

# Single Shot of Ketamine May Herald 'Last Call' for Problem Drinking

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An experimental treatment that includes a single infusion of [ketamine](#) may lead to long-term improvement in problem drinking, new research suggests.

In an study of 90 heavy drinkers, those who received a single dose of intravenous (IV) ketamine plus cognitive behavioral therapy (CBT) that focused on reactivating drinking-related "maladaptive reward memories" (MRMs) significantly curbed the urge to drink and reduced alcohol intake compared with those who received the ketamine alone or a placebo infusion.

In addition, the combination group reduced their average weekly alcohol consumption by 50% over 9 months of follow-up.

MRMs can cause the brain's reward-learning system to produce an exaggerated desire to take a drug. However, the ketamine plus CBT intervention worked to "reboot" the brain, in order to relearn healthy associations. "This is a first demonstration of a very simple approach," lead investigator Ravi Das, PhD, associate professor, University College London (UCL) Clinical Psychopharmacology Unit, United Kingdom, told *Medscape Medical News*.

"We hope that with more research into optimizing the method, this could turn into a helpful treatment for excessive drinking, or potentially for other drug addictions," Ravi added in a statement.

The findings were [published online](#) November 26 in *Nature Communications*.

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## Hijacking the Brain

MRMs are "central to drug and [alcohol addiction](#)," the investigators note.

Drug abuse "hijacks the brain's in-built reward-learning system so that you end up associating environmental 'triggers' with the drug," Das said.

"Unfortunately, once these reward memories are established, it's very difficult to re-learn more healthy associations, but it's vital in order to prevent relapse," he added. "We were interested in the processes underlying why people react and the main thing seems to be these learned responses to their environment."

"It's a bit like Pavlov's dog," a famous research subject who learned to associate the reward of food with the ringing of a bell, which induced salivation, he said.

"Humans have the same kind of automatic learning process. So we were looking at ways to break those associations, and one of the most promising methods is this process of memory reconsolidation," Das added.

In addition, because destabilized memories rely on an N-methyl D-aspartate receptor (NMDAR) mediated protein cascade to re-stabilize themselves, adjunctive ketamine, an NMDAR antagonist, was added to the protocol.

"The main reason we were interested in using ketamine is because we knew it blocks this receptor. And we thought we could use it as a tool to weaken alcohol memories," Das said.

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## Heavy Drinkers

Ninety individuals (61% men; mean age, 27.5 years) with harmful drinking behavior, but without a formal diagnosis of [alcohol use](#) disorder, were enrolled in the study. All had a score greater than 8 on the Alcohol Use Disorders Identification Test.

Participants consumed an average of 74 units of alcohol (8 g) per week, five times the recommended limit. Participants preferred beer, and so 74 units was the equivalent of 30 pints of beer per week.

In the study, all were given a glass of beer, told they could not drink it until they finished a task, and were then asked to rate the intensity of their urge to drink.

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Baseline drinking urges were determined on Day 1 when the participants were permitted to drink the beer. On Day 3, the beer was unexpectedly taken away in order to destabilize a retrieved reward memory.

"Typically the brain would then undergo an active process to re-stabilize and store the memory. However, ketamine prevents this memory re-storage process by blocking a receptor in the brain needed to re-stabilize memories," the researchers noted in the release.

Immediately after the beer was removed, one third of study participants received an IV infusion of ketamine hydrochloride, while another third received a saline placebo infusion. The remaining third received the ketamine infusion but without going through the memory retrieval procedure. All participants underwent blood draws before, and after, the infusions.

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## Long-Term Improvement

Results at the 10-day follow-up showed that compared with the other two groups, the ketamine plus memory retrieval group had significant reductions in "urge to drink" ratings ( $P \leq .007$ ).

They also showed pre-drink reductions in their anticipated enjoyment of beer ( $P < .001$ ) and in actual enjoyment after drinking the beer ( $P = .004$ ). They also experienced a reduction in weekly alcohol consumption ( $P < .001$ ), and had a significant reduction in binges, defined as more than 6 drinks per weeks ( $P < .001$ ).

All three groups decreased their drinking behavior over the 9-month follow-up period. However, the ketamine plus memory retrieval group had greater initial improvement than the other groups, and a greater overall improvement over time.

Both ketamine groups significantly reduced their drinking volume at the 9-month assessment, but only the combination group lowered their total number of drinking days and bingeing behavior.

Finally, blood levels of ketamine predicted beneficial changes in drinking behaviors — but only after MRM reactivation.

Overall, "we found that heavy drinkers experienced a long-term improvement after a very quick and simple experimental treatment," Das said.

"An advantage of our study, alongside the pronounced, long-term effect on drinking, is that it's based on a strong understanding of how the drug is working in the brain to achieve its effect," senior author Sunjeev Kamboj, also from the UCL Clinical Psychopharmacology Unit, said in the release.

Das admitted that he was somewhat surprised that the process worked.

"I've been doing research in this field for about 10 years and you get used to expecting not much because getting people to change their behavior around drug use is very difficult," he said.

So seeing their findings was a pleasant surprise, Das noted. However, he cautioned that this is still an experimental procedure and more research is needed before any recommendations can be made.

In addition to looking into whether they can replicate the findings in a large clinical trial, the investigators hope to assess whether other, more noninvasive drugs may be helpful and whether the treatment regimen is effective in conditions such as [posttraumatic stress disorder](#).

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## "Promising Hypothesis"

Commenting on the study for *Medscape Medical News*, George Koob, PhD, director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), said the findings "open a promising hypothesis" that should be tested further.



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"There are multiple aspects of treatment for alcohol use disorder, one of which is behavioral treatments," Koob said. If the results of this bear out in other studies, this particular intervention "could be a great add-on to the armamentarium," he said.

"Similarly, we're always looking for medications that will help. And both of those are woven into the fabric of this paper," Koob said.

However, he added that ketamine can be a major drug of abuse.

"Ketamine itself may not be the 'drug of drugs,' but the target that they are hypothesizing, working through the glutamatergic system, may indeed be a very good target," Koob said.

He noted that the behavioral part of the investigators' process has demonstrated efficacy in animal studies.

"So this is a very nice confirmation that you can trigger craving and, by manipulating that craving, decrease drinking in humans," he said.

Koob added that the combination of a behavioral therapy, of which there could be others, plus a drug "could be potentially powerful."

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