

A helping hand

A single pill could draw people out of addiction and back to their loved ones, finds Alice Klein

JOSEPH SHARP remembers the first time he injected methamphetamine. “It shot up like a geyser into my brain and I actually spluttered aloud, involuntarily, ‘I want to do this every day for the rest of my life,’” he says. “It was like the euphoric feeling of being madly in love.”

Sharp first used the drug – also known as crystal meth or ice – to lower his inhibitions and make him “super social”. Having recently moved to Los Angeles to become a screenwriter, he was eager to make friends. But as addiction took hold, he gradually withdrew from those close to him. “In the end, it was just me alone in a room with a needle in my arm,” Sharp says. “Talk about social.”

This story sounds familiar to Iain McGregor at the University of Sydney, who has been studying substance abuse for over 25 years. One of the hallmarks of addiction is a waning interest in human contact and a growing fixation on seeking out the vice – be it alcohol, amphetamines, cocaine, heroin, prescription opioids, nicotine or any other addictive substance.

A decade ago, this observation gave McGregor an idea. Would it be possible to reverse substance addiction by switching the brain back from drug-chasing mode to social mode? If McGregor’s hunch was right, this could be the silver bullet – a universal treatment for all addictions at once.

It was worth a shot. Alcohol, tobacco and illicit substances are implicated in 13 per cent of global deaths each year. Prescription opioids are adding to this crisis. In 2016, in the US alone, 46 people died each day from overdoses involving prescription opioids.

But even though addictive substances

claim almost as many lives as cancer each year, no cures are available and few drug firms are interested in developing them. “Substance users are not a very popular population for health funding and not many pharmaceutical companies want to associate with them,” says Femke Buisman-Pijlman at the University of Adelaide in Australia. Existing treatments for substance addictions have had limited success.

To try to restore the social behaviour of drug users, McGregor set his sights on oxytocin, known as the love hormone or cuddle chemical. Naturally released during social interactions, sex and when women give birth, it helps to strengthen human bonds.

As a starting point, McGregor tried injecting oxytocin into rats that were so heavily addicted to methamphetamine that they would push a lever hundreds of times just to get one hit. “We actually had to limit their intake or they’d overdose and die,” he says. The results were astounding: the oxytocin-treated rats almost completely stopped pressing the lever, a sign they had lost interest in the drug.

Next he tried it with alcohol. Along with Michael Bowen, who was then his student but is now a colleague, McGregor showed that alcoholic rats halved their beer consumption during a 2.5-hour drinking session if they were given an oxytocin injection directly beforehand. Other research groups found that oxytocin reduced self-administration of cocaine and heroin in rats.

Following these promising findings, several small clinical trials were set up in the US to test the potential of oxytocin for treating dependency on alcohol, cocaine, heroin, >

prescription opioids, marijuana and nicotine. Unlike in rat studies, the hormone couldn't be injected in large doses into peoples' bloodstreams or directly into their brains due to safety issues. So to get the oxytocin into the brain, they sprayed it up the nose.

However, the results from these trials so far have been disappointing: intranasal oxytocin relieves drug cravings only slightly, if at all. This is probably because only a small amount of intranasal oxytocin actually makes

“The drug seems to prevent relapse, one of the biggest barriers to recovery”

it into the brain. The large molecule has trouble crossing the blood-brain barrier and is known to break down easily in the circulation.

To overcome this problem, McGregor and Bowen teamed up with Michael Kassiou and his then student William Jorgensen, medicinal chemists at the University of Sydney, to help develop an oxytocin mimic that was small enough to cross the blood-brain barrier, but still had similar actions. They came up with an idea, but it was a tricky molecule to make, and Kassiou's team ran into problems trying to put its three individual parts together.

Growing impatient, McGregor suggested to Jorgensen that they test these three precursor fragments in rats “just for the hell of it”, says Bowen. The first two fragments did nothing. But after they injected the third one, they found the rats became more social, showing an increased preference for spending time with other rats rather than objects, and even cuddling up to rats they had never met before. “Bingo. That was when we thought it must be activating the oxytocin system,” says Bowen.

To confirm this, they looked at what was happening in the rats' brains. Sure enough, they found the fragment was strongly activating the brain's two major oxytocin-producing factories.

Since then, the team has tested this small molecule – named synthetic oxytocin-like compound 1 (SOC-1) – in rats addicted to methamphetamine, rhesus monkeys hooked on cocaine and baboons with an alcohol habit. The results have been “nothing short of incredible”, says Bowen.

For example, when SOC-1 was injected into the rats, their motivation to consume methamphetamine – measured by how many times they pressed a lever to get a hit – dropped by more than 85 per cent. Similarly,

with the rhesus monkeys, their interest in self-administering cocaine fell by 90 per cent. In other words, instead of pressing a lever almost 350 times to get one intravenous shot of cocaine, the monkeys gave up after 35 goes.

Impressively, the molecule also seemed to prevent relapse, one of the biggest barriers to recovery in those with substance use disorders. Research shows that around 40 to 60 per cent of people relapse within the first year of leaving rehab. “The biggest problem is not quitting, but staying quit,” says Sharp, who relapsed after four years, then took two years of stopping and starting to get clean again.

There are three common triggers for relapse. The first is stress – for Sharp, it was breaking up with his boyfriend. The second is a cue – for example, walking past your drug dealer on the street. And the third is a prime – “like one sip of beer that turns into 20 beers and half a bottle of vodka”, says Bowen.

SOC-1 seems to weaken the power of these triggers. In one experiment, rats were trained to push a lever to self-administer methamphetamine. Once they were addicted, the set-up was changed so the lever no longer released any drug. Eventually, the rats gave up pressing it – this was the “rehab” phase. But then they were given one tiny dose of methamphetamine. Immediately, they switched into a frenzied state, hammering the lever over 120 times during a 2-hour period to try to get another hit. In contrast, those treated



It might be possible to stop drug addiction by inoculating people when they are teenagers



with SOC-1 just before receiving this prime barely touched the lever.

According to McGregor, the effects of SOC-1 could be long-lasting. “We know that oxytocin brings about what psychologists call a state change,” he says. “For example, in childbirth, mothers don't want to be in love with their babies just for a few minutes. The initial oxytocin surge needs to have an enduring effect.” This idea is borne out by his and Bowen's research. They showed, for example, that alcoholic rats given a single dose of oxytocin halved their intake of a raspberry-flavoured vodka drink across the full six weeks of the experiment. They also found that administering a short course of oxytocin to adolescent rats reduced their risk of developing alcohol and methamphetamine addictions in adulthood.

The big question the team is now trying to answer is: how exactly does SOC-1 work? Their research so far suggests it stimulates a rush of oxytocin that recalibrates the brain's focus towards social engagement.

We have known for a long time that pleasurable sensations are orchestrated by dopamine – the “feel-good chemical” – in a part of the brain called the nucleus accumbens. But over the past two decades, we have discovered that there are two types of dopamine receptor in this area. D1 dopamine receptors are activated by stimulation from objects like food

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