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https://www.wsj.com/articles/synthetic-alcohol-no-hangover-511fc418

Enjoy Alcohol, Without the Hangover

Scientists are finding ways to help people sober up faster and feel fewer bad effects

July 28, 2023 10:55 am ET

What if you could indulge in your favorite cocktails with no hangover or other ill effects?

That's one of the goals for researchers working to make one of the world's oldest vices less harmful. Some are developing hormone shots to help people sober up quickly. Others are working on alcohol substitutes that target receptors in the brain that affect happiness, while dodging those that make imbibers slur and weave.

"Alcohol is like playing the piano with boxing gloves on. You hit too many keys," says David Orren, managing director of GABA Labs.

The London-based company is developing a synthetic alcohol that it says will bring pleasurable effects without hangovers, health problems or slurred speech. Its basis is gamma-aminobutyric acid, an amino acid that targets receptors in the front of the brain that trigger the relaxation and sociability alcohol brings, while avoiding the chaos it wreaks on the body.

Dr. David Nutt, the chief scientific officer of GABA Labs, says his interest in alcohol and GABA receptors first began nearly 40 years ago when his research led him to discover the interaction between the two. A psychiatrist and neuropsychopharmacologist, he spent two years as chief of section of clinical science in the National Institute of Alcohol Abuse and Alcoholism at the National Institutes of Health and has long argued in scientific papers that alcohol causes more harm to society than other drugs.

GABA receptors are the first contact for alcohol in the brain, opening up and relaxing people, Nutt says. But alcohol then also floods the brain with other neurotransmitters that can cause nasty aftereffects.

Creating a substance that targets only the GABA receptors allows the brain to then turn on dopamine and serotonin naturally as the pleasures of the evening take off, he says. "It feels like what a glass of wine feels like. It feels relaxing. It makes you a bit more chatty, a bit more socially engaged with people," he says of the product GABA Labs is developing, dubbed Alcarelle.



Dr. David Nutt, the chief scientific officer of GABA Labs, is working to develop a synthetic alcohol. PHOTO: CJMORLEY

The company is working to raise about £8 million (around \$10.3 million), with an aim to complete food-safety testing in the U.S. by mid-2026, where it will launch ahead of European and U.K. markets. "Only inventors are allowed to use it at this stage," Nutt says.

Along the way, Orren and Nutt say, there was a lot of self-testing, with many earlier iterations in which they felt nothing. Both remember the day they had a glass of their latest iteration of Alcarelle and knew they'd finally gotten it right. "It feels like a warm glow," Orren says. "You're being you. And you're being with somebody that's being them. You're being real."

The company says it has a U.S. partner in place to help find volunteers to test the product, a project manager and has identified a number of laboratories to help produce Alcarelle once the funding is in place.

As part of the testing, the company will weigh the effects of mixing Alcarelle with real alcohol or using it at excessive amounts, Nutt says.

The synthetic alcohol is a tasteless ingredient formulated to be added to versions of nonalcoholic drinks from beer to wine and spirits, the inventors say. It could be added to drinks produced without alcohol or those where alcohol has been removed.

Some consumers, concerned about health effects, have moved to consume less

alcohol in recent years. The isolation of the pandemic contributed to a spike in drinking in 2020, research has shown, but alcohol consumption has since retreated, particularly among younger people. Sales of no- and low-alcohol beverages rose in 2022, according to industry tracker IWSR.

In addition to its addictive properties, alcohol can cause various harmful effects beyond hangover headaches and loss of motor control. With an enzyme called alcohol dehydrogenase, the liver breaks down ethanol into a toxic compound called acetaldehyde, a carcinogen. The National Institutes of Health says the substance contributes to more than 200 health conditions.

Alcohol can contribute to health problems for anyone, not just people with alcohol-use disorder, says Dr. Joseph Volpicelli, medical director and founder of the Volpicelli Center for Addiction Treatment in Pennsylvania. "Alcohol use is on a spectrum. It's not a dichotomous condition."

Some researchers are working on ways to help people cut back on the amount of alcohol they drink.

