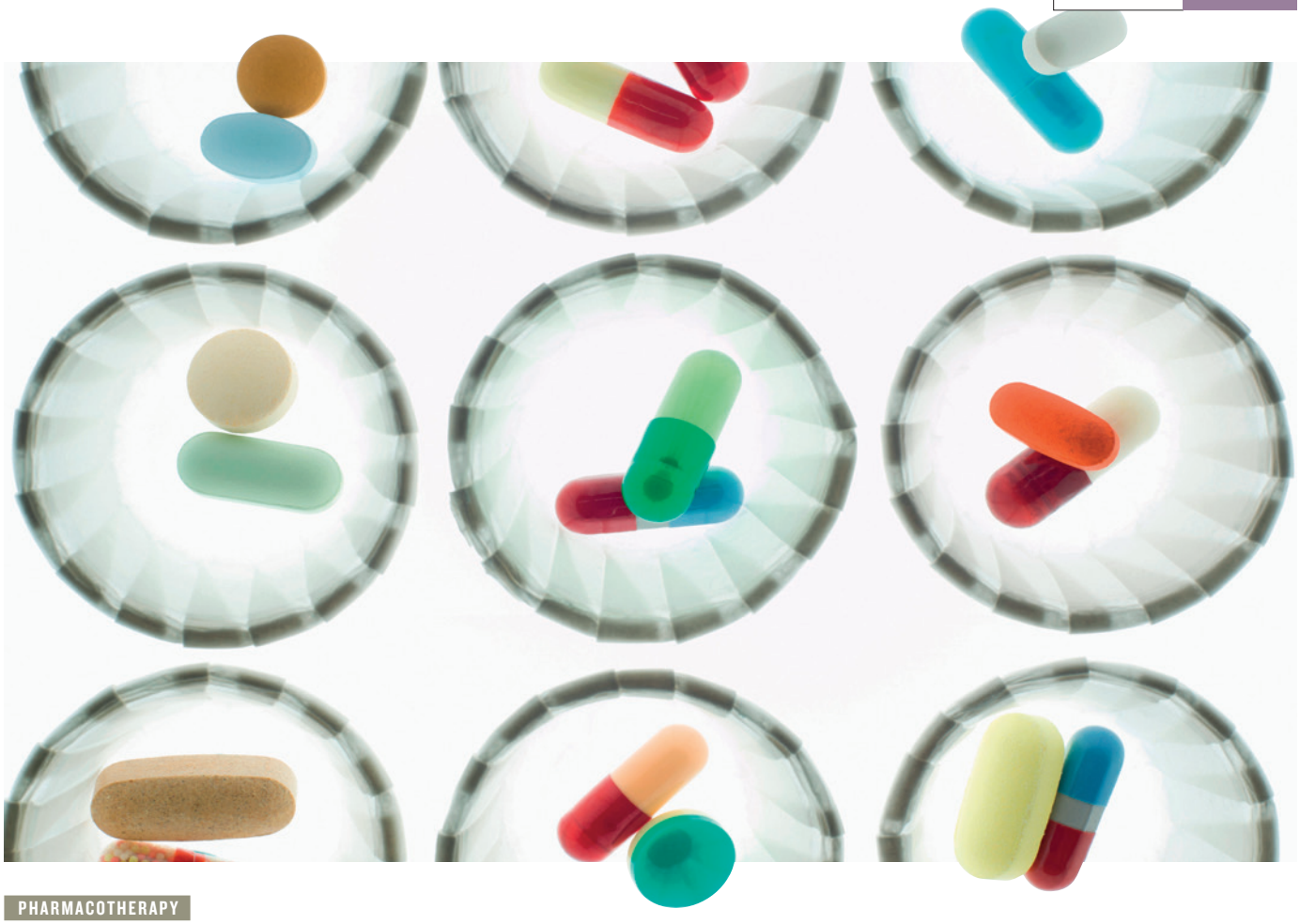

IMAGE SOURCE/GETTY

PHARMACOTHERAPY

Quest for the quitting pill

Addiction researchers are optimistic that they can create effective medication to treat addictions. But the key question is, will pharmaceutical companies bring them to market?

BY CASSANDRA WILLYARD

In 1948, a group of American businessmen purchased a farmhouse in Center City, Minnesota, and helped to turn the rambling wood structure into a sanatorium for professionals who had become dependent on alcohol. The facility, called Hazelden, spawned one of the largest drug and alcohol addiction treatment networks in the United States, with 16 centres in 9 states.

