New research is identifying the molecular reasons why alcohol and drug habits are so difficult to break, which could point the way to new medicines to help addicts go cold turkey.

Scientists have known for years how heavy use of alcohol and drugs works on reward centers in the brain to drive dependence. The new research, including a study published in November in JAMA Internal Medicine and early-stage drug testing at the National Institute on Alcohol Abuse and Alcoholism, is revealing another, darker side to how such substances impact the brain. By transforming its chemical architecture, drinking and drug use trigger feelings of anxiety and tension that can only be eased by more consumption.

"There's been a huge amount of progress understanding what drives alcoholism and makes it difficult to stop," says Barbara Mason, co-director of the Pearson Center for Alcoholism and Addiction Research at the Scripps Research Institute in La Jolla, Calif.

While this dark side has been documented in laboratory animals and in some human testing, its validity in people was significantly bolstered by the recent JAMA-published study, led by Dr. Mason, indicating that a drug that targets dependency's stressful effects helped quitters. Its findings: About 45% of the 150 alcoholics who took the highest dose of the drug, known generically as gabapentin, either stopped drinking altogether or did so only occasionally.

In 2011, more than 21 million Americans needed treatment for a problem related to alcohol or drugs, according to the federal government's most recent National Survey on Drug Use and Health. Many try to quit, but studies show 60% or more of alcoholics and drug addicts relapse within a year of trying to kick their habit, addiction specialists say.

Support groups like Alcoholics Anonymous and Narcotics Anonymous only work in a fraction of alcoholics and addicts, according to Michael Fingerhood, who heads Johns Hopkins University School of Medicine's division of chemical dependency. The few pharmaceuticals taking aim at alcoholism often don't work or are dropped by addicts before they achieve recovery. And while chemical-replacement therapies like methadone have proved effective at reducing pleasure and blocking cravings for certain opiates, there is no known effective prescription medicine available for treating cocaine addiction, he says.

Until now, most research has focused on the pleasure provided by drinking or drug use, studying how neurotransmitters like dopamine help give rise to rewarding feelings—a buzz or high—that encourage further consumption. But heavy substance abuse can compromise this reward system, researchers say, requiring the production of ever-increasing amounts of dopamine to realize the same high. Addiction can follow.

More recent research is showing that the brain's stress response also contributes to dependence. Years of heavy drinking or drug use remolds the circuitry in and around a part of the brain known as the
amygdala where these feelings of anxiety are triggered, says George Koob, who pioneered study of this dark side of addiction. The brain's stress system is sent into overdrive.

The result: constant feelings of tension that alcohol or drugs temporarily lighten, but which worsen over the longer term. "You're kind of digging a hole every time you fix the hole," says Dr. Koob, a Scripps scientist who is the incoming director of the National Institute on Alcohol Abuse and Alcoholism.

One chemical found to play a role in the brain's stress response is known by the initials CRF (corticotropin-releasing factor). It springs into action when there is a bang in the night or a tight deadline approaching. It is also triggered by alcohol or drug use because it helps the brain return to a normal state after the heightened sensation of pleasure. But years of heavy drinking or drug taking makes the brain more sensitive to CRF.

In effect, the brain remembers that the substances relieve stress, says Paul Kenny, who studies the molecular underpinnings of addiction at the Icahn School of Medicine at Mount Sinai. The brain's stress response gets stuck in high gear.

CRF is sometimes referred to as a "misery neurotransmitter" because it is thought to cause the anxiousness felt by addicts until they receive temporary relief by drinking again or taking drugs. The chemical is also thought to be a driver behind the difficulties that alcoholics or addicts have trying to quit, especially during stressful episodes that add to the feelings of tension.

The NIAAA, a part of the National Institutes of Health, is conducting early-stage testing in alcoholics of two experimental drugs that aim to stop CRF from revving up the brain's stress centers, says Markus Heilig, the agency's clinical director. NIAAA is also testing in alcoholics and heroin addicts a third drug that stymies another neurotransmitter involved in stress response, called neurokinin 1.

Kathy Selman says she failed several times to wean herself from alcohol because struggles to stay afloat amid the recent economic downturn propelled her to drink again.

Ms. Selman, a 57-year-old sales and marketing professional from San Diego, says she slipped into alcoholism around 2007, after her husband lost his job and the couple lost three parents, their savings and then their rental properties and home.

Afraid her two sons would only know her as an alcoholic, she enrolled in the Pearson Center's trial testing gabapentin in 2011. The drug, which is also sold under the brand name Neurontin, is approved for the treatment of epileptic seizures. It also calms the brain's stress system, addiction researchers say.

Ms. Selman doesn't know for certain whether she received gabapentin or a placebo as part of the study. She believes she got the medicine because her mood lightened during the 12 weeks she was taking the capsules and she felt depressed for a period afterward. And quickly, she quit drinking entirely, Ms. Selman says.

She says she remains sober, but admits that as she tries to launch new ventures in business networking and addiction coaching, the daily stresses can be trying. As part of the study, Ms. Selman also received
counseling, and through it, she says she learned how stress triggered her desire to drink and ways to
cope with the related wave of anxiety. One of her strategies: She carries index cards that remind her
how she felt while drinking and how she feels since going sober.

Nora Volkow, director of the National Institute on Drug Abuse, says successfully treating addiction will
probably require a combination of behavioral and cognitive counseling with the prescription of multiple
medicines tailored to the phase of recovery and targeting both the light and dark sides of dependence.

"These two systems interact very, very clearly with one another," Dr. Volkow says.