Ibogaine inspires new compounds to treat addiction, depression

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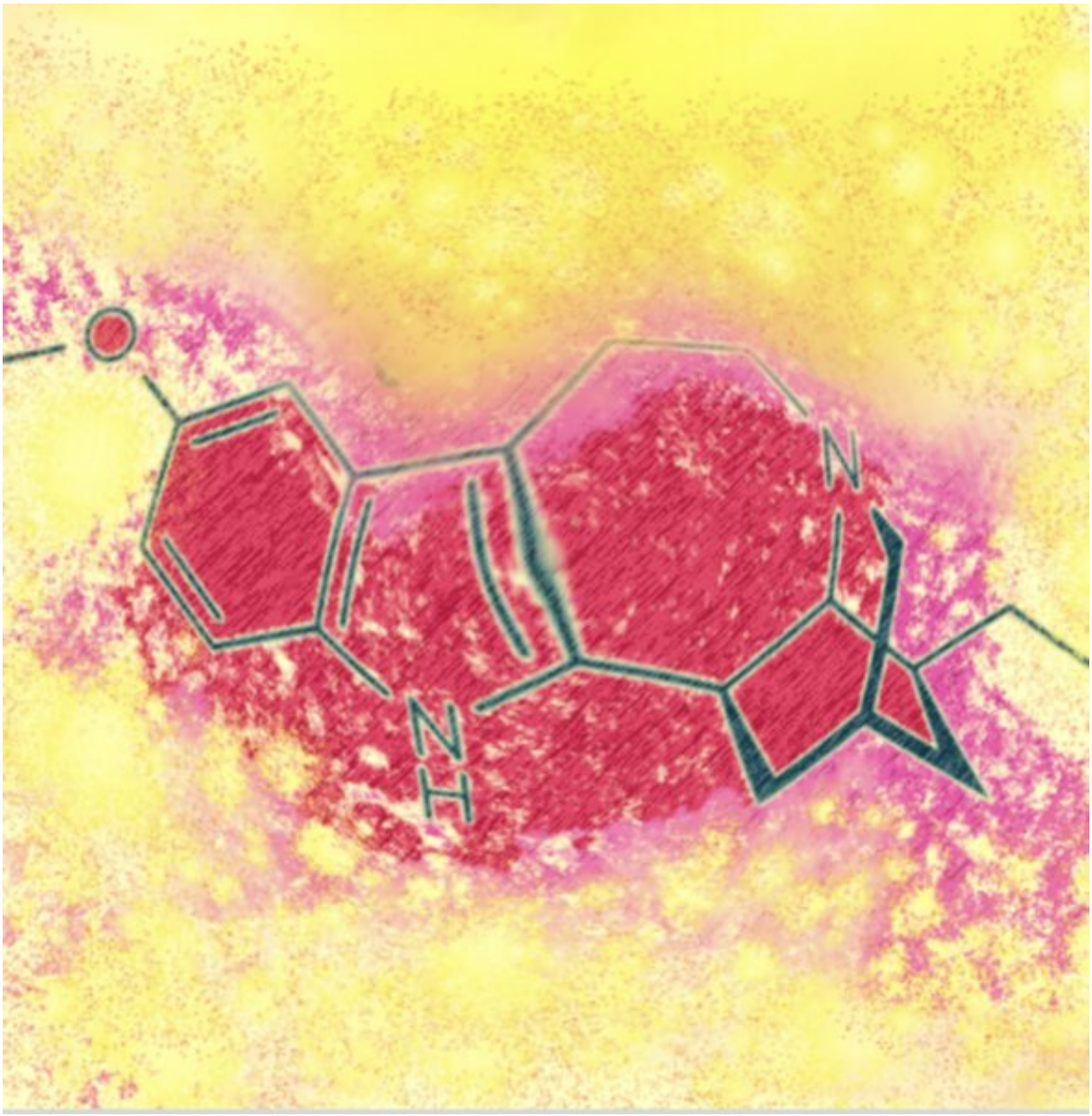

Graphic art showing the chemical structure of the ibogaine alkaloid. Credit: David S. Soriano/Wikimedia Commons, CC BY-SA

Scientists have developed two new drug candidates for potentially treating addiction and depression, modeled on the pharmacology of a traditional African psychedelic plant medicine called ibogaine. At very low doses, these new compounds were able to blunt symptoms of both conditions in mice.