Since its inception, abstinence has formed the backbone of Hazelden's approach to recovery. But in 2009, Marvin Seppala, the institution's chief medical officer, began pushing for the network to use medication to treat opioid addiction. For the past 20 years the United States has been in the midst of an opioid-addiction epidemic, and as the number of Hazelden residents receiving treatment for opioid dependence grew, Seppala noticed a few disturbing trends. More people seemed to be leaving their programme before completing their course of treatment, or continuing to use drugs while at Hazelden. Seppala returned to Hazelden in 2009 after two years working in private practice. He had seen the effectiveness of drugs such as Suboxone (buprenorphine and naloxone), an opiate substitute manufactured by Reckitt Benckiser Pharmaceuticals that helps to reduce cravings, and Vivitrol (naltrexone), a long-lasting injectable medication manufactured by Alkermes that blocks the effects of heroin and other opiates. Seppala thought that these medicines might be able to address some of the problems that Hazelden's patients were having adhering to their programmes.

The move was controversial. For decades, Hazelden had helped people with addictions to recover by promoting abstinence and a belief in the power of the 12-step programme, as used by Alcoholics Anonymous. "The use of a maintenance medication like Suboxone wasn't necessarily seen as appropriate," Seppala says. So in 2012, he began holding forums with Hazelden staff to educate them about his vision. "We thought they were going to throw tomatoes and rotten eggs," he says. But there was surprisingly little resistance. Too many of the clinicians had seen former Hazelden residents relapse and die of a drug overdose.

In 2013, the centre began offering patients Suboxone and Vivitrol as well as group counselling for opioid dependence. Although the number of people involved in the new programme is still small, Seppala has seen some encouraging signs. At Hazelden, the typical dropout rate for people receiving treatment for opioid addiction is 22%, he says. But among those with opiate dependency enrolled in the new programme, the dropout rate was just 5% in 2013 and 2014. Six of Hazelden's patients relapsed and died of opioid overdoses in 2013, but none of them were in the new programme that offers both medication and counselling. "You can't say there's a direct correlation," Seppala says. "However, when it's six to nothing, you've got to say that

there's a dramatic shift, and that we're doing something correct."

Hazleden's adoption of opioid-addiction medication is a sign of a much larger societal shift — a growing recognition that addiction is a complex chronic disease that, like other neurological disorders, often responds to prescription drugs.

But there is nothing on the market for people who are addicted to cocaine or methamphetamines. Only a handful of drugs currently exist to treat nicotine, alcohol and opiate addiction, and those medicines do not always work. "All the addiction medications that are on the market, at best they're successful 30% to 35% of the time," says Stanley Glick, an addiction researcher at Albany Medical College in New York. "We don't only need new medications, we need better medications." Glick and others are exploring a variety of promising targets, and they are optimistic that they can create the next generation of anti-addiction drugs (see 'Drugs against drugs'). But some addiction researchers question whether pharmaceutical companies, which have shied away from addiction therapies in the past, will be willing to bring the advanced therapies to market.

TARGET PRACTICE

Addictive drugs wreak havoc on the brain's reward circuitry. Some, including heroin, mimic natural neurotransmitters. Others, like cocaine, bind to receptors and prompt the brain to release its own. But the end result is the same: a brain awash in dopamine, the chemical responsible for pleasure. That overlap in the molecular pathways means that it may be possible to develop treatments that target multiple addictions. "What we're interested in is molecular mechanisms that may transcend a particular addictive drug," says Phil Skolnick, director of the division of pharmacotherapies and medical consequences of drug abuse at the US National Institute on Drug Abuse (NIDA) in Bethesda, Maryland. That is important, he says, because "many people who abuse drugs don't abuse just one drug".

Glick thinks that he may have found one such compound. In the late 1980s, Glick received a call from Howard Lotsof, who was formerly addicted to heroin. Lotsof claimed that he had discovered a cure for opiate addiction. He told Glick about a psychoactive compound called ibogaine that occurs in several plant species, including the West African *Tabernanthe iboga* shrub. Lotsof had already approached a number of scientists with his cure. "For better or for worse, I was the first one that was fool enough to become interested in it," Glick says. Glick imagined that he would be able to give the drug to a few morphine-addicted rats and quickly debunk Lotsof's claims. But to Glick's surprise, ibogaine worked. "So we started to get more interested in it," Glick says. Ultimately, it turned out that the drug has some significant drawbacks. It can slow the heart and, at high doses, can damage the nervous system. "There was no way ibogaine was ever going to be an approvable drug in the United States," Glick says.

KPZFOTO/ALAMY

Lobelia inflata **is a source of lobeline, which may help to curb the rush from methamphetamine use.**

So Glick partnered with a medicinal chemist and began searching for a new drug, something that would produce the same response as ibogaine, but without all the toxic side effects. The pair landed on a compound[1] called 18-MC. "It doesn't work like any other medication that's ever been proposed to treat addiction," Glick says.

