nature OUTLOOK

ADDICTION

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Cover art: Nik Spencer

Addiction can devastate the lives of people and their families. Researchers are disentangling its myriad causes and developing new treatments.

Addiction tends to run in families, but scientists are finding that there is no simple 'addictive personality'. Instead, factors that include genes, character traits and early life experiences combine to make the inheritance of addiction a complicated problem (see page S48).

As an addiction develops it changes the brain: neural circuits related to pleasure and reward are hijacked and rewired (S46). Researchers are studying people from birth to try to tease out how these changes affect, and are affected by, brain development — and how they might be reversed (S50).

Treatments for addiction are becoming more sophisticated, but still face major challenges to acceptance. Medication can help to wean people from their addiction (S53). One controversial but effective technique is to reward people for staying clean (S57). Just as important as repairing the addicted brain is fixing the social environment in which people susceptible to addiction live (S56). Another approach is to make the drugs themselves harder to misuse (S60).

It is not only substances that can be addictive. Gambling is, so far, the only behaviour that has been recognized as an addiction, but researchers are considering adding Internet use, sex and shopping to that list (S62). But despite all the progress, the questions still to be answered are daunting (S63).

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Brian Owens
Contributing editor

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THE HIJACKED BRAIN

Addiction is a devastating disease that alters the brain's circuitry, notably in young adults. But the changes need not be permanent: improved understanding of them will help in developing ways to lessen the burden. By **Margaret Munro**. *See a* Nature *Video at go.nature.com/e1gqkk.*

ADDICTION CYCLE

Addiction is characterized by bingeing, withdrawal, cravings, dysfunctional emotions and an inability to abstain from the substance or behaviour. It quickly leads to disruption of interconnected brain circuits that are involved in reward, learning and control.

With time, other brain areas are recruited, including those involved in stress and anxiety — in effect an 'anti-reward' system.

STAGE 1
BINGE/ INTOXICATION

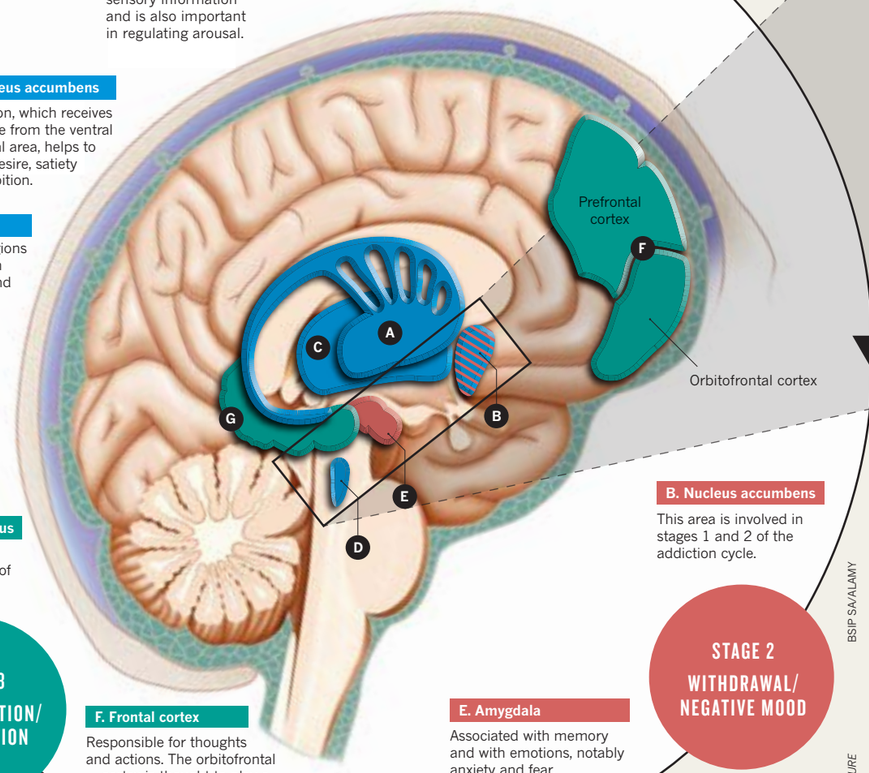
Overstimulation of the reward circuit leads to loss of control and bingeing.

D. Ventral tegmental area
A primitive structure at the top of the brain stem in which dopamine is synthesized (see 'The dopamine connection').

C. Thalamus
Acts as a hub to relay sensory information and is also important in regulating arousal.

B. Nucleus accumbens
This region, which receives dopamine from the ventral tegmental area, helps to control desire, satiety and inhibition.

A. Basal ganglia
Interconnected regions that are involved in learning, reward and habit formation.



G. Hippocampus
Important for consolidation of memory.

B. Nucleus accumbens
This area is involved in stages 1 and 2 of the addiction cycle.

STAGE 3
PREOCCUPATION/ ANTICIPATION

F. Frontal cortex
Responsible for thoughts and actions. The orbitofrontal cortex is thought to play a part in controlling behaviour.

E. Amygdala
Associated with memory and with emotions, notably anxiety and fear.

STAGE 2
WITHDRAWAL/ NEGATIVE MOOD

People with dependencies have compulsive cravings to repeat the addictive behaviour. Drug misuse is thought[2] to alter the function of the frontal cortex (F) and the hippocampus (G) and helps to embed desires even if they have negative consequences.

Chronic exposure to addictive substances and behaviours reduces the number of dopamine receptors in the nucleus accumbens (B), so more of the addictive substance or behaviour is needed to feel normal. Changes to the amygdala (E) circuitry have been tied to the irritability, anxiety and stress associated with withdrawal[1].

BSIP SA/ALAMY

DESIGN BY **MOHAMED ASHOUR**/*NATURE*

27 MILLION
people had problematic drug use[3] in 2012.

183,000
drug-related deaths were reported[3] in 2012.

1 BILLION
or more people smoke, with the majority living in low- to middle-income countries[4].

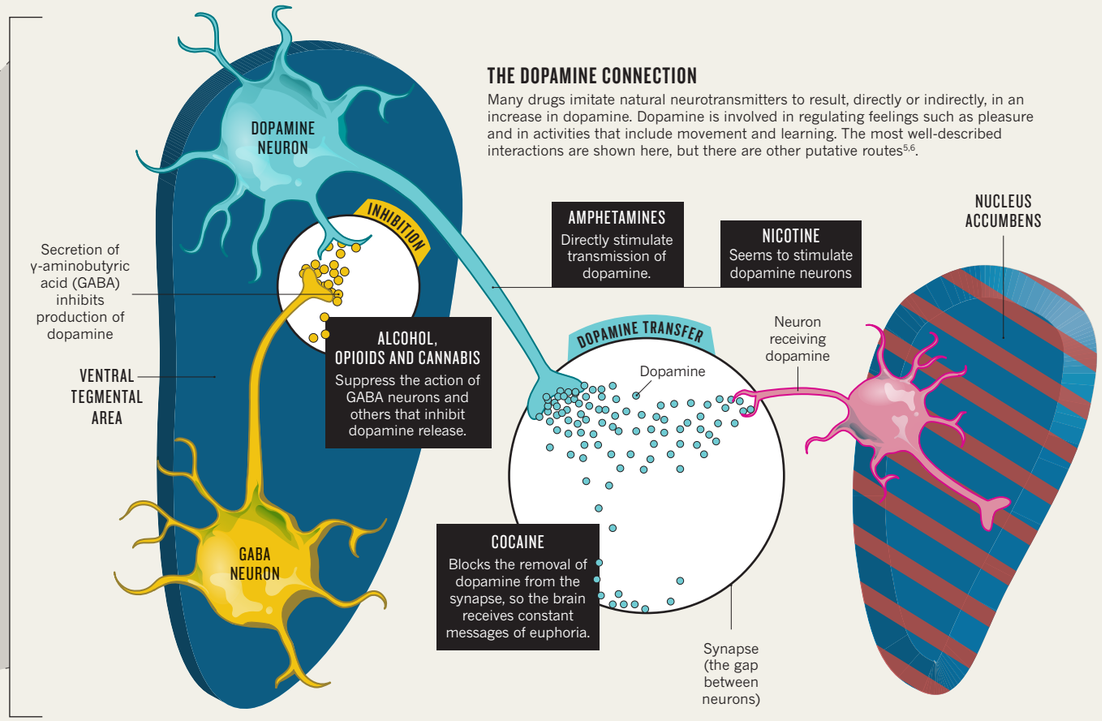
6 MILLION
smokers die every year; more than 5 million of the deaths are directly related to tobacco use[4].

38.3%
of the global population drinks alcohol, with an annual average of 17 litres per person[4].

3.3 MILLION
deaths in 2012 were attributed to alcohol consumption[4].

THE DOPAMINE CONNECTION

Many drugs imitate natural neurotransmitters to result, directly or indirectly, in an increase in dopamine. Dopamine is involved in regulating feelings such as pleasure and in activities that include movement and learning. The most well-described interactions are shown here, but there are other putative routes[5,6].

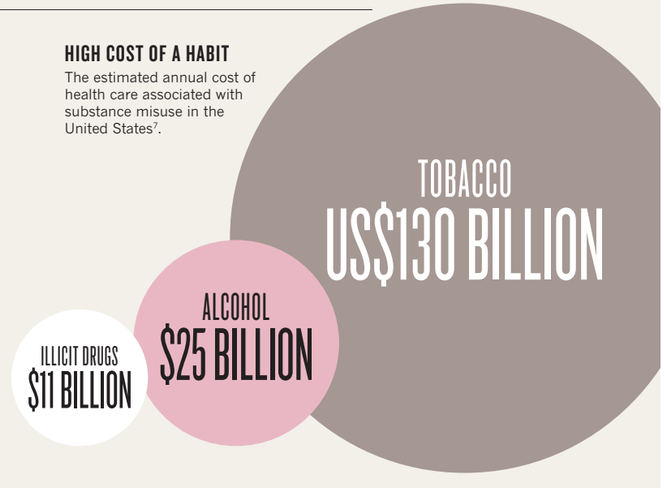


DANGEROUS AGE

Many people have their first experience of drugs at a young age, placing them at high risk of addiction. The developing brain may not form properly under the influence of drugs or alcohol[7].

HIGH COST OF A HABIT

The estimated annual cost of health care associated with substance misuse in the United States[7].



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NORDICPHOTOS/ALAMY

Genetics can influence addictive behaviour later in life, but linking genes to addiction is complicated.

GENETICS

No more addictive personality

The role of temperament, metabolism and development make the inheritance of addiction a complex affair.

BY MAIA SZALAVITZ

One drunkard begets another, wrote the Greek philosopher Plutarch nearly 2,000 years ago, demonstrating the age-old wisdom of the observation that alcoholism runs in families.

But determining exactly what it is that addicted parents pass down to their children has proved difficult. Scientists have searched for decades for an 'addictive personality' that leaves someone vulnerable to drug problems, but without success. Researchers have tried to identify the genes responsible for addiction, and they have examined the role of early exposure to trauma. Yet they have failed to isolate a single genetic factor that reliably distinguishes between the 10–20% of people who try alcohol or illegal drugs and get hooked and the majority who do not.

Now, however, research into genetics and epigenetics is finally starting to shed some light on the causes of addiction — and it turns out that the idea of an addictive personality is a myth. Instead, an enormous number of factors, ranging from early life trauma to genes that code for metabolic enzymes, have a role in how the genetics of addiction unfold. By understanding how these factors fit together, researchers hope to develop strategies for the prevention and treatment of addiction.

Plutarch was right to say that addiction is often a familial trait — and it seems that much of this risk is carried genetically. Joni Rutter, director of the Division of Basic Neuroscience and Behavioral Research at the US National Institute on Drug Abuse in Bethesda, Maryland, says that regardless of the drug involved, about 50% of the risk is genetic, within a range of about 40–60%.

Alcoholism is the most widely researched addiction because alcohol use has such a long history in many cultures. According to George Koob, director of the US National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, the children of people who are dependent on alcohol are 3–5 times more likely to develop the disorder than the rest of the population — and this risk is roughly the same regardless of whether they are raised by their alcohol-dependent parents or adopted by parents who are not dependent on alcohol. The condition is about 60% heritable, he says, adding that this is "reasonably high".

Researchers may have managed to demonstrate that genetic predispositions exist, but linking particular genes or traits with addictions has proved much more difficult. Initial genetic findings are often announced with great fanfare, only to fail in replication or be found to have extremely small effects. "Addiction is very heterogeneous," says Rutter, "There are many ways to get there."

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DRUGS AND DISORDERS

Some temperaments and disorders do raise the risk of addiction, however. About half of people with drug-use disorders have an additional psychiatric diagnosis, often a mood, anxiety or personality disorder. "What we're finding is that the addictive personality, if you will, is multifaceted," says Koob. "It doesn't really exist as an entity of its own." Some people with addictions have many personality traits, others have none, but only a few have all of them.

The personality disorder most commonly associated with addiction is antisocial personality disorder (ASPD), which involves dishonest, manipulative, insensitive and criminal behaviour. These characteristics make up the stereotype of someone with an addiction.

"Antisocial behaviour and alcoholism and drug abuse share a bunch of genetic risk factors," says Kenneth Kendler, professor of psychiatry and human genetics at Virginia Commonwealth University in Richmond, who has studied these links in twins. "That's replicated pretty robustly."

A large epidemiological study found that 18% of people with illegal-drug-use disorders have ASPD[1], as do 9% of people with alcohol-use disorders[2] — much higher than the 4% found in the general population. But although having high levels of antisocial traits is one of the best predictors of substance-use disorders, most people with addictions do not have fully fledged ASPD, and most people with ASPD do not have addictions.

Indeed, many people with substance dependency do not have abnormal levels of antisocial traits at all. However, because breaking the law is itself a diagnostic symptom for antisocial behaviour, this trait will automatically be associated with illegal drug addiction, even if the only laws that are violated are drug laws.

Moreover, being extremely sensitive and overly cautious — essentially the opposite of a callous, impulsive criminal — also raises the risk of addiction, although not by as much.

This suggests both that the stereotype of the addictive personality badly mischaracterizes many people who have a substance-use disorder, and that the genetic risk associated with ASPD does not account for most addictions.

Koob points out that addiction research, like the rest of psychiatry, is increasingly focusing on the genetics that underlie symptoms, such as poor impulse control, rather than on syndromes such as alcoholism or ASPD. "There are specific types of symptoms that have underlying neurobiological bases," he says.

These temperamental or physiological predispositions can potentially develop into many different disorders. For example, impulsivity could lead to a range of problems: it is a characteristic of addiction, ASPD, bipolar disorder, borderline personality disorder and many more. Impulsive behaviour also increases the risk that teenagers will try drugs — and make it harder for them to resist the urge when they want to stop.

By contrast, anxiety can drive addiction in a different way: people who feel anxious may take drugs to cope with social fears, and their difficulty stopping is not through a lack of control, but because of a lack of alternative ways to manage their emotions. This means that programmes must be tailored to individual needs, not based on the idea that all people with addictions are the same.

PHYSIOLOGICAL FACTORS

Personality is not the only way in which genes can influence addiction risk. The strongest and most replicated genetic risk factors for alcoholism involve genes linked to metabolism. These genes encode proteins that convert alcohol into acetaldehyde, and acetaldehyde into acetate. Acetaldehyde is particularly toxic, and genes that cause it to build up in the blood, such as a variant of *ALDH2*, make even light drinking unpleasant. "When it is floating in their system, people don't like it," says Rutter. "They get really hot or feel nauseous." Hangovers and the anti-alcohol drug disulfiram produce pretty much the same effect.

Genes that lead to slow alcohol metabolism are common in the Asian population. A 2006 meta-analysis of 15 studies included 4,500 Chinese, Japanese, Korean and Thai participants who were tested for genes related to the metabolism of acetaldehyde and acetate. The largest protective factor was the *ALDH2* variant, which makes people nine times less likely to develop alcoholism than those with other variants of the gene[3].

But even a gene that provides this much protection can be overridden by environmental pressures. Between 1979 and 1992, for example, the percentage of Japanese people who misused alcohol and who had this variant rose from 2.5% to 13%, as a heavy-drinking culture developed among businessmen that made it much harder to refuse to drink.

One gene that is strongly associated with cigarette addiction, *CHRNA5*, has essentially the opposite effect on smoking risk as *ALDH2* variant has for alcohol. Having just a single variant can double the risk of nicotine addiction[4]. This link is one of the best supported in any disease, not just in addiction, Rutter says.

Researchers initially thought that the *CHRNA5* variant, which codes for a subunit of the acetylcholine receptor that is affected by nicotine, would make nicotine more pleasurable. This would explain why people who smoke and who have the variant smoke more heavily than those without it. But instead, it softens nicotine's initial negative effects. Nearly everyone who has ever smoked reports that the first time is nauseating at best. "When I tried cigarettes when I was a kid, I turned green and hated it," says Rutter.

"Antisocial behaviour and alcoholism and drug abuse share a bunch of genetic risk factors."

But people with the *CHRNA5* variant have a less unpleasant experience, says Paul Kenny, a pharmacologist at New York's Mount Sinai Hospital. "Instead of the drug being more rewarding, what happened was that the aversive effects were diminished," he says.

Investigation of the *CHRNA5* gene in knockout mice showed that it is active in a brain region called the habenula, which is involved in avoidance and aversion, even though it had not previously been strongly linked with addiction. The evidence also suggests that heavy smoking may damage the habenula by harming the neurons that inhibit it. This would create strong negative feelings and distress in those who smoke, which they may try to fight with even more nicotine.

ADDICTION AND DEVELOPMENT

Epigenetic mechanisms, which control the activity of genes by switching them on and off, are also being seen as increasingly important in addictions. Kenny's lab studies these as well and found that one way that addiction can epigenetically 'rewire' the brain is by turning on genes that are normally activated only during brain development.

For instance, a mutation in the *MECP2* gene is known to cause Rett syndrome, a developmental disorder found mainly in girls that is associated with intellectual disability and autistic symptoms. During fetal and childhood development, *MECP2* regulates nerve-cell growth, and then it is silenced. However, when rats are allowed to binge on cocaine, *Mecp2* expression "goes through the roof", says Kenny. Bingeing on cocaine rewires the brain, turning on genes that are usually quiescent in adults.

Other animal experiments have shown that switching off the gene in the reward regions reduces cocaine intake[5]. This suggests that the aberrant learning, which resists the negative consequences of addiction, may be especially deeply engrained. But the actions of *MECP2* have not been studied in normal emotional learning processes in humans that activate similar circuitry, such as falling in love, so it is not clear whether this is unique to addiction. It is also not known whether these genes are normally reactivated during adolescent brain development, which might help to explain why adolescence and early adulthood is the highest-risk period for addictions. Because Rett syndrome is profoundly disabling, those affected are rarely exposed to drugs, so it is not known how the disorder affects addiction risk.

Kenny thinks that other genes linked to developmental disorders may also be important in addictions — and not just in people who have these conditions, whose brains are wired differently from the start. If addiction does reactivate brain-development genes, more common variants could be involved. "We should be looking for genes that cause developmental disorders," he says.

Another factor that affects both epigenetics and addiction risk is childhood trauma. Severe stress in early life is known to dramatically increase the risk of addiction, and the risk increases with greater trauma exposure. For example, a recent study of the entire Swedish population showed that people who as children either lost their parents, experienced a parent's diagnosis of cancer, or witnessed domestic violence had twice the risk of a substance-use disorder later in life compared with those who did not have such stressful experiences[6].

Indeed, some risk genes, such as those linked to the serotonin transporter, may not cause any problems unless there is a stressful early environment. Both chronic stress and addiction can induce some of the same epigenetic changes in stress systems and in those involved with pleasure, which may partly explain why addiction and trauma are so tightly linked. "Early life experience may dictate whether or not those genes or variations in those genes in those different circumstances tend to come into play," says Rutter.

Given the increasing evidence of how varied addiction is, treatment and prevention programmes will need to be significantly updated. Some researchers are trying to work out how to target prevention to particular temperaments, rather than attempt to reach both the anxious and the impulsive with the same message.

"That's the blessing and the curse," says Rutter. "There are many ways to get there, but that also means many ways to intervene." ■

Maia Szalavitz *is a science writer based in New York City.*

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NIK SPENCER

NEUROSCIENCE

Rewiring the brain

Neuroscientists are learning how to repair neural circuits damaged by addiction.

BY KATHERINE BOURZAC

Neuroscientist Woody Hopf opens a cabinet in his alcohol research laboratory at the University of California, San Francisco. Inside is a cage containing a rat that is being taught addictive behaviours. The rat has been conditioned to press a lever to release a squirt of alcohol when it hears a beep. Hopf closes the cabinet so that the rat will not be distracted by the sights and sounds of human visitors. Just as it takes time for people to undergo the characteristic brain changes that enforce addiction, he says, it will take time for his rat to become dependent on alcohol.

Researchers such as Hopf view addiction as a disease of the brain circuits responsible for pleasure, stress and decision-making. "Addictive substances come at the brain in different ways," says George Koob, director of the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) in Bethesda, Maryland. "But in the end, they're activating some of the same circuitry and patterns of behaviour."

For decades, researchers have been mapping the electrical and chemical circuits that underlie addiction. Now they are working on strategies for healing these neural pathways. Imaging studies show how the brain rewires during recovery from addiction. When combined with studies of how the brain develops during adolescence, the work could help researchers to understand how the brain changes that are characteristic of addiction occur, as well as who is most vulnerable and why. This work is rapidly being translated into treatments. By using electrodes and fibre-optic cables, researchers can intervene in neural circuits with great precision, causing animals to lose their taste for alcohol or their interest in cocaine, not just for days but for weeks or months. This work is now being tested in people. Researchers hope that therapies to heal damaged brain circuits will improve the odds of people overcoming addictions.

CROSSED WIRES

Koob divides addiction into three stages, each with its own brain circuit — groups of neurons or larger structures that interact in a characteristic way (see page S46). Addiction starts with the feel-good binge stage, which is fuelled by the brain's reward circuit, particularly at the nucleus accumbens. Withdrawal brings stress, centred in the emotional amygdala. Finally, craving and compulsion circuits extending from the prefrontal cortex keep someone using a drug, regardless of negative consequences. Impulsive bingeing leads to habits as the user needs the drug to feel normal.

The changes to the brain's circuitry are long-lasting, so people trying to give up will often relapse. Even years after recovery, people often start using again when some cue, such as the smell of alcohol or the site of an old hangout, retriggers old patterns. But the changes are not permanent. "The brain can enjoy some recovery, probably through remodelling to override the broken parts," says Edith Sullivan, an experimental psychologist at Stanford University in California.

Some of the physical damage caused by alcohol misuse can be undone. For example, says Sullivan, the brains of people who have misused alcohol for a long period shrink, but some of that brain volume can be regained by sustained sobriety. There is also some functional recovery — even if the pathways are not fully restored, the recovering brain starts to find workarounds.

Sullivan's group has been using functional magnetic resonance imaging (fMRI) to study cognition in those recovering from alcoholism. A cognitive skill the researchers focused on is spatial working memory — the thinking that helps you to remember where you parked your car, for example. Poor spatial working memory is characteristic of alcohol misuse.

Sullivan's research suggests that people recovering from alcohol addiction manage to work around brain damage; in other words, their brains find ways of accomplishing tasks by avoiding using damaged areas and they start to regain their working memory[1]. The group found that alcohol-dependent people who had been sober for at least a month performed as well as non-alcohol-dependent controls on spatial working-memory tasks, but used a different part of the brain to do it. Sullivan gave them a more abstract task than looking for a lost object

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or a parked car, but like those tasks it required visual processing, which can take one of two broad neural paths. Patients without brain damage typically rely on a 'where' pathway to do the task, whereas those in recovery from alcohol dependence activate a 'what' pathway, which tends to be used for recognizing and identifying what we see.

"The next step is to find out how to train a person with brain damage to use these new pathways," says Sullivan. Encouraging the natural recovery process could help people who are dependent on alcohol to make faster progress. Sullivan compares the brain damage from alcohol addiction to that caused by stroke. "Recovery won't take three days, it may take three or six months, or a year," she says. It takes time for changes to occur in the brain when someone develops a dependence on alcohol, and it takes time to undo that.

Sullivan is currently investigating whether there is a cost to this rewiring. She suspects that people in recovery are performing the cognitive steps needed for these tasks sequentially, so they take longer than people without addictions who do the steps rapidly in parallel. The damaged brain has fewer circuits to use, so the brain finds it harder to multitask.

EARLY START

Our understanding of the addicted brain comes from animal studies and from research on people who are already addicted or are in recovery, such as Sullivan's participants. Researchers can only guess at how these changes develop in people. Henning Tiemeier, a psychiatric epidemiologist at Erasmus Medical Center in Rotterdam, the Netherlands, says that the only way to see these changes is to follow people over time. "There is a lot of debate about how harmful substance abuse is for brain development, and you cannot prove it with one brain image," he says.

Two studies, one planned in the United States and one already underway in the Netherlands, could provide some answers. Both will follow adolescents. The adult brain is already formed, although it is still plastic, which is why alcoholism and drug addiction become so engrained, and why the resulting damage cannot be fully repaired. The worry, says Koob, is that the developing brain may not form properly under the influence of drugs and alcohol. Children do not have the cognitive skills to make good choices, making them particularly vulnerable. "Young people have a well-developed reward system but they don't have a good executive control centre," says Koob. The key part of that centre, in the brain's prefrontal cortex, does not finish developing until about the age of 25.

The US National Institutes of Health (NIH), a federal agency that includes the NIAAA and the National Institute on Drug Abuse (NIDA), is currently accepting proposals for the Adolescent Brain Cognitive Development study, which will enrol 10,000 children aged 10 and follow them into adulthood, using neuropsychological tests, brain imaging and surveys, focused specifically on addiction.

A woman receives transcranial magnetic stimulation, a non-invasive therapy that is being used in Italy to treat cocaine addiction.

Tiemeier is working on the Generation R study in the Netherlands, which has a broader focus on fetal and childhood development and has been following 10,000 children from before birth. The youngest are now aged 9, and the oldest are 12, a stage when some will begin experimenting with cigarettes and alcohol.

Generation R is collecting the first set of brain MRI scans from children in the study, and has about 3,300 so far. By continuing to collect them as the children grow, changes over time will become clear. This is by far the largest brain-imaging study on adolescents in the world, says Tiemeier, so it should provide evidence about how substance use affects the developing organ. He does not expect to see major developmental changes associated with the occasional substance use likely to be found in Generation R because it is a general population study, rather than being focused on people who are addicted to a substance. For this reason, such studies need to be as large as possible if they are to find out what damage drug use does, and how it interacts with puberty, when surges of hormones affect behaviour and brain development.

More information will be available when the Generation R data are combined with results from the NIH study, says Nora Volkow, director of NIDA. These studies will provide a better understanding of the brain changes that reflect what she calls "the skeleton of addictive behaviours". Addiction to cigarettes is different from addiction to heroin, for example, but all addictions have a common neurological framework. These studies will show how it grows. They should also yield insight into who is vulnerable and why, and how they might be helped sooner.

But as further research deepens our understanding of addiction as a disease characterized by changes in the brain, researchers and policymakers need to think about better ways to evaluate medications and therapies, says Volkow. Currently, any pharmaceutical treatment for addiction needs to show that the patient is now completely free of their addiction, which is difficult to prove and takes a long time (see page S53). "Rather than ask for an outcome of complete abstinence, shouldn't we evaluate these treatments on their ability to counteract these brain changes?" she asks.

PAINFUL REALITIES

This focus on reversing changes to the addicted brain is leading to therapy ideas that are showing promising early results in animals. Hopf's rat studies, for example, have led to a potential therapy for alcoholism that is focused on countering the compulsion to use despite negative consequences such as the loss of relationships with family and friends, employment or health. Because rats do not fear these outcomes, Hopf uses simpler analogues. In some experiments, alcohol-dependent rats are given extremely bitter alcohol instead of the expected normal flavour, or in the lever-pressing test they occasionally receive a painful electric shock to their paw. "The rats want the alcohol but they are not happy about it," Hopf says.

After years of painstaking research and some luck, Hopf found that a particular group of neurons in the reward-centred nucleus accumbens has a key role in promoting compulsive drinking. This year, he found that an approved drug called D-serine binds to receptors on these neurons, causing them to fire less often, leading the alcohol-dependent rats to drink less[2]. It seems to work by disabling the compulsive behaviour — by turning off the power to deny painful realities. Rats that experience bitter or painful consequences drink less when given the drug. Rats have no such negative consequences to fear and are not affected by the drug and drink as normal.

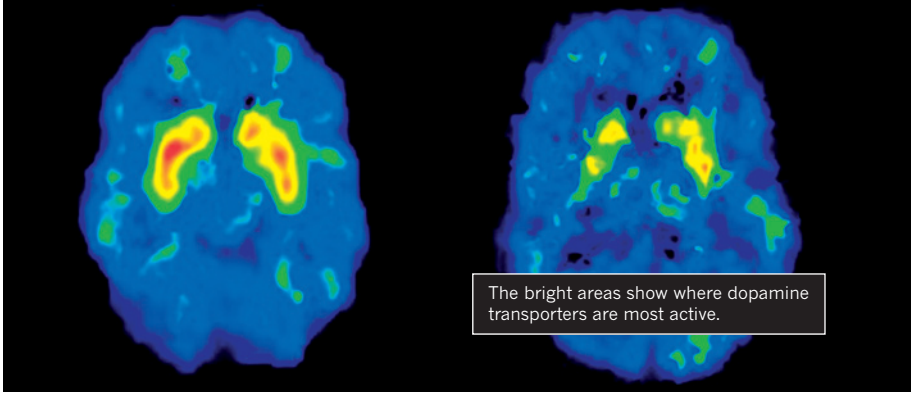
"There is a lot of debate about how harmful substance abuse is for brain development."

The nucleus accumbens and a denial of the reality of the situation are involved in multiple stages of addiction, according to Koob, and have a role in both intoxication and the withdrawal process. Hopf is now writing up a plan for a clinical trial of D-serine.

Other techniques target addiction circuits by using physical interventions, rather than drugs. Researchers at the University of Geneva in Switzerland led by neurologist Christian Lüscher have used a method called optogenetics to target a particular group of cells and receptors involved in cocaine addiction in mice. Optogenetics allows researchers to turn off gene expression precisely by shining light into the brain through implanted optical fibres. When Lüscher's group

METHAMPHETAMINE MISUSE

Brain scans of someone who has never tried the stimulant methamphetamine (left) and of a user (right). Use of the illegal drug affects dopamine transporters in the brain. Eventually, users need more drug to achieve the desired effect. Dopamine is a neurotransmitter that plays a key part in the brain's pleasure pathways.



The bright areas show where dopamine transporters are most active.

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used the method to calm a group of overactive dopamine-receptor neurons in the nucleus accumbens, the mice stopped seeking cocaine[3].

However, optogenetics cannot be used to treat people. The method first requires genetic engineering to render the target cells sensitive to light, and it is not yet possible to safely implant optical fibres in the human brain.

STIMULATING RECOVERY

Instead, Lüscher's team is attempting to emulate the effects of optogenetics by using methods that translate better to the clinic. They are developing a variation on deep-brain stimulation (DBS), a technique that uses an electric current to silence overactive neurons, which is commonly used to treat movement disorders such as Parkinson's disease. By careful placement of the electrodes, clinicians can target DBS to a particular region in the brain. Researchers have tried using it to treat addiction in people, but results have been mixed.

Lüscher is combining DBS with drugs to block particular receptors in the rat brain, making it possible to silence specific cell types. First they implant an electrode in the nucleus accumbens. Then they use a drug that blocks the neurons' dopamine receptors. Finally, they switch on the electrode for ten minutes. The effects of DBS for treating Parkinson's are transient: when the electric field is turned off, the tremor returns. But Lüscher's combined therapy had a longer-lasting effect[4]. After 10 minutes of stimulation, the rats exhibited normal behaviour for the following 21 days. Lüscher thinks this means that the treatment may be repairing part of the circuit that was damaged by addiction. He says that the group's next step will be to test this approach in primates, or possibly take it to clinical trials.

This demonstration of an apparently long-term reversal of drug-related behaviour is "a miracle", says Jessica Wilden, a neurosurgeon at the Louisiana State University Health Center in Shreveport. Could this lead to a therapy in which you give a patient a pill and a day of brain stimulation and then they are drug free? "In a small way that's what they're showing," she says. But doing it in people will be harder, she warns.

Wilden is investigating whether DBS can be used to treat methamphetamine (meth) addiction. Meth affects dopamine receptors (see 'Methamphetamine misuse') and is a growing problem, particularly in Iran and in the southern United States, often for military veterans. Unlike other drugs, which tend to be misused mostly by men, meth use is equally common in women, and has a burden on children because women tend to be the primary caretakers, says Wilden.

> *"It's up to us to figure out who's getting better and why, and how many sessions it takes."*

"I'm trying to set up a stable model of meth abuse, abstinence and relapse in rats, and then try DBS treatment," says Wilden. It is a huge challenge. The drug is a potent stimulant, with effects lasting for 16–20 hours in the rats; the animals become agitated and stressed, and get tangled up in the equipment used to administer the drug and the cables that connect them to the DBS system.

Although DBS is a helpful research tool, Wilden and Lüscher both doubt whether it can be widely used to treat addiction — and Wilden's work with meth illustrates the difficulties. The therapy is expensive, invasive and requires patients to care for the implants and to return to the clinic for regular follow-ups. Those motivated to overcome alcoholism might be able to do it. But people with more destructive addictions, particularly to meth, are less cooperative and have high rates of homelessness, making the treatment even less suitable. "The deep-brain stimulator is a pacemaker, with wires going under the skin into the chest where they connect to a battery," says Wilden. "That's a lot of metal, especially in people who are fragile. There's no way I can implant this in someone living on the streets."

Lüscher and Wilden plan to validate their interventions with optogenetics and DBS in animals, and then adapt the results to clinically realistic techniques. The most likely candidate is transcranial magnetic stimulation (TMS), which uses a magnetic field to stimulate electrical activity in neurons deep in the brain. One advantage is that TMS is non-invasive: treatment simply involves wearing a magnetic helmet for a few minutes. It is currently used to treat depression and migraines.

So TMS is more patient friendly, but it is also more mysterious — researchers do not know why it works. Furthermore, it has poor spatial precision, which frustrates neuroscientists who want to target specific brain locations. But this might not matter, says Antonello Bonci, a clinical neurologist and scientific director at NIDA.

In 2013, Bonci published a paper describing how his team had used optogenetics to reactivate an area of the prefrontal cortex that was abnormally quiet in cocaine-addicted rats[5]. The treated rats lost interest in pressing a lever to get cocaine. A few months later, Luigi Gallimberti and Alberto Terraneo at the University of Padova in Italy started using TMS to target the equivalent area in the brains of people addicted to cocaine. They have since been successfully using the technique to treat such people.

Bonci says that the results are anecdotal, but exciting: most people who stuck with the treatment for a few weeks have now been clean for several months, and testify that they do not even think about cocaine any more, he says. With this black cloud lifted, they are able to enjoy food, sex, reading, family time and all the other good things in life. Bonci is now working with the Italian group to design a double-blind clinical trial, and is collaborating with another group to work out how the TMS works. "It's up to us now to figure out who's getting better and why, and how many sessions it takes," he says.

In addition to TMS, the Italian patients also received supportive medical care and psychological therapy. Even with brain stimulation or medication, people still need emotional support, as well as therapy "to identify triggering cues and memories, and practise making new grooves of thought", says Hopf. But with tools such as DBS and TMS, neuroscientists' deepening understanding of the circuitry of addiction is now being translated to the clinic much more rapidly than ever before.

"For the first time in the history of neuroscience, we can think about translating basic science to the clinic in months, as opposed to the 15 years it can take for drug development," says Bonci. Thanks to the new technologies, he says, "we're close to a treatment". ■

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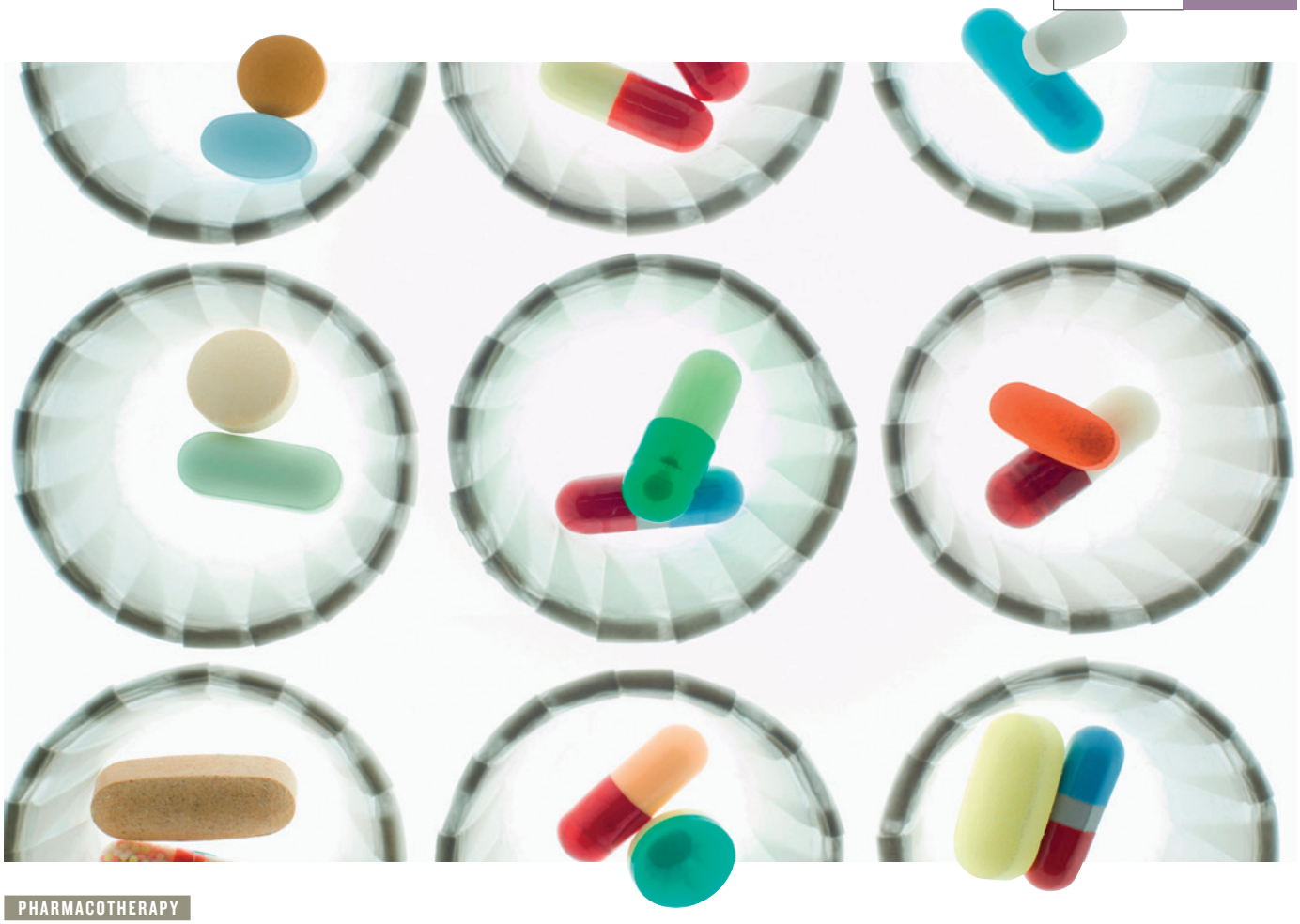

IMAGE SOURCE/GETTY

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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PERSPECTIVE

Beyond the neural circuits

To treat addiction, people need help to develop psychosocial skills in addition to taking medication, says **Kenneth E. Leonard**.

We have known many of the fundamental aspects of addiction for some time. Individuals with addictions gradually give up other pleasures in favour of alcohol or other drugs; they experience cognitive difficulties and find it hard to stop thinking about their substance, and they often fail to control its intake or to cope without it. Remarkable progress has been made in identifying neurological factors and changes associated with these behaviours; this in turn has led to pharmaceutical treatments. However, although neurological aspects are crucial, they are not sufficient to explain, prevent or ameliorate addiction.

The development of an addiction is a continuous process, beginning with occasional substance use followed by habitual heavy use and culminating with seemingly incessant or episodically excessive use. Throughout this process, there are neurophysiological changes that occur. After a substantial period of frequent, heavy and patterned use, the term addiction is applied. The concept of disease, representing the underlying neurophysiological changes that occur, is commonly invoked to explain the addictive behaviours. But addressing substance use also requires that we recognize the social and psychological processes that underlie the development of addiction. These processes remain influential even as the circuitry of the brain adapts to the escalating use of a drug. In this sense, addiction is more than a disease and involves more than the brain: it is a systemic behavioural disorder arising from and maintained by psychological, social and biological processes operating both independently and in concert.

In most cases, the development of addiction emerges from an acquired pattern of substance use that serves some motivational function: enhanced positive feelings or states, and reduced unpleasant feelings or states. Individuals who expect that a substance can improve these moods are more inclined to use that substance. Whether someone progresses to addiction depends in part on how well that substance meets those expectations. Over time, sustained excessive substance use can increase negative emotions and reduce the impact of positive ones through the neurophysiological changes to the brain[1], potentially magnifying the importance of the substance to the individual. But it is important to recognize that increased negative emotions and decreased positive emotions also arise through the impact of use on the individual's cognitive capabilities and the social environment. And that progression into addiction can be impeded by the availability of options other than drugs for enhancing positive states and for coping with negative states.

Furthermore, when it comes to quitting, changes in brain function that have been caused by an addiction do not always lead to cravings, loss of control or relapse. Individuals are able to adjust their intake of a substance or abstain altogether in response to environmental rewards. For example, studies have shown that providing prizes or vouchers for goods or services can increase abstinence from cocaine, tobacco, alcohol and opiates[2]. Moreover, relapse is influenced by intra-personal processes, including self-efficacy, expectancies about the effects of alcohol, negative emotions and coping abilities. These psychosocial problems remain, even if the underlying neurophysiology of the brain can be rectified.

ADDICTION IS **MORE THAN** A DISEASE AND INVOLVES MORE THAN **THE BRAIN:** IT IS A SYSTEMIC **BEHAVIOURAL** DISORDER.

A NETWORK OF SUPPORT

An essential element in addressing these issues for each addicted individual is to identify and improve their relationships with friends and family, because these connections directly and indirectly affect both the addictive process and recovery[3]. Addiction makes its mark on a person's social life: he or she may lose friends, alienate family and develop a new social network that supports their habits. The social environment has a significant effect on substance use. Research has demonstrated that marriage and a satisfying marital relationship reduce relapse among men with alcohol dependence and that incorporating relationship counselling into treatment for alcoholism leads to improved outcomes, such as abstinence[4]. Conversely, a critical partner, anger and psychological aggression are associated with poorer outcomes such as relapse[5]. The impact of interpersonal relationships also extends to adult peers and the broader social network, both in terms of general support as well as specific support for abstinence. A network of supportive friends and family are key elements to recovery[6].

Relieving and perhaps reversing the neurophysiological aspects of addiction with medication is an important element of treatment. However, advances in medication for treatment will not, on their own, cure addiction. Individuals must also develop the skills and resources to cope with the inevitable negative and stressful experiences of everyday life and to experience meaning and pleasure in social and intimate relationships without the use of the addictive substance. Although these coping processes are represented in the brain, they are most effectively addressed through treatments such as cognitive therapy or training to improve coping skills that focus directly on the psychosocial aspects of addiction. The development and testing of psychosocial strategies to develop these skills and resources must remain an essential aim of research to help prevent and treat addiction. ■

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BRUNO VINCENT/GETTY

CONTINGENCY MANAGEMENT

Why it pays to quit

Giving a gift or a cash incentive to someone to give up an addiction sounds like a prize for behaving badly, but the practice works. The real challenge is deciding who should pay for it.

BY SUJATA GUPTA

Anna smokes almost two packs of cigarettes per day. Her brand of choice is Marlboro, full flavour, no menthol. Anna is 14 weeks pregnant, so that is what her fetus smokes, too.

Aged 33 with short, curly blondish-red hair, and a hot-pink iPhone dangling from the pocket of a hooded sweatshirt, Anna (not her real name) is at the University of Vermont's Center on Behavior and Health in Burlington to learn about a smoking-cessation study for pregnant women. She knows that smoking is bad for her baby. She also knows that she cannot afford the habit, which costs her more than US$7,000 each year — approximately half of what she earns as an in-home childcare provider.

At the laboratory, Anna learns that she will be randomly assigned to one of two treatment groups. Treatment A will involve three brief educational sessions and nine phone calls from a trained smoking-cessation coach. At each visit, including the one today, she will earn $50; completing all 9 calls will earn her an additional $65. She will also receive money for having ultrasound scans taken of her baby at 30 and 34 weeks and for participating in 8 additional assessments in the year following the birth of her baby. Participants receiving treatment A can be compensated by up to $655 for their time.

In treatment B, the 'incentives for abstinence' condition, the protocol for participants is the same as for those in treatment A, but they are also screened for drug use through frequent breath and urine tests at the clinic, and are rewarded when their results are negative. The women earn gift cards that can be used to pay for things such as baby clothes, films, fuel for their car and groceries. In addition to the $655, participants in treatment B can earn $1,200–$2,400 in incentives. "You guys definitely got the right idea, throw money at people," says Anna, who is hoping that she will be assigned to treatment B.

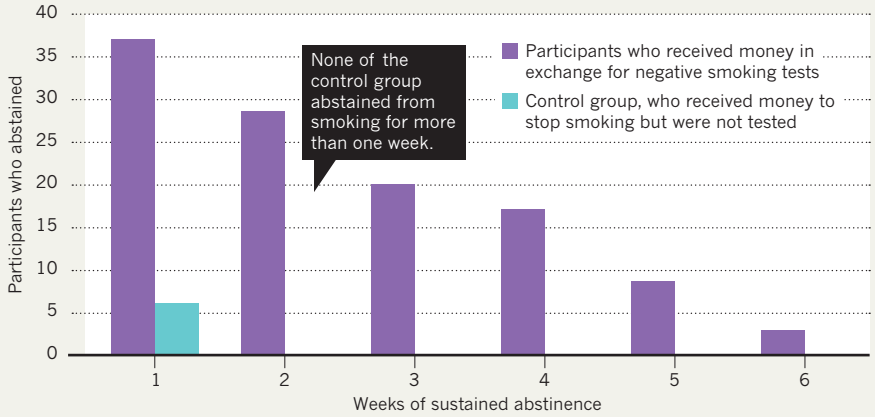
Giving tangible rewards to reinforce positive behaviours, such as abstaining from drugs, underlies a field known as contingency management. Studies[1] have shown that rewards that are contingent on good behaviour help people to refrain from addictive habits, including taking drugs or eating unhealthy food. The rationale is that financial incentives activate the same reward systems in the brain as addictive behaviours.

Moreover, even though quitting an

NATURE.COM
A film on a new treatment for addiction is at:
go.nature.com/e1gqkk

SMOKE FREE

In a contingency-management trial, participants who received monetary rewards in exchange for negative smoking tests were more likely to abstain from the habit than those who were paid but were not tested.



SOURCE: STOOPS, W. W. *ET AL. DRUG ALCOHOL DEPEND.* **105**, 56–62 (2009).

addiction improves a person's life in the long run, research has demonstrated that people are biased towards immediate gratification[1]. In other words, receiving an instantaneous cash reward is more desirable than saving the money that would have been spent on drugs and medical care over a long period.

But despite proven results, treatment schemes like this are rarely offered. "I think in some ways that relates to the controversial nature of it," says Nancy Petry, an addiction specialist at the University of Connecticut in Farmington. "You're providing tangible rewards to people who were engaging in illegal or unhealthy behaviours." To help to change that perception, an array of scientists are working on ways to improve contingency management by tweaking how it is offered, in the hope that it will finally cross the boundary to an acceptable and commonplace treatment.

OFFSHOOT OF THE COCAINE EPIDEMIC

Contingency management arose out of the work of psychologist B. F. Skinner, who challenged the idea that all behaviours stem from free will. Instead, through experiments on rodents that he began in the 1930s, Skinner showed that behaviours can be reinforced by systematic punishments or rewards.

Addiction seemed to be a suitable disease on which to test Skinner's ideas. Addiction is "a concrete behaviour, one that's very difficult to manage, but can be very easily measured", says Maxine Stitzer, an addiction-treatment researcher at Johns Hopkins University in Baltimore, Maryland.

Case studies dating to the 1960s and 1970s provided tantalizing evidence[1] that financial and other incentives might help people to quit drugs or lose weight. But the field really took off in the 1980s with the rise of the cocaine epidemic. Many pharmacological and psychosocial interventions failed, but financial incentives dramatically increased cocaine abstinence.

In the 1970s, Stitzer, one of the first researchers to study contingency management with drug users, and her colleagues developed a simple protocol for people who were addicted to a substance: rewards for negative drug tests and nothing for positive tests. She experimented by providing people who are addicted to opiates with special privileges, such as letting them take methadone (a medication used to control cravings) at home rather than at a clinic. In one study[2], one group of patients could automatically take methadone home, but another group had to earn the privilege through abstinence from other drugs. Over a four-week period, Stitzer found that people who had to earn their privileges were four times more likely to abstain from drugs (32% abstinence versus 8%) than those who received automatic privileges.

"Vouchers allow the individual to express what's rewarding for them."

But researchers soon began to favour cash incentives. "Everybody likes money," Stitzer says. "And more importantly, you can vary the amount." Also, unlike Stitzer's methadone approach, which was specific to people who were dependent on opiates, cash incentives can be applied to any addiction. In the 1990s, Stephen Higgins, director of the centre that Anna visited in Vermont and a former postdoc in Stitzer's lab, developed a financial incentive programme for cocaine addiction. Outpatients with negative test results received vouchers that could be redeemed for retail items. By giving vouchers instead of cash, says Higgins, patients can buy something meaningful without using the money for drugs. "What's a reward for you might differ a lot from what's a reward for me," Higgins says. Like cash, "vouchers allow the individual to express what's rewarding for them".

By the 2000s, Stitzer had combined the methadone take-home privilege with vouchers. In one experiment[3], she divided cocaine users on a methadone treatment programme into three groups: one group received take-home methadone privileges for negative test results; a second received the take-home privileges plus vouchers totalling up to $5,800 over 52 weeks; and a third followed the normal protocol of taking methadone at the clinic. Both sets of people with the take-home privileges submitted three times more drug-negative urine samples than the normal maintenance group over a one-year period. Furthermore, those who received vouchers showed longer periods of abstinence.

A number of meta-analyses[4] have shown that incentives work considerably better than more conventional addiction-management programmes, particularly when vouchers are added to the protocol. What is more, says Higgins, vouchers are the only treatment so far that works for cocaine users.

Contingency management is popular in helping people to stop smoking, an addiction that is seen as more amenable to low-intervention treatment than addictions to other drugs, such as heroin or cocaine. To give an example, in Scotland's deprived Greater Glasgow region, 20% of women report smoking during pregnancy. David Tappin, who specialises in clinical trials for children at the University of Glasgow, recruited more than 600 women, all of whom smoked. At their first prenatal appointment, he randomly assigned half to the routine smoking-cessation programme run by the UK National Health Service (NHS), and the others to the service plus the possibility of receiving up to £400 (US$610) in shopping vouchers. By the end of their pregnancies, Tappin found that just shy of 9% of women in the control group had stopped smoking, compared to almost 23% in the incentive group[5].

REAL-WORLD CHALLENGES

But moving contingency management from the lab to the real world has proved to be challenging. The problems are multifold. For one, asking participants to travel frequently to a drug-testing centre is often untenable. Even though Anna lives only 8 kilometres from the University of Vermont, getting to the lab took her one hour by bus. Then there is the issue of acceptability. To many taxpayers, giving money to people addicted to a drug seems baffling — or morally wrong. But the real hitch is: who should pick up the tab?

Financial incentives make sense in closed health-care systems in which a single entity — such as the NHS — covers all of an individual's health costs, says Petry. Although the initial pricetag may seem high, contingency management is cheaper than treating addiction with more conventional programmes down the line. It can also thwart the sorts of chronic health problems that can arise from prolonged use of a given substance.

Tappin estimates that it would cost the

ALLISON KURTI

NHS £400,000 to roll out a contingency-management programme for all pregnant women who smoke in and around Glasgow. By comparison, he says, the NHS already spends £4.6 million per year on cholesterol-lowering statin drugs in the same region. Compared to other treatments or procedures already in place, "it's quite a cheap intervention", he says — and cheaper still if it improves the long-term health of mothers and their babies.

In countries such as the United States, which lack a single-payer health-care system, contingency management can be more difficult to implement. But it can work for specific groups. For instance, the Department of Veterans Affairs, which covers all the health needs of military veterans, adopted a contingency-management programme across its outpatient substance-abuse clinics in 2011 (Petry is an independent consultant for the department). Individuals with negative test results are rewarded with gift cards to the Veteran's Canteen Service, which sells numerous goods at a discount.

GETTING CREATIVE

Researchers have also started to experiment with alternative methods to overcome the cost and delivery barriers associated with giving every participant a high-value reward when he or she has a negative drug test.

One way to reduce costs is to encourage people to buy into an incentive programme with their own money, a practice known as a deposit or commitment contract. That money then has to be 'earned' back through negative urine tests. In a study published this year[6], researchers put the concept to the test with more than 2,500 employees of CVS Caremark, a pharmaceutical chain based in Woonsocket, Rhode Island, plus their relatives and friends who wanted to stop smoking.

They divided those individuals into several groups, including one whose members could receive $800 if they abstained from smoking for six months and another group whose members had to pay $150 to participate. They could then earn back that $150 plus a $650 reward if they did not smoke for 6 months.

The researchers found that both the reward and deposit groups quit at higher rates than those receiving more conventional care, such as nicotine replacement therapies and counselling. Moreover, those who paid the $150 deposit were twice as likely to quit than those receiving a straightforward reward. But there was a catch. Because participation was optional, 90% of those assigned to the rewards group agreed to give abstinence a try, compared with just 14% in the 'penalty' group. "The data are overwhelming in showing the limitation of deposit contracts. The vast majority of folks will not join them," Higgins says. "The straight incentive programme is the way to go."

Other solutions have proved to be more successful. For instance, the Department of Veterans Affairs uses a 'fishbowl' model developed by Petry in which participants with negative test results are eligible to draw a slip of paper from a bowl in much the same way as a raffle. Rather than giving everyone the same lump sum, prizes on the slips vary — half of the slips carry no reward, others are for vouchers ranging in value from $1 to the cost of a new TV. The fishbowl model substantially reduces costs, Petry says, with results rivalling those seen with conventional voucher programmes[7].

Vouchers as a reward for a negative drug test.

Researchers at Johns Hopkins have developed the 'therapeutic workplace', in which jobseekers who abuse substances and present negative drug-test results are rewarded with the opportunity to work and earn wages.

> *"You're providing tangible rewards to people who were engaging in illegal or unhealthy behaviours."*

Others are looking at ways to ease the delivery of contingency management. Jesse Dallery, a behaviour analyst at the University of Florida in Gainesville, has developed a model in which people who smoke are sent a carbon monoxide testing kit in the post. Using a web camera or smartphone, participants video themselves blowing into the machine and holding up the value. Negative results are rewarded with vouchers, or by returning a cash deposit made by the participant (see 'Smoke free').

Dallery's former graduate student Bethany Raiff, a behaviour analyst at Rowan University in Glassboro, New Jersey, is now looking to couple that online test with video games — one for smartphones and one for Facebook — in which people who smoke earn rewards in the game instead of money or vouchers. She has partnered with video-game designers who specialize in making health-focused products. "You have to make the games fun and addictive," Raiff says — and then corrects her choice of word — "but not in a bad way".

Each of Raiff's games lasts about five minutes — the time it takes to smoke a cigarette. To stop people smoking while playing, Raiff and her colleagues are incorporating preventative strategies, such as two-handed playing. In the long-term, Raiff would like to work with insurance companies who have a vested interest in keeping clients healthy. Some, she notes, already cover preventative care, such as gym memberships.

BACK IN VERMONT

Although contingency management is more effective than conventional treatments, similar issues arise in both approaches — patients struggle to stay abstinent. Bolstered by his short-term success in getting people who have become dependent on cocaine to quit, Higgins began searching for a population in which short-term changes could produce substantial benefits.

Twelve years ago, Higgins began his research into helping pregnant women who smoke to end their habit. Even short-term abstinence, he reasoned, could dramatically improve their babies' health. So far, his research has shown that women in the incentive group carry larger fetuses, as measured by ultrasound scans at 30 and 34 weeks, and give birth to larger babies. Now, he is offering incentives to women to continue to abstain from smoking for three months after they give birth, and is considering extending that time frame. His research indicates[8] that providing a reward after childbirth helps women to breastfeed for longer and decreases the risk of postnatal depression.

Back at the centre, Anna finds out that she is in treatment A and will receive compensation for her time but no extra incentives. "There are benefits to both," Allison Kurti, the postdoc running the study, tells her. "If you've got a real busy schedule, it's kind of nice if we don't have to see you as often. Some people find that more convenient." Convenient, perhaps, but as effective? Anna's not so sure. Just as Skinner observed in rodents so many decades ago, rewards and reinforcement really are key. "I know if someone's on my ass," Anna says, "I'm more apt to do it." ■

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NIK SPENCER

TECHNOLOGY

Barriers to misuse

Ingenious pill formulations and the latest manufacturing technologies are helping to stem the tide of painkiller addiction.

BY ELIE DOLGIN

Mary Marcuccio's life was turned upside down by drug misuse and addiction. Her son, now 26, started with alcohol and marijuana. Then came cocaine and hallucinogens. By 14, he was stealing prescription painkillers from friends' medicine cabinets, crushing and snorting the pills to achieve a quick and euphoric high. Within one year, he had graduated to injecting heroin.

This progression is "so stereotypical", says Marcuccio, founder of My Bottom Line, a Florida-based consulting business for families dealing with substance misuse. According to US survey data, 77% of heroin users say that, like Marcuccio's son (who remains addicted to heroin), they misused prescription opioids — derivatives of natural or synthetic forms of opium or morphine — before trying heroin.

But substance-misuse specialists think that this chain of addiction might be broken with the aid of the latest manufacturing processes to make powerful opioid pain medication more resistant to various forms of tampering. Such drug preparations could also save lives. The death toll from misusing prescription opioids has skyrocketed around the world in the past 20 years, with opioid-linked overdoses exceeding fatalities from road accidents or deaths from heroin and cocaine in countries including the United Kingdom, the United States and Australia. "It behooves us to make a greater effort at creating unabusable formularies," Marcuccio says.

Fortunately, the science and manufacturing of misuse-deterrence are advancing rapidly — and so is the political climate. In the United States — a country that consumes more than 80% of the global opioid supply — politicians are beginning to craft bills to incentivize the development of misuse-resistant formulations. "The idea is to transition the market," says Dan Cohen, chair of the Abuse Deterrent Coalition, a network of advocacy organizations, technology manufacturers and drug companies based in Washington DC. "There are now so many different abuse-deterrent formulations that are either in products or in development that there's enough variety out there for any product to be able to put abuse-deterrence in it."

THE NEW GUARD

Some of the latest tablet formulations are so hard that even a hammer-blow cannot pulverize them. Many pills form a gelatinous goo when dissolved that renders them difficult to inject. Others contain reversal agents that negate the high when the tablets are messed with. The idea is to create pain-relief medicines that are less prone to misuse yet work when taken as directed.

The technologies in place today are not ironclad, though. A quick perusal of online message boards and videos reveals numerous tips on how to circumvent the defences of even the most reinforced tablets. What is more, not all prescription opioids on the market are misuse-resistant. "We're still in abuse-deterrent formulations 1.0," says Richard Dart, director of the Rocky Mountain Poison and Drug Center in Denver, Colorado. But, he adds with a touch of hyperbole, "there are a zillion abuse-deterrent formulations coming".

Manufacturers have been worried about prescription-drug misuse for decades. When the first controlled-release formulation of the opioid oxycodone hit the US market 20 years ago, the drug's manufacturer, Purdue Pharma of Stamford, Connecticut, touted the twice-a-day medicine as a less-addictive alternative to the faster-acting painkillers that provide a big opioid hit all at once. In reality, however, Purdue's longer-lasting pill, sold under the trade name OxyContin, had the opposite effect.

Drug users easily defeated OxyContin's time-release mechanism by crushing or chewing it. Just one OxyContin could contain more oxycodone than a dozen instant-release pills but no extra ingredients such as paracetamol that make people sick if taken at high doses. OxyContin quickly became the number one addiction problem in many parts of the world, particularly in the United States and Australia. The drug was so popular among the rural poor of Appalachia in West Virginia and Kentucky that it earned the street name 'hillbilly heroin'.

Purdue set to work to guard against some of the worst forms of misuse. In 2010, the company introduced a misuse-averting version of OxyContin that contains a polymer made of long-chain molecules. This makes the new tablet more difficult to crush — although it is not rock hard. "It behaves more like plastic," explains Richard Mannion, executive director of pharmaceutics and analytical development at Purdue. "So, it will deform if subjected to force, but it doesn't break into a powder easily." The revised formulation is thus much harder to snort. Plus, Mannion says, when combined with water, the polymer forms a gummy substance that makes it very difficult to draw into a syringe (although misuse is still possible).

PURDUE PHARMA LP

The original OxyContin pill could be crushed (left) and snorted; and (right) the new tamper-resistant form.

The new version of OxyContin has proved to reduce the incidence of therapeutic misuse. A