Gene variant predicts medication response in patients with alcohol dependence

8 February 2008

Patients with a certain gene variant drank less and experienced better overall clinical outcomes than patients without the variant while taking the medication naltrexone, according to an analysis of participants in the National Institutes of Health's 2001-2004 COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence) Study.

About 87 percent of patients with the variant who received naltrexone. experienced good outcomes, compared with about 49 percent of those who received a placebo. About 55 percent of patients without the variant experienced a good outcome regardless of whether they received naltrexone or placebo. Good outcome was defined as abstinence or moderate drinking without related problems, according to an article in the Feb. 4 issue of the *Archives of General Psychiatry* (http://archpsyc.ama-assn.org/cgi/content/abstract/65/2/135).

Drinking alcohol increases the release of endogenous opioids, compounds that originate in the body and promote a sense of pleasure or well-being. An opioid antagonist, naltrexone blocks brain receptors for endogenous opioids, making it easier for patients to remain abstinent or stop quickly in the event of a slip. In clinical studies, naltrexone has been shown to reduce relapse and craving for alcohol in some but not all treated patients. Earlier studies had suggested that a specific DNA variant of the opioid receptor gene (OPRM1) might have role in patients' response to naltrexone.

"Analysis of the large COMBINE patient population increases confidence that the OPRM1 variant is in part responsible for positive responses to naltrexone. This study points to the promise of research on gene-medication interactions to refine treatment selection, improve clinical results, and inform ongoing medications development," said National Institute on Alcohol Abuse and Alcoholism (NIAAA) director Ting-Kai Li, M.D.

Of the original 1383 COMBINE Study participants, 1013 were available to be genotyped for the current study, conducted by Raymond F. Anton, M.D., Medical University of South Carolina, and other COMBINE Study principal investigators in collaboration with David Goldman, M.D., and his colleagues in NIAAA's Laboratory of Neurogenetics. The researchers successfully genotyped 911 of the available patients and conducted their initial analysis in 604 who are white, 135 of whom were found to carry the genetic variant. Approximately 15 to 25 percent of humans carry the variant, with considerable variation among ethnicities.

As in the COMBINE clinical trial, drinking variables evaluated in the pharmacogenetic study included the percentage of days abstinent from alcohol, the percentage of heavy drinking days, and clinical outcome during 16 weeks of active treatment. In addition to naltrexone or placebo, all patients received medical management (nine brief, structured outpatient sessions delivered by a health professional) and some also received a combined behavioral intervention (integrated cognitive-behavioral and motivational enhancement therapies, together with techniques to enhance mutual-help participation).

The researchers found that, compared with patients who do not carry the variant, white variant carriers who received naltrexone fared substantially better than other groups on all measures, including almost a 6 times greater likelihood of good clinical outcome. Extending the clinical outcome measure to variant carriers of all ethnicities reduced the benefit to just over a 3 times greater likelihood of good outcome. The researchers found no gene-medication interaction in patients who received specialized alcohol counseling, leading to them to conclude that genotyping for the variant may be most useful when naltrexone is used without

intensive counseling.

Approved by the U.S. Food and Drug Administration in 1994, naltrexone is one of three indicated medications* shown to help patients reduce drinking, avoid relapse to heavy drinking, achieve and maintain abstinence, or gain a combination of these effects. The COMBINE trial showed either specialized counseling or naltrexone--each delivered with medications management--to be effective options for treating alcohol dependence. "Given that alternative treatments such as combined behavioral interventions, acamprosate, and topiramate can be offered, one could make the case that naltrexone should be used first or used primarily in carriers of the OPRM1 [variant]," state the authors. (Guidance regarding the use of approved medications and other tools to help patients with drinking problems is provided in Helping Patients Who Drink Too Much: A Clinician's Guide (http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/guide.htm).

"Research studies designed to ensure appropriate medication targeting are critical, especially as treatment for alcohol use disorders increasingly involves primary care physicians as well as specialists," notes Mark L. Willenbring, M.D., director of NIAAA's Division of Treatment and Recovery Research. "Without the ability to predict response for a specific patient, we must use trial-and-error to determine the correct medication—a process that may prolong illness and lead to more side effects. This study highlights the promise of truly personalized medicine and could help to move treatment of alcohol dependence into the medical mainstream."

Source: NIH/National Institute on Alcohol Abuse and Alcoholism