

Why Haven't We Cured Addiction Yet?

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Millions of people are struggling with addictions to smoking, drinking and taking drugs, but the search for new medications to help them quit remains elusive. Here's why.

Scientists may seem as if they can do a lot, like genetic engineering or controlling neurons with light, but cures for many conditions remain elusive. One such condition is addiction, which involves compulsive drug-taking over a long period of time that interferes with a person's ability to lead a normal life. Drug addiction has many negative effects on the health of the drug user and causes problems for other people at home, at work and through increased crime.

Despite the problems addiction creates for an individual and their community, most drugs of addiction have no, or only modestly effective, anti-craving medications available. The result is that most patients will relapse even if they are given the best available counselling and medical treatment. Demand for anti-craving medicines is so strong that patients will turn to miracle cures that are more hype than substance, such as baclofen, a drug which became popular in France after a doctor wrote a book about using it to treat his own alcohol addiction.

However, as courageous as testing new treatments on yourself is, most scientists working to develop cures have a lot more hoops to jump through. The first step is to find a biological target that a new medicine can work on. For addiction, these are usually the signalling molecules in the brain, such as GABA which is mimicked by baclofen, or

the brain's natural opioids which are blocked by naltrexone to treat alcohol addiction.

One potential target that has been in preclinical testing for over a decade is the orexin system. The orexins are small signalling proteins in the brain that were discovered in 1998 to regulate wakefulness and feeding. Since 2005, it has been shown that the orexins are involved in how animals experience the pleasurable effects of various drugs of abuse, such as morphine, cocaine and alcohol.

Rats on Drugs

Of course, scientists cannot just take an experimental drug and stick it in human addicts to see what it does, especially if no one knows if the experimental drug has a reasonable chance of helping. So we have to start by doing preclinical testing with laboratory animals, usually rats or mice.

Addiction is a complex disorder and there are lots of ways that this is modelled using animals. Early studies tested the way orexins are involved in how the brain processes the drug 'high'. For example, if a mouse gets pleasure from morphine or cocaine, it will like spending time in places that remind it of those drugs. Activating orexin neurons increases this preference, suggesting that they are involved in those pleasurable experiences.

Another way is to just let rats take as much drug as they want. In these experiments, rats learn to do something, like press a lever, to get a few drops of alcohol, a bit of nicotine or a tasty food pellet. The advantage of this approach is that the rat is only taking drugs it wants to take, just like how humans only take drugs they want to take. Using this approach, Australian scientists at the Florey Institute of Neuroscience and Mental Health were the first to show that the orexin system might be involved in alcohol addiction.

Rats can also experience cycles of rehabilitation and relapse. During the rat-rehab phase, lever presses do not produce any drug no matter how hard the rat tries. Over time, the number of lever presses they make decreases, but during rat-relapse it can be rekindled by the same kinds of things that trigger relapse in humans – cues or places that are associated with the drug, stress, the drug itself or simply the passage of time.

Does it Really Work?

Once a potential target for a new medicine has been identified, it needs to be tested in different ways to see if it will really work and, if it does, how it works. Together with my supervisors and colleagues, I have spent the past 5 years testing the effects of experimental drugs that block orexin signals in rats that are taking, or trying to take, alcohol, nicotine or junk food. But our results, like the disorder of addiction, are a bit complicated.

Neurons that receive orexin signals actually recognise orexin proteins with two different receptors. Most of the time the orexin signal will do the same thing at either receptor, but there are some subtle differences. For example, using experimental drugs that block orexin signals at one receptor reduced both the amount of alcohol consumed and the severity of rat-relapse in rats with a genetic predisposition to alcohol consumption. But when we tested a drug that blocked the other orexin receptor, only the amount of alcohol consumed decreased and rat-relapse was unaffected. Importantly, these drugs

worked when injected directly into the reward circuitry of the brain, suggesting that orexins are involved in driving motivation.

Different drugs of addiction also have different effects on the brain, so it's important to look at more than one. Legal drugs of abuse (alcohol and nicotine) cause just as much harm, if not more, than illegal drugs, so we also studied the effect of blocking orexin signalling in rats taking nicotine. We found that experimental drugs that blocked both orexin receptors had only a very small effect on rat-relapse and only if the rats had spent more than a month taking nicotine. However, the effect was far too small to recommend targeting orexins for smoking.

Addiction scientists dream of a new medication able to reduce craving for addictive drugs while not affecting normal motivation. Addictive drugs work through similar psychological processes and brain circuits as things that normally motivate people and animals, like food. Current medications, like naltrexone, are not very good at this but our studies suggest that an orexin medication might be able to.

Junk food is a great motivator that is not an addictive drug, so we also tested the effect of experimental anti-orexin drugs in rats with a taste for food pellets high in fat and sugar. We tested four different experimental drugs which blocked one or both of the orexin receptors and found no effect on how much food the rats would consume. Even when we looked in the brains of our rats for signs of orexin neuron activation during rat-relapse, we found that their activity was not specifically related to cues that were associated with junk food. It seems as if the orexin system is picky about when it gets involved in motivation, which can be a good thing if it is ever used to treat addiction.

Miracle Cures and Dead Ends

These results do not point to a simple answer for whether we should use anti-orexin drugs to treat addiction. In some cases, they may be effective but it will depend on the addictive drug, the

patient and the aim of treatment. For example, a medicine which targets orexins might work for patients with a family history of alcohol addiction, like it did for rats with a genetic predisposition to alcohol consumption. However, this might not work for everyone because in other studies we did not find any effect of blocking orexin signals in rats with no genetic predispositions.

Other researchers have had much better luck with anti-orexin drugs and cocaine. Scientists at the University of Texas Health Science Center registered a clinical trial in 2016 to begin testing suvorexant, an insomnia medication that blocks orexin signals, in patients with cocaine addiction.

There are also other clinical trials underway testing medicines that target systems other than the orexins, such as glutamate and GABA. The glutamate and GABA systems are the brain's main way of controlling its level of excitability, with glutamate increasing excitability and GABA decreasing excitability. Topiramate targets both by mimicking GABA and blocking glutamate signals and is being trialled for alcohol and cocaine addiction, while N-acetyl cysteine blocks glutamate signalling and is being tested against cannabis, alcohol, smoking and cocaine.

Meanwhile, the miracle cure of baclofen is losing its shine. In France, baclofen overdoses occur in patients with alcohol addiction on a weekly basis, nearly 75% of which are intentional, and its side-effects are involved in hundreds of adverse drug reactions each year. One recently reported clinical trial sponsored by the pharmaceutical company Ethypharm found approximately 90% of patients relapsed, even if given baclofen.

Careful research at preclinical stages can help prevent ineffective and potentially unsafe drugs from making their way into the clinic. Progress is slow because addiction has many psychological and neural aspects, like motivation, reward, stress and craving. For every potential biological target, of which the orexins are just one, this process of preclinical testing has to happen again. While trying to find cures we run into many dead ends, but new medications in clinical trials give hope that better treatments will eventually become available. Just don't rush out for the miracle cures.

Shaun Khoo completed his PhD at the University of New South Wales and is now a postdoctoral fellow at Concordia University.