With pot now legal, therapies sought to blunt high of marijuana

Marijuana is going mainstream in the US. On 1 January, Colorado became the first state in the country to allow recreational use of the drug. Washington is set to do the same within the next few months, and many others are considering similar measures.

Critics of these moves say that legalizing marijuana will increase consumption, leading to an uptick in substance use problems. And with more than 4 million Americans already dependent on or abusing marijuana—making cannabis the number 3 recreational drug after alcohol and tobacco—scientists and public health officials are increasingly fretting over the dearth of available pharmacologic treatments for marijuana addiction. "Every day we are growing more concerned about the number of people seeking treatment," says Ivan Montoya, a psychiatrist and epidemiologist who serves as deputy director in the division of pharmacotherapies at the US National Institute on Drug Abuse (NIDA) in Bethesda, Maryland.

Fortunately, new therapeutic strategies could be on the way. Reporting on 3 January in *Science*, a team led by Pier Vincenzo Piazza, a neuroscientist at the University of Bordeaux in France, found that a naturally occurring hormone called pregnenolone helped curb marijuana intoxication in mice and rats by inhibiting the cannabinoid receptor in the brain that responds to tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana[1].

Piazza's approach targets the endocannabinoid system—the neural network that mediates the effects of THC—by using pregnenolone as an antagonist, which blocks the effects of the drug much like naltrexone does for heroin. The idea is that the drug user stops seeking out marijuana because it no longer elicits a high. Other scientists have tried manipulating the endocannabinoid system with agonists, which substitute a medication with similar effects to THC to help control cravings and withdrawal symptoms, comparable to the way methadone or buprenorphine is used to treat heroin addiction.

Rafael Maldonado is pursuing a wholly different approach, one that ignores the endocannabinoid system entirely and instead focuses on other neurotransmitters that can neutralize the brain's reward system or alleviate symptoms of withdrawal. Last year, Maldonado and his colleagues at Pompeu Fabra University in Barcelona, Spain, showed in mice that blocking the hypocretin/orexin receptor-1, which plays a part in reward circuits and has been linked to addiction to various drugs, prevented the transmission of the neurotransmitter dopamine, which reinforces THC's rewarding effects in the brain[2]. Maldonado says that several pharmaceutical companies have shown an interest in his team's work. "It will not be hard to test in humans," he says.

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Roach control: Scientists blaze a trail to anti-addiction drugs for marijuana.

High hopes

The quest for drugs to treat marijuana addition has seen highs and lows. Scientists were hopeful, for example, that the antiobesity drug rimonabant, an endocannabinoid antagonist, could work. But the weight loss pill turned out to have serious neuropsychiatric side effects and was withdrawn from the market. Research into rimonabant's potential for marijuana dependence subsequently stopped.

Antagonists based on the natural effects of marijuana itself, like pregnenolone, have had more success. José Crippa, a neuroscientist at the University of São Paulo in Brazil, has been studying how cannabidiol, another chemical present in marijuana, can counteract the effects of THC. The two compounds both target the type 1 cannabinoid receptor (CB1) but seem to have opposite effects. Crippa and his colleagues successfully used cannabidiol to treat withdrawal symptoms in a 19-year-old woman[5]. Now, Crippa has partnered with researchers in California to test the psychoactive compound in larger groups of patients. "It's funny that one compound in the plant can help to recover from addiction to another," says Crippa.

One promising drug in the endocannabinoid agonist category is dronabinol, which is currently approved to treat nausea in cancer patients undergoing chemotherapy. In a 156-person trial, this synthetic version of THC reduced the magnitude of withdrawal symptoms significantly more so than placebo treatment[3]. Dronabinol has also proven effective in helping people quit using marijuana when taken in combination with lofexidine, an agonist of the α2-adrenergic receptor used to treat withdrawal from heroin and other opiate drugs[4]. Phase 2 trials of the combination therapy are ongoing.

Yet, despite some promising leads, experts continue to worry that the amount of research going into effective drug treatments for marijuana addiction is not keeping pace with the size of the addiction problem. According to Montoya, there are only a dozen academic groups working on the problem in the US—with just a handful more in Europe, Israel and South America. A 2012 literature review by Crippa and his colleagues found just ten relevant case reports or controlled clinical trials published on drug therapies that had been tested in humans[6].

Besides drug therapies, the medical community has tried behavioral and cognitive treatments for marijuana addiction. But, says Piazza, "they have two problems: the effects of marijuana mean that patients don't remember what they learned in their sessions, and they are very demotivated."

Newer drug options could complement or even bolster these nonpharmacological approaches. "Psychologists are very excited about these drugs," Piazza says.

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