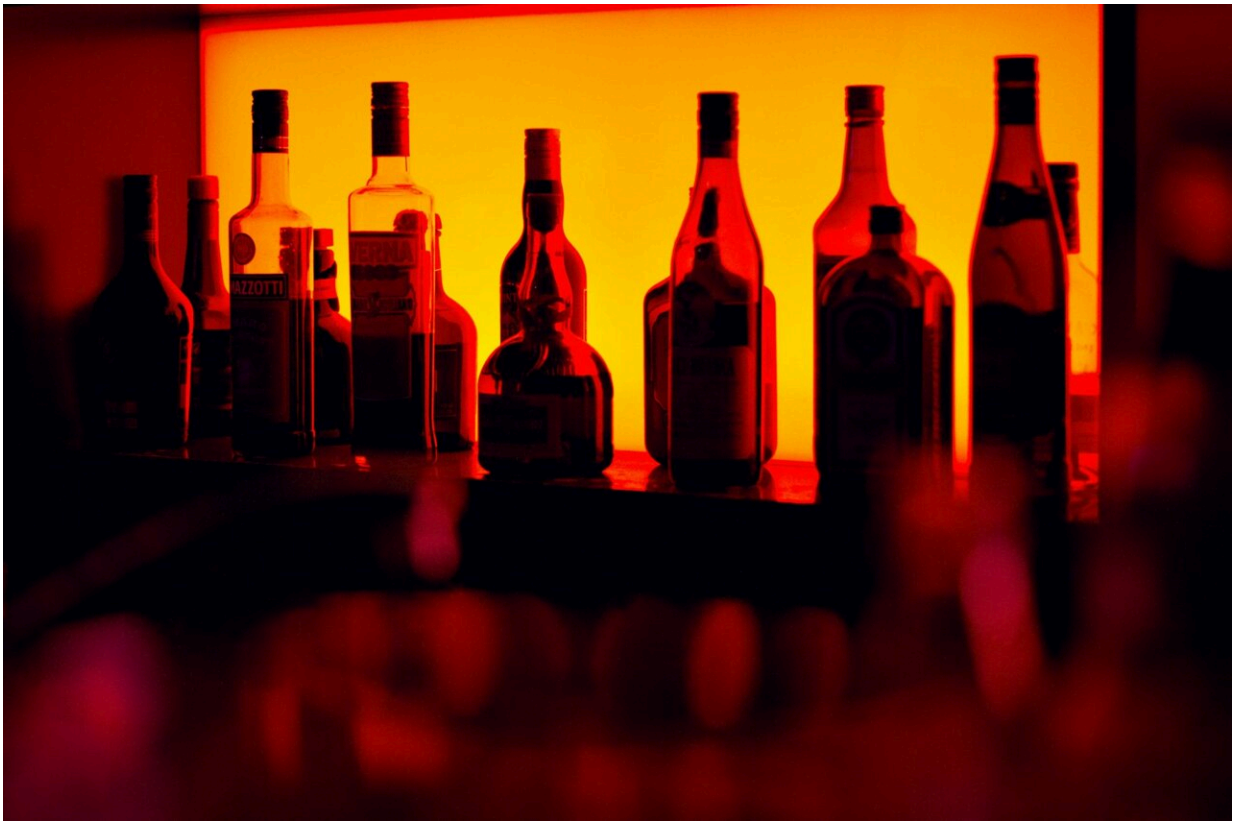


Can pharmacotherapies prevent alcohol use disorder in people with PTSD?

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Survivors of abuse and trauma are vastly more likely than other people to develop alcohol use disorder (AUD); according to some estimates, as many as three-quarters of people with post-traumatic stress disorder

(PTSD) report drinking problems.

Now, Scripps Research scientists have identified a class of drugs that might break this link. In animal models of PTSD, the drug decreased [alcohol](#) preference and intake as well as other behaviors associated with PTSD, including aggression, excessive fear and hyperarousal. The findings were published in *Neuropsychopharmacology* on November 18, 2022.

"The overlap of PTSD and AUD is a major problem," says co-senior author Marisa Roberto, Ph.D., the Schimmel Family Chair of Molecular Medicine and a professor of Neuroscience at Scripps Research. "We've shown that there is potential to alleviate both disorders by targeting brain pathways that they share."

According to the U.S. Department of Veterans Affairs National Center for PTSD, about 12 million adults in the U.S. have PTSD during a given year. Men and women who have PTSD at any point in their lives are more than twice as likely as other people to have [alcohol abuse](#) or dependence. Moreover, people who suffer from both PTSD and AUD are at a higher risk of suicidal thoughts and extreme aggression compared to those with either disorder alone.

Researchers have known that FKBP5, a protein found in the brain, plays a role in both disorders. The FKBP5 gene is responsible for lifting the brakes on the brain's stress response pathways, and its genetic variants are associated with increased risk of AUD and PTSD. In animals, higher levels of FKBP5 have been linked to both stress exposure and alcohol exposure.

In the new study, co-first authors Bryan Cruz, Ph.D., and Valentina Vozella, Ph.D., and additional colleagues studied rats with symptoms similar to comorbid human PTSD and AUD. Like people with the

disorders, the animals drink more alcohol than average, are irritable and fearful, and exhibit anxiety and sleep disturbances, the team showed. The researchers treated the animals with either of two drugs known to target FKBP5: benztropine (Cogentin), which is FDA-approved to treat Parkinson's disease and targets a number of molecules in the brain, or SAFit2, an experimental compound designed specifically for blocking FKBP5.

They found that benztropine reduced alcohol preference in stressed male and female animals, as well as aggressive behavior in the females. SAFit2 reduced alcohol drinking in stressed males, and decreased levels of extreme fear in both male and females. Neither drug impacted sleep.

"The results may have varied between male and female animals because of reproductive hormones," says Cruz. "There is new literature suggesting that the activity of these kinds of compounds varies in females throughout the estrous cycle."

The team says that the fact that benztropine is already FDA-approved suggests the potential for repurposing it in people with PTSD.

"We think FKBP5 inhibitors might be useful in preventing AUD after the onset of PTSD," adds co-senior author Eric Zorrilla, Ph.D., associate professor in the Department of Molecular Medicine. "More work is needed to determine whether these compounds also can prevent the recurrent relapse that hampers recovery."

More information: Bryan Cruz et al, FKBP5 inhibitors modulate alcohol drinking and trauma-related behaviors in a model of comorbid post-traumatic stress and alcohol use disorder, *Neuropsychopharmacology* (2022). [DOI: 10.1038/s41386-022-01497-w](https://doi.org/10.1038/s41386-022-01497-w)

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