

# Tackling Alcoholism With Drugs

**New treatments, some now in clinical trials, reflect a growing awareness that people with different genetic profiles and drinking histories may need different therapies**

Jennifer started drinking more heavily in her early 30s, about the time her marriage started going sour. She split up with her husband and moved with her daughter from California to live with her mother in the Washington, D.C., suburbs. Sometimes while her daughter was at school, Jennifer would polish off a 1.5-liter bottle of wine and then another at night. She blacked out from drinking about once a week, she says, and twice ended up in the emergency room in the throes of alcohol withdrawal. Her life was spinning out of control.

Last year, at age 36, she found herself in a hospital at the National Institutes of Health in Bethesda, Maryland, where she had volunteered for a study on a potential drug treatment for alcoholism. She got a physical exam, filled out a series of questionnaires, and endured a test in which a researcher gave her a small glass of vodka and asked her to hold and sniff it—no drinking

allowed. “My hands got sweaty, and I started to salivate,” she says. “I imagined myself being on the deck on a warm day having cocktails with friends.”

For the next 4 weeks, Jennifer would stay in the hospital, taking a pill once a day—either a placebo or a drug that dampens stress responses in the brain. The study, led by Markus Heilig, director of clinical research at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), was designed to test a drug Heilig hopes will help people he describes as “anxious alcoholics.” Instead of drinking for the rewarding buzz, anxious alcoholics drink for relief—from either the mental stress of life events or the physiological stress caused by abstaining from alcohol when the body has come to depend on it, Heilig says.

His study is one of several recent efforts that are raising hopes of new and improved treatments for alcoholism that work by restoring balance to various biochemical pathways in the

brain that are thrown off kilter by extended heavy drinking. Much of the work also reflects a growing realization that there may be different types of alcoholism and that people with different genetic profiles and drinking histories may respond better to different types of drugs.

“It’s a fascinating time in our field,” says Selena Bartlett, who directs the Preclinical Development Group at the Ernest Gallo Clinic and Research Center at the University of California, San Francisco. “It feels like we’re heading for a sea change for new therapies for alcoholism.”

## Why drugs?

Alcohol dependence afflicts 4% of the adult population and is the third leading cause of preventable death in the United States, according to NIAAA. Yet only 10% to 15% of those affected get treatment, mostly in group counseling or support sessions, says Mark Willenbring, NIAAA’s director of treatment and recovery research. There’s a lingering perception in the general public and among some primary care physicians that alcoholism is a problem best remedied with willpower, not medicine. Willenbring disagrees. “That’s like saying ‘Why do we treat diabetes with insulin? Why don’t we just have people ... learn to eat right and exercise?’” Behavioral interventions help many people, Willenbring and other clinicians say, but they often work better when combined with drugs that help loosen the grip of addiction.

Three drugs are currently approved for treating alcoholism in the United States. The oldest, disulfiram (better known as Antabuse), has fallen out of favor with many doctors. It makes people violently ill if they drink, providing a powerful disincentive but one that can easily be skirted by anyone with enough foresight to stop taking it before a binge.

Naltrexone, approved in 1994, is more widely used. The ultimate buzz killer, it blocks opioid receptors in the brain to prevent the euphoric effects of alcohol.

The third drug, acamprosate, approved in 2004, blocks receptors for the neurotransmitter glutamate and is thought to quell hyperactive glutamate signaling caused by alcohol dependence. Acamprosate has shown modest benefits in Europe, where clinicians have used it to treat alcoholism





## Antialcoholism Drugs

DRUG (TRADE NAME)	MANUFACTURER	MECHANISM	NOTES
Disulfiram (Antabuse)*	PLIVA	Interferes with alcohol metabolism	Makes patients violently ill when alcohol is consumed.
Naltrexone (Depade, ReVia, Vivitrol)*	Several companies	Blocks opioid receptors	Curtails euphoria; monthly injection approved in U.S. in 2006.
Acamprosate (Campral)*	Merck Santé	Inhibits glutamate signaling	Thought to reduce withdrawal symptoms; efficacy differs in European and U.S. trials.
Topiramate (Topamax)	Ortho-McNeil Neurologics	Inhibits glutamate signaling, enhances GABA signaling	Approved for epilepsy and migraine; encouraging results in two trials for alcoholism.
Ondansetron (Zofran)	GlaxoSmithKline	Blocks 5HT <sub>3</sub> serotonin receptors	Approved for treating nausea; reduced drinking in early-onset alcoholics in two studies.
Baclofen (Baclofen)	Several companies	Stimulates GABAB receptors	Approved for treating spasticity; reduced drinking in several small trials for alcoholism.
Varenicline (Chantix)	Pfizer	Weakly activates nicotinic acetylcholine receptors	Approved for smoking cessation; human tests for alcoholism now beginning.
LY686017	Eli Lilly and Co.	Blocks NK1 receptors for substance P	Reduced stress and alcohol craving in preliminary test with hospitalized alcoholics.

