more severe adverse events.

If these results are replicated in studies of other groups of heavy drinkers, Kranzler said, clinicians will be able to use a personalized or precision

medicine approach: using topiramate only in patients with the CC genotype, because they are the only ones likely to benefit. A test that detects this genotype from blood samples has already become commercially available.

Kranzler and his Penn colleagues are currently conducting a follow-up study in a new group of patients to confirm their findings. Kranzler is also collaborating on a separate replication study led by Dr. Paul Haber at the Royal Prince Alfred Hospital in Sydney, Australia. In addition to clinical studies, Kranzler is working with Penn colleague Mariella De Biasi, PhD on studies to better understand how kainate receptors alter the susceptibility to heavy drinking and how they might be targeted with new drugs.

Topiramate was first approved by the FDA in 1996 for the prevention of seizures. It was then approved for migraine headaches in adults in 2004 and in adolescents in 2014.

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