Although some addiction therapies work directly on the circuitry that shuttles dopamine through the brain, the pathway that seems to play a crucial role in most forms of addiction, 18-MC works indirectly. It binds to a nicotinic receptor called α-3 β-4, which is concentrated primarily in the middle of the brain. These receptors are not part of the dopamine pathway, but Glick's research suggests that by blocking the α-3 β-4 receptors, 18-MC dampens the dopamine pathway's euphoric response to drugs[2]. Glick and his colleagues have found that 18-MC works in all kinds of addiction models, curbing animals' use of cocaine, methamphetamines, morphine, alcohol and nicotine. "It opens the door for a whole new approach for affecting the reward system and for reducing addictive behaviour," he says.

Lotsof, who spent much of his life pushing for an anti-addiction therapy, died of cancer in 2010. But Glick kept working to make Lotsof's dream a reality. The same year that Lotsof died, Glick began to work with a biotechnology company called Savant HWP, headquartered in the San Francisco Bay Area, California, to help develop 18-MC further. The first human study began in Brazil in July 2014, led by Savant's South American partner, Brazil-based Hebron Farmaceutica, which is developing 18-MC for a different condition: the parasitic disease leishmaniasis. The collaboration makes good financial sense, Glick says. Both companies need to demonstrate that the compound is safe before they can move forward, and phase I studies, which assess safety in disease-free participants, are similar regardless of the intended use.

The results have yet to be published, but Steven Hurst, Savant's CEO, says that so far, the compound seems to be safe. The next study, slated to begin this year, will start to gather data on whether 18–MC can help people who smoke to break their nicotine habit.

Savant's researchers are not the only ones pursuing the α-3 β-4 receptor as a target for addiction medications. Nurulain Zaveri, a medicinal chemist, was already hunting for medicines to curb nicotine addiction when she learned about Glick's findings in 2003. She was intrigued by the prospect that the largely overlooked receptor could be a good target for nicotine dependence. But she noticed that Glick's compound hit a variety of different targets, not just α-3 β-4. Zaveri wanted something more selective, so she began screening compounds. In 2007, she found one that seemed to be not only selective but also potent — a chemical called AT-1001.

In 2008, Zaveri founded a company called Astraea, headquartered in Mountain View, California, to develop AT-1001 and similar compounds as therapies to help people stop smoking. In 2012, her team showed that AT-1001 can block self-administration of nicotine in rats[3], and in June 2015, they reported that the compound may also prove valuable for treating alcohol addiction following studies on rats[4]. Zaveri says she also has data to suggest that AT-1001 might help to stop cocaine dependence. Her other leading compounds seem to show similar effects, and Zaveri is currently trying to decide which compound to move into clinical trials.

Linda Dwoskin, an addiction researcher at the University of Kentucky in Lexington, is working on a different target in the brain's reward pathway. In the 1990s, she began working with lobeline, a compound derived from a group of plants, including *Lobelia inflata*, commonly known as Indian tobacco.

"It doesn't work like any other medication that's ever been proposed to treat addiction."

Lobeline binds to nicotinic receptors that are involved in nicotine addiction — others were already investigating it as a potential smoking-cessation tool. But Dwoskin discovered that the compound also binds to a protein in the brain called VMAT2, a transporter that carries neurotransmitters such as dopamine and serotonin. VMAT2 is also the target for methamphetamines, but lobeline did not seem to produce the drug's pleasurable

effects[5]. Dwoskin realized that it might be possible to use lobeline to block VMAT2, thereby preventing the addictive rush associated with methamphetamine use.

Dwoskin launched Yaupon Therapeutics in 2002 and took the compound from the lab to clinical trials. But when people addicted to methamphetamines began taking the lobeline tablets, she immediately realized there was a problem. The drug tasted terrible, and many of the participants developed nausea — not that surprising, because physicians used to prescribe *L. inflata* to induce vomiting, earning it the nickname 'puke weed'. "It was a minor untoward effect, but enough that compliance to the trial was probably going to be an issue," Dwoskin says. "We decided we could probably do something better."

So Dwoskin went back to the drawing board and began working on compounds that would specifically target VMAT2. Over the past decade, she and her colleagues have developed several generations of VMAT2-targeting compounds. "The ones that we're looking at now are extremely exciting," she says. They stop animals from self-administering the drug, and even seem to prevent drug-seeking behaviour. "I've never seen anything like that before," she says. Dwoskin will need funding to continue developing the drug in preparation for a human trial. "I feel a need to see this to completion because it looks so promising," she says.

DRUGS AGAINST DRUGS

A variety of promising pharmaceuticals are currently being developed to treat addiction. But it will be years before any of them join the small number that are already on the market.