\* Approved in U.S. for treating alcoholism.

for nearly 20 years, but it did no better than a placebo in a large U.S. trial published in 2006 in the *Journal of the American Medical Association (JAMA)*. It's a mixed bag, says Stephanie O'Malley, an alcoholism researcher at Yale University. "We have effective treatments, but they don't help everyone," she says. "There's lots of room for improvement."

In the case of naltrexone, genetics may offer a clue to why some alcoholics respond better than others, says Charles O'Brien, a clinician and psychopharmacologist at the University of Pennsylvania who pioneered the drug's use for treating alcoholism. O'Brien's team reported in 2003 that alcoholics with a particular variant of the  $\mu$ -opioid receptor gene respond better to naltrexone treatment. An independent study, reported in the February *Archives of General Psychiatry*, confirmed this finding in a larger sample of 911 alcoholics. In that study, 87% of patients with the variant either abstained from alcohol or tipped only moderately during the 16-week study period. Among patients without the variant, only 55% had a similar outcome, regardless of whether they got naltrexone or a placebo.

"This is a milestone in pharmacogenetics," says Rainer Spanagel, a psychopharmacologist at the Central Institute of Mental Health in Mannheim, Germany. For all the talk about using patients' genetics to select the best drugs, there are only a handful of success stories so far in all of medicine, Spanagel says. Some researchers offer more tempered enthusiasm, however, pointing out that one smaller study failed to find a connection between the opioid receptor gene variant and response to naltrexone.

### Meet the candidates

Other drugs that are generating a buzz among alcoholism researchers take aim at a wide variety of molecular targets (see table). One of the more promising contenders is topiramate, an anticonvulsant currently approved for treating epilepsy and migraines. In two double-blind randomized controlled trials, one published in 2003 in *The Lancet* and a larger follow-up published last October in *JAMA*, researchers led by psychiatrist and psychopharmacologist Bankole Johnson of the University of Virginia, Charlottesville, reported that alcoholics who took topiramate daily had fewer heavy drinking days and more abstinent ones. In the *JAMA* study, the trend toward sobriety seemed to be growing even stronger at the end of the 14-week trial in the topiramate group—a very encouraging sign, says NIAAA's Willenbring. "The level of effectiveness seemed to be at least as good as naltrexone and maybe better."

Topiramate alters the activity of glutamate, GABA, and other neurotransmitters, but exactly how it dampens the desire to drink isn't known. Animal studies have suggested that the drug reduces the release of dopamine from neurons in the brain's reward circuitry, and Johnson hypothesizes that it may work by inhibiting the rewarding surge of dopamine an alcoholic gets from knocking back a drink.

Another drug suspected to dampen hyperactive reward mechanisms is just entering its

first tests in human subjects. In a 2007 paper in the *Proceedings of the National Academy of Sciences*, Bartlett and her Gallo Center colleagues reported that a drug called varenicline substantially reduces drinking in alcohol-dependent rats. Varenicline, which is sold as a smoking-cessation aid, weakly stimulates receptors for the neurotransmitter acetylcholine but at the same time keeps them from getting overexcited by an influx of nicotine or, perhaps, alcohol. As with topiramate, the mechanism is murky, but Bartlett and others speculate that varenicline's moderating influence on acetylcholine receptors may exert an overall calming influence on the brain's

reward circuitry, preventing huge highs without revoking the ability to feel pleasure. "It may stabilize those systems in a way that makes the patients happy enough to stay on the drugs," says Heilig, who suspects that the pleasure-blocking effects of naltrexone may explain why many patients who take it don't stick with their drug regimen. Heilig is collaborating with Bartlett on

human studies with varenicline that are about to begin at NIAAA. O'Malley's group has already started similar work at Yale.

### Stress effects

At the same time, Heilig suspects that the rewarding aspects of drinking are only part of the story. Epidemiological and clinical studies have identified two basic types of alcoholics, he says. So-called reward drinkers are the ones

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—SELENA BARTLETT,  
UNIVERSITY OF  
CALIFORNIA,  
SAN FRANCISCO

who get a big rush from drinking. “If you think back to high school, ... in every class there’s two guys who when they got alcohol, they got wild and got up on the table and started doing crazy things,” Heilig says. They are the ones who tend to have a family history of alcoholism and get into trouble with alcohol in their teens or early 20s. They’re also the ones who respond best to naltrexone, Heilig says. The second type, the anxious alcoholics, often start out as moderate drinkers and get into trouble in their 30s or 40s. They drink mainly to relieve anxiety and stress, and they tend to respond poorly to naltrexone, Heilig says.