The findings, published May 2 in *Cell*, took inspiration from ibogaine's impact on the serotonin transporter (SERT), which is also the target of SSRI antidepressants like fluoxetine (Prozac). A team of scientists from UCSF, Yale and Duke universities virtually screened 200 million molecular structures to find ones that blocked SERT in the same way as ibogaine.

"Some people swear by ibogaine for treating addiction, but it isn't a very good drug. It has bad side effects, and it's not approved for use in the U.S.," said Brian Shoichet, Ph.D., co-senior author and professor in the UCSF School of Pharmacy. "Our compounds mimic just one of ibogaine's many pharmacological effects, and still replicate its most desirable effects on behavior, at least in mice."

Dozens of scientists from the laboratories of Shoichet, Allan Basbaum, Ph.D., and Aashish Manglik, MD, Ph.D., (UCSF); Gary Rudnick, Ph.D., (Yale); and Bill Wetsel, Ph.D., (Duke) helped demonstrate the real-world promise of these novel molecules, which were initially identified using Shoichet's computational docking methods.

Docking involves systematically testing virtual chemical structures for

binding with a protein, enabling scientists to identify new drug leads without having to synthesize them in the lab.

"This kind of project begins with visualizing what kinds of molecules will fit into a protein, docking the library, optimizing, and then relying on a team to show the molecules work," said Isha Singh, Ph.D., a co-first author of the paper who did the work as a postdoc in Shoichet's lab. "Now we know there's a lot of untapped therapeutic potential in targeting SERT."

Ibogaine is found in the roots of the iboga plant, which is native to central Africa, and has been used for millennia during shamanistic rituals. In the 19th and 20th centuries, doctors in Europe and the U.S. experimented with its use in treating a variety of ailments, but the drug never gained widespread acceptance and was ultimately made illegal in many countries.

Part of the problem, Shoichet explained, is that ibogaine interferes with many aspects of human biology.

"Ibogaine binds to hERG, which can cause heart arrhythmias, and from a scientific standpoint, it's a 'dirty' drug, binding to lots of targets beyond SERT," Shoichet said. "Before this experiment, we didn't even know if the benefits of ibogaine came from its binding to SERT."

Shoichet, who has used docking on brain receptors to identify drugs to treat depression and pain, became interested in SERT and ibogaine after Rudnick, an expert on SERT at Yale, spent a sabbatical in his lab. Singh picked up the project in 2018, hoping to turn the buzz around ibogaine into a better understanding of SERT.

It was the Shoichet lab's first docking experiment on a transporter—a protein that moves molecules into and out of cells—rather than a

receptor. One round of docking whittled the virtual library from 200 million to just 49 molecules, 36 of which could be synthesized. Rudnick's lab tested them and found that 13 inhibited SERT.

The team then held virtual-reality-guided "docking parties," to help Singh prioritize five molecules for optimization. The two most potent SERT inhibitors were shared with Basbaum and Wetsel's teams for rigorous testing on animal models of addiction, depression, and anxiety.

"All of a sudden, they popped—that's when these drugs looked a lot more potent than even paroxetine [Paxil]," Shoichet said.

Manglik, an expert with cryo-electron microscopy (cryo-EM), confirmed that one of the two drugs, dubbed '8090, fit into SERT at the atomic level in a way that closely resembled Singh and Shoichet's computational predictions. The drugs inhibited SERT in a similar way to ibogaine, but unlike the psychedelic, their effect was potent and selective, with no spillover impacts on a panel of hundreds of other receptors and transporters.

"With this sort of potency, we hope to have a better therapeutic window without side effects," Basbaum said. "Dropping the dose almost 200-fold could make a big difference for patients.

Shoichet has submitted the structures of both new molecules to Sigma Aldrich, the chemical manufacturing company, aiming to make the them available for further testing by other scientists, while he continues to hunt for more precise molecules

With millions of patients continuing to suffer from depression or addiction, new prospective therapies are needed.

"This is really the way science should be done," Basbaum said. "We took

a group with expertise in disparate fields and came up with something that might really make a difference."

More information: Brian K. Shoichet, Structure-based Discovery of Conformationally Selective Inhibitors of the Serotonin Transporter, *Cell* (2023). DOI: 10.1016/j.cell.2023.04.010. www.cell.com/cell/fulltext/S0092-8674(23)00406-3