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Disulfiram: New support for an old addiction drug

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Disulfiram was the first medication approved for the treatment of alcoholism over 50 years ago. It works, at least in part, by preventing the metabolism of an alcohol by-product, acetaldehyde. High levels of acetaldehyde in the body quickly cause unpleasant symptoms, including nausea, vomiting, headache, and accelerated heart rate. Thus, disulfiram provides a very strong incentive to avoid drinking.

Beginning in the late 1990s, a series of studies conducted at Yale University found that disulfiram reduced the consumption of cocaine, particularly in the context of alcohol or opiate dependence. One mechanism introduced to explain this phenomenon was the ability of disulfiram to inhibit dopamine β-hydroxylase, or DβH, an enzyme that converts dopamine to norepinephrine. This hypothesis was supported in a new pharmacogenetic study by Thomas Kosten and colleagues, published in *Biological Psychiatry*.

The researchers recruited cocaine- and opioid-dependent patients who were randomized to receive either disulfiram or placebo for ten weeks. They also genotyped the DBH gene, which alters DβH levels, to determine which variant that each patient carried. Prior work has already shown that individuals with the CC genotype have normal DβH levels, whereas those carrying the T allele have lower DβH levels. This allowed them to determine whether the functional DBH variant influences the success of disulfiram treatment.

Disulfiram was effective in reducing cocaine use in patients with the CC

genotype and normal DβH levels, whereas those with the low DβH level T genotype showed no disulfiram effect. These data support the hypothesis that disulfiram reduces drug consumption, in part, by blocking DβH.

Senior author David Nielsen at Baylor College of Medicine said, "We found significantly greater efficacy in cocaine addicts who carried a genetic variant of the dopamine β-hydroxylase gene that codes for an enzyme with 10 to 100 fold greater enzyme expression and occurs in about 60% of addicts. Thus, pharmacogenetic matching is critical for the optimal efficacy of disulfiram in cocaine addiction, and this matching includes the majority of these patients."

Disulfiram is not an FDA-approved treatment for cocaine addiction, and in fact, there are currently no approved medications to treat cocaine addiction.

"Cocaine has proven to be a particularly difficult challenge from the perspective of medication development. No doubt this reflects the powerful control that cocaine and cocaine-related cues exert on behavior. However, the current study suggests that pharmacogenetic approaches might be a strategy to match medications like disulfiram to patients who would be more likely to respond," commented Dr. John Krystal, Editor of Biological Psychiatry.

More information: The article is "Pharmacogenetic Randomized Trial for Cocaine Abuse: Disulfiram and Dopamine β-Hydroxylase" by Thomas R. Kosten, Guiying Wu, Wen Huang, Mark J. Harding, Sara C. Hamon, Jaakko Lappalainen, and David A. Nielsen (doi: 10.1016/j.biopsych.2012.07.011). The article appears in *Biological Psychiatry*, Volume 73, Issue 3 (February 1, 2013)

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