More than a decade of rodent studies, many of them conducted in the laboratory of George Koob, a neurobiologist at The Scripps Research Institute in San Diego, California, have provided the rationale for treating anxious alcoholics with drugs that target stress mechanisms. (Heilig was a postdoctoral fellow with Koob before moving to NIAAA.) Koob and others have found hyperactive stress signaling in the brains of alcohol-dependent rodents, including increased sensitivity to corticotropin-releasing factor (CRF), a hormone that kicks off a cascade of stress responses. Drugs that block CRF curtail excessive drinking in alcohol-dependent rodents and reduce the likelihood that a stressful event—such as an electric shock—will cause a recovering rodent alcoholic to relapse, researchers have found.

Human studies have also hinted at a link between stress mechanisms and alcoholism. In 2006, German researchers reported in *Molecular Psychiatry* that binge drinking is more common in people with certain variations of the gene that encodes the receptor for CRF. Adolescents who possess a particular one of these gene variants are more likely to engage in heavy drinking after a stressful life event, the same research team reported in *Biological Psychiatry* in January.

Based on the growing body of animal and human research, Koob, Heilig, and like-minded researchers suspect that drugs that block the CRF receptor would be extremely promising for treating alcoholism. Unfortunately, no such drugs are currently approved for human use. “Drugs are in development, ... but that’s still several years away,” Heilig says.

In the meantime, Heilig’s recent study with anxious alcoholics investigated a drug that

blocks a different stress pathway. It blocks a receptor for substance P, a neurotransmitter involved in signaling pain and stress. (The drug, dubbed LY686017 by its creator, Eli Lilly and Co., had proved safe in clinical trials for depression but not effective enough to merit further development, Heilig says.) Heilig and co-workers recruited 50 recovering alcoholics, including Jennifer, all of whom scored high on questionnaires that measure anxiety.

During the monthlong study, the researchers took blood samples to monitor stress-hormone levels in the volunteers and queried them about their alcohol cravings. Near the end of the study, they subjected them to a mock interview intended to evoke the type



**Downward spiral.** In the 1962 movie *Days of Wine and Roses*, Lee Remick plays an alcoholic who gradually became addicted. New therapies may offer better results in such cases.

of social stress that can drive a recovering alcoholic back to the bottle. Volunteers were told to imagine that they were applying for their dream job and had 5 minutes to convince the hiring committee—three stone-faced research assistants in white coats—that they were the right person for the job. Then they were asked to perform a daunting test of mental arithmetic. This ordeal caused a smaller outpouring of stress hormones and evoked milder cravings for alcohol in the patients who’d been on a daily dose of LY686017, Heilig and colleagues reported online 14 February in *Science*.

The researchers also conducted a brain-scanning experiment with the volunteers. Recent research in press at the *Journal of Studies on Alcohol and Drugs* suggests that

alcoholics exhibit exaggerated responses in certain brain regions when they look at unpleasant images (such as photos of car crashes) and exhibit diminished responses to positive images (photos of children or animals, for example). This was also true of the subjects who received the placebo in Heilig’s experiment, but the ones who received the drug showed the opposite effect. Taken as a whole, the study provides preliminary evidence that LY686017 suppresses the stress and negative emotions that drive anxious alcoholics to drink, Heilig says.

When the study was over, Jennifer was told that she’d been among those who received the drug. She says she’d noticed a difference in her reaction when she took the vodka-sniffing test again at the end of the study. “This time, I wasn’t romanticizing it ... [and] picturing good times,” she says. “It didn’t make me want to go find some ice cubes and cranberry juice like the first time did.”

Other researchers agree that the work looks promising but caution that LY686017 has not yet been shown to reduce drinking in anybody with a drinking problem—all of the subjects were hospitalized and on enforced abstinence. “It reportedly reduced alcohol craving, which may be very important, but you’ve just got to test it in an outpatient clinical trial to see whether it actually reduces drinking,” says O’Brien. That’s the next step, Heilig says: “Two companies are taking this to full-scale clinical trials. After that, we’ll have some answers.”

Even if those trials go well, questions will still remain—as they do for all of the drugs in development—about how long patients would need to be medicated. There are simply not enough data at this point to know whether a recovering alcoholic would have to take medication indefinitely or whether a shorter drug regimen would lead to the desired outcome. Even the desired outcome is somewhat controversial. Although some studies have found that a small minority of former alcoholics are able to drink moderately without relapsing, many experts argue that abstinence is always the safest bet.

Despite such uncertainties, veteran alcoholism researchers are convinced that there are brighter days ahead. Willenbring predicts that in the next 5 to 10 years the field will have its “Prozac moment”: “I think we’re going to have a medication that’s perceived as effective, that’s well-marketed by a pharmaceutical company, and that people receive in a primary-care setting or general-psychiatry setting.” If so, the abysmally low proportion of people who get effective treatment for alcoholism may finally begin to rise.

—GREG MILLER