Therapy	Status	Developer	Indication
18-MC	Phase I clinical trial	Savant HWP	Nicotine dependence
AT-1001	Animal studies	Astraea Therapeutics	Nicotine dependence
GZ-793A	Animal studies	Linda Dwoskin	Methamphetamine dependence
HeroVax	Animal studies	Kim Janda	Heroin dependence
TV-1380	Phase II clinical trial	Teva Pharmaceuticals	Cocaine dependence

A SHOT IN THE DARK

Although many researchers have been focused on developing drug treatments, others have been trying to develop vaccines to curb addiction. The goal is to induce an immune response against addictive substances such as cocaine or nicotine. Then, when the vaccinated individual takes the drug, natural antibodies would prevent the drug's active ingredient from reaching its target in the brain. Without a pleasurable rush, people might be less prone to relapse. Kim Janda, a chemist at the Scripps Research Institute in La Jolla, California, began working on a vaccine in the 1980s. Over the past three decades, he has worked on vaccines against nearly every type of addictive compound: methamphetamines, cocaine, heroin, nicotine, tetrahydracannabinol (or THC, the active compound in marijuana) and rohypnol. Each one required a different approach.

Of these, Janda thinks that his vaccine against heroin holds the most promise. It combines a heroin-like molecule with a carrier protein designed to elicit an immune response. Heroin breaks down quickly in the body into a compound called 6-acetylmorphine and then into morphine. Janda's vaccine is designed to mop up all three components, keeping them out of the brain and preventing the rush that heroin typically provides. In 2013, Janda and his colleagues reported[6] that the vaccine seems to prevent both drug-seeking behaviour and relapse in a rat model. In the most challenging experiment, researchers forced rats that had become addicted to heroin to abstain for 30 days. When they gave the rodents free access again, rats that had received a sham vaccine quickly ramped up their use of the drug, a behaviour that in humans often leads to overdose because the body has lost its tolerance. Vaccinated rats resumed taking the drug, but their consumption did not escalate.

Janda has since tweaked the vaccine and method of injection, and this second vaccine seems to be more effective. But finding someone to help him move to clinical testing might prove difficult. Clinical trials are enormously expensive, and so far Janda has not had much interest from investors or the pharmaceutical industry. He thinks that some companies might also be turned off by previous vaccine failures. A vaccine for nicotine reached a phase III clinical trial in 2009, but ultimately flopped. There is a mentality of "well, you guys had your chance, and it didn't work", he says.

PROFIT MOTIVE

Any compound that makes it into clinical trials risks failure because of unexpected side effects or because it does not work as well as hoped. But some addiction researchers are worried that their experimental therapies will fail for a different reason: lack of interest.

The pharmaceutical industry tends to shun addiction therapies because they are viewed as unprofitable, Janda says. "Pharmaceutical companies don't view drug addicts as good investments." But, according to Skolnick, that perception is wrong. In 2012, before Suboxone went off-patent, sales topped US$1.5 billion. The drug outsold blockbusters like Pfizer's impotence pill, Viagra (sildenafil). "Those numbers have made it a more interesting game," Skolnick says. And he thinks that today more companies are willing to take the risk. For example, NIDA recently partnered with Teva Pharmaceuticals, an Israel-based company with the ability to both manufacture and sell medicines, to test the efficacy of a compound called TV-1380 to curb cocaine addiction. Teva "isn't one of these little biotech companies where once you do a trial, they look for a partner," he says. "They understood that you can do good and do well at the same time."

Skolnick thinks there may be an even more serious barrier keeping drug companies at bay. For addiction therapies, the US Food and Drug Administration views abstinence as the gold standard for approval. That is, the agency wants to see a higher rate of abstinence in the treatment group than the placebo group. So even a medication that helps people to use less of a drug might not gain regulatory approval.

"I feel a need to see this to completion because it looks so promising."

"That seems to be a very, very high bar to jump over," Skolnick says. "I think that that puts some drug companies off." Skolnick does not think that such a stringent outcome makes much sense. "It would seem intuitively obvious, especially for an illegal drug, that if you use it less frequently it would have some benefit."

To doctors such as Seppala, who witness the aftermath of drug addiction on a daily basis, the need for new medicines seems obvious. "This is a remarkably complex illness," Seppala says. "Recovery rates are similar to other chronic illnesses, but we don't feel that's adequate. Better treatments are necessary." But Seppala, who has struggled with addiction himself, cautions that even the best medicines will not be a panacea. "People with addiction have often destroyed relationships, done things they don't even want to admit to anyone," he says. "If you just give a medication, you're basically saying it's only a biological illness and ignoring the rest of this problem." That is why Hazelden combines a 12-step programme with medication and therapy. To overcome the epidemic of opiate addiction, "we have to use everything at our disposal," Seppala says. "We can't rely on a single approach." ■

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