Medical News & Perspectives

More Treatments on Deck for Alcohol Use Disorder

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Thirteen years have passed since the US Food and Drug Administration (FDA) last approved a new medication to help the nation's millions of people with alcohol use disorder (AUD) stop or moderate their drinking.

Only 3 such formulations exist, and 1, disulfiram, dates to the Prohibition era. Known commercially as Antabuse and introduced in 1923, it makes people memorably ill if they ingest alcohol, but it doesn't stop the cravings. The other 2, naltrexone and acamprosate, approved in 1994 and 2004, respectively, can alleviate cravings but only in some people.

Attempts are under way to remedy this lack of options. At least 5 promising, if mostly repurposed medications, are at some point in the pipeline as the National Institute on Alcohol Abuse and Alcoholism (NIAAA) steps up efforts to bring more therapeutics to the marketplace. One of those is a familiar name, gabapentin. The 1990s-era anticonvulsant, which has shown some efficacy against alcohol addiction in early studies, was the subject of a just-completed national trial sponsored by the NIAAA. The final results of the trial are still being analyzed and will not be reported for several months, but Raye Z. Litten, PhD, acting director of the NIAAA's Division of Medications Development and principal investigator of the trial, says the agency is "excited."

Nevertheless, the science of alcohol addiction has seen its share of medicines that failed to live up to their early promise during full-scale testing. So Litten said the agency isn't putting all its eggs in one basket. "You need as many weapons as possible to treat a complex disease like alcohol use disorder," he said.

But therein lies a second difficulty. What few medications are out there remain vastly underused. A 2015 NIAAA study found that only 8.7% of US adults who have had AUD in the past have ever sought medical treatment from health care practitioners for the disorder, probably because they are not ready to quit, lack health insurance, or fear being stigmatized. Most only see a physician for the comorbid ailments that result from their addiction.

Meanwhile, of the 8.7% who have sought medical help, even fewer received prescriptions for their condition. Although precise population-wide data do not exist, a 2012 study by the Veterans Health Administration found that less than 4% of all military veterans seeking medical treatment for AUD were actually prescribed an AUD medication.

It is a complicated problem, says John Rotrosen, MD, a psychiatrist and addiction specialist at New York University School of Medicine. "To a large extent primary care physicians don't screen for alcoholism," he said. "When they do, they may note it, but don't really do anything about it."

As far as the failure to prescribe existing medications for AUD, Rotrosen blames a lack of knowledge. "A lot of doctors in primary care haven't been educated in medical school about treatment for alcohol and other addictions. [They] don't think these drugs work, which is untrue. And a lot of them are uncomfortable prescribing for addictive disorders they don't know how to manage." Many primary care physicians also don't see managing addiction as part of their role.

AUD on the Increase

In 2015, the number of Americans 18 years or older with AUD was pegged at 15.1 million, according to the National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Services Administration. But a study led by NIAAA researchers in conjunction with the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions reported that a far larger number, 32.6 million, had AUD in the previous 12 months. Moreover, a staggering 70.4 million—29.1% of the adult population—have had AUD at some point in their lives. Notably, the study also found that the rate of AUD increased substantially over the decade following 2001-2002.

Given these numbers, AUD affects at least as many, if not more, people than depression, a condition that often coincides with it and is estimated to affect some 16.1 million adults. Yet in startling contrast with the armamentarium for alcoholism, there are currently more than 20 medications approved by the FDA to fight depression, and the big pharmaceutical companies are heavily involved in marketing to that population.

Other Potential Treatments for Alcohol Use Disorder

Additional medications the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is pursuing that have shown potential against alcohol use disorder (AUD) include:

Varenicline

The NIAAA and others conducted a 2013 trial on this drug, which under the name Chantix is marketed for smoking cessation. It significantly reduced heavy drinking days and cravings among 200 smokers and nonsmokers.

ABT-436

A 2016 phase 2 trial of this antianxiety medication that works by blocking the V1b receptor of the stress-inducing hormone vasopressin had a statistically significant effect on abstinence, especially in people with high baseline anxiety.

Glucocorticoid Receptor Antagonist

Better known as mifepristone, or RU-486, this abortifacient has also been found to reduce alcohol intake in humans. Like ABT-436, it works on the stress system by regulating the amygdala. A clinical trial assessing the efficacy of mifepristone in treating AUD is currently under way at Brown University.

Citicoline

A well-tolerated, over-the-counter supplement, this medication modulates cholinergic systems. Results of a 12-week placebo-controlled trial to see if citicoline reduces heavy drinking are forthcoming. The drug may mitigate initiation and maintenance of substance abuse by enhancing cognitive function and better decision-making via increased acetylcholine signaling.

Baclofen

An agonist of metabotropic $GABA_B$ (γ-aminobutyric acid) receptors that has been approved by the US Food and Drug Administration for muscle spasticity. It has shown mixed results in small trials but is currently undergoing additional testing and review in the United States and Europe.

"The drug industry has been able to create huge markets for antidepressants, and it's continuing to develop more," noted Rotrosen, "but in general there is little motivation to do the same for addiction."

He attributed this lack of interest to stigma. "The historical view of addicts is that they are street people, poor, and homeless. They are seen as not having insurance or ways to pay for medicine."

Other experts cite alternative reasons for the gap, including the reluctance of many people with AUD to recognize that they have a problem and the difficulty patients with AUD have in adhering to prescribed regimens.

Gabapentin on the Scene

Gabapentin, if it performs to expectations and goes on to receive FDA approval for AUD, would bring some built-in name recognition. Besides its use against epilepsy, the well-tolerated drug has been widely prescribed for shingles, diabetic neuropathy, and restless leg syndrome.

The newly completed study of gabapentin was a 6-month "pivotal" trial involving 348 patients at 10 US sites. Both randomized and double-blinded, it compared the effectiveness of 1200 mg a day of gabapentin enacarbil (the enacarbil is for increased bioavailability) with a placebo. The desired efficacy end point was a favorable percentage of participants who experienced no heavy drinking days during the final 4 weeks of treatment. Such an outcome is 1 of 2 end points the FDA considers crucial when deciding whether the medication is efficacious or not, the other, of course, being total abstinence.

Heavy drinking days are officially defined as more than 4 standard drinks a day for males and more than 3 for females. Anything below this is considered "low-risk" drinking because it is less likely to cause intoxication and associated injuries and health risks, as well as associated chronic medical and mental health conditions. Although this still sounds like an excessive amount of alcohol, Litten says, "The people we recruit for these studies generally average 8 to 12 drinks a day."

The FDA requires 2 successful pivotal studies, each 6 months long, for approval, but if gabapentin passes the just-completed trial, Litten said it is likely that the drug maker, Arbor Pharmaceuticals, of Atlanta, which holds the patent and markets the drug under the name Horizant, will seek a new drug application (NDA).

Helping to pave the way for the current trial was a smaller, 3-month study of gabapentin that was completed with 85 of its original 150 participants several years ago at the Scripps Research Institute in La Jolla, California, under the leadership of Barbara Mason, PhD, director of the Pearson Center for Alcoholism and Addiction Research.

The medication significantly improved the rate of abstinence and no heavy drinking, Mason's team reported. At 1800 mg a day, the abstinence rate observed was 17%, compared with 4.1% for the placebo group, and the no-heavy-drinking rate was 44.7% vs 22.5% for placebo. The drug's number-needed-to-treat (NNT)—the average number of patients one must treat to have a beneficial effect on 1 patient—was 8 for abstinence and 5 for no heavy drinking, putting it in the efficacy range of mainstream antidepressants.

This compares favorably with the efficacy of acamprosate and oral naltrexone based on a 2014 meta-analysis. For promoting abstinence, acamprosate had an NNT of 12 and oral naltrexone, an NNT of 20. For preventing a return to heavy drinking, naltrexone had an NNT of 12, and acamprosate was not associated with improvement.

Although gabapentin showed some effectiveness at reducing cravings and the amount of alcohol consumed, it is particularly helpful against withdrawal symptoms, said Mason.

"Usually people who are cutting down or quitting not only have cravings but get irritable, dysphoric, and anxious, plus they do not sleep well. This prompts many people in early recovery to return to drinking," she said. "Evidence suggests that gabapentin not only has an effect on cravings, but also on sleep and mood. Sleep improves without sedation or daytime drowsiness."

Mason considers drugs like naltrexone that work by blocking reward receptors a "punitive" approach to alcoholism, while gabapentin works "by reversing the activation of stress systems that occur in the brains of folks when the drinking ceases."

Like Mason, Nasir Naqvi, MD, PhD, an assistant professor of psychiatry at Columbia University Medical Center in New York City, has also found gabapentin effective in treating patients experiencing anxiety and insomnia in withdrawal. "It's a fairly benign medication, with relatively few side effects apart

from sedation," he said. "Naltrexone has potential effects on the liver, but gabapentin is not metabolized by the liver. Since many people with AUD also have liver problems, that's important."

However, clinical research has yet to clearly address whether gabapentin reduces the health consequences of drinking or whether there is a risk of gabapentin misuse, which has been raised as a real concern in the treatment of neuropathic pain.

Other Off-Label Pursuits

Two other medications are often prescribed off-label for AUD: Topiramate is an anticonvulsant that has been found to blunt alcohol-induced cravings but has a number of unpleasant adverse effects, including cognitive slowdown, paresthesia, and pruritus. Nalmefene is an opioid antagonist that the FDA has approved for opioid overdose. It has not performed much better than placebo in trials in the United States but did well in 3 multisite trials in Europe, where it has been approved for AUD.

To Litten, who is shooting for a precision-medicine approach, even if some treatments under consideration do not pan out, the process of studying them is shedding light on the various neurological domains of addiction, and how different drugs act on them. "There's lots of targets out there," he said. "We have 35 of them now. The more you learn about mechanisms, you open up even more." Among these targets are the old standbys, involving the mesolimbic dopamine system, but also newer ones, including the stress-related vasopressin system.

Litten says the pharmaceutical industry needs to do for AUD what it has already done for depression. "There are 13 or 14 antidepressants out there [that] are heavily marketed. If one antidepressant doesn't work, you have another. We'd love to see something similar for AUD in the next 10 years." ■

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