Amygdala Neurosciences in San Francisco is developing an oral drug that aims to inhibit alcohol cravings by targeting dopamine pathways that are triggered when people encounter places and people they associate with drinking. Their drug, a small organic molecule, blocks an enzyme that is critical in dopamine pathways. That results in in dopamine becoming a completely different molecule that reduces the production of dopamine, with its pleasurable effects, during a craving. Fewer cravings can help lower drinking to healthier levels, the company says.

"People who can't control drinking don't always want to stop drinking completely," says Dr. Mack Mitchell, senior medical advisor for Amygdala. "They just want to be able to drink normally."





Some companies are working on drugs that will lower cravings for alcohol during a big night out. PHOTO: ISTOCK

Pharmaceutical company Indivior has completed a clinical trial for a nasal spray people could take before a big night out on the town to make them want to drink less than usual. "I arrive in the parking lot. I don't want six or seven drinks. I'll top up with a nasal spray," says Chief Executive Officer Mark Crossley, laying out a use case for the product.

The drug, naltrexone, works on opioid receptors in the brain's reward system and blocks the pleasant effects of alcohol. Indivior wants to make a short-acting version of naltrexone that works within five minutes, says Christian Heidbreder, the company's chief scientific officer.

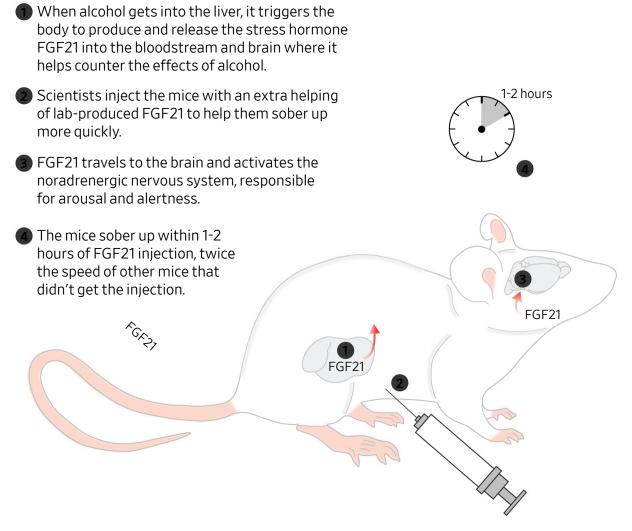
What about when someone drinks too much? Researchers from UT Southwestern Medical Center in Dallas and Howard Hughes Medical Institute at Rockefeller University in March demonstrated that inebriated mice injected with a stress hormone sobered up within one to two hours—more than twice as quickly as inebriated mice without the shot.

They tested it on inebriated mice that had passed out on their backs. The first time the mice came out of their booze-induced slumber after being injected with the hormone, researchers were shocked. A research assistant at the Dallas laboratory leaped up and declared it a miracle.

"This is one of those experiments that you never think will work," says Steven Kliewer, a biologist at UT Southwestern Medical Center and a co-author on the study published in the journal Cell Metabolism. "It was a career-defining moment."

Clearheaded

In an experiment on counteracting the effects of alcohol, inebriated mice injected with a stress hormone sobered up more quickly.



Source: Mihwa Choi et al, 2023, "FGF21 counteracts alcohol intoxication by activating the noradrenergic nervous system" Elizaveta Galkina/THE WALL STREET JOURNAL

The hormone, FGF21, is produced in the liver in response to alcohol. Previous studies showed that it leads mice to drink less alcohol, drink more water and also protects against alcohol-induced injury to the liver. The hormone activates noradrenaline, a neurotransmitter essential to arousal, attention, cognitive function and stress.

Mice injected with the hormone were also able to walk on a rotating rod—a rodent equivalent of walking a straight line. It's unclear if the mice had hangovers.

The idea isn't for bartenders to have a tool to sober up drunk patrons. Instead, the researchers say they envision selling the treatment as a tool to reverse alcohol poisoning or sober up people in emergency rooms. "It would be more harmful than good behind a bar," Kliewer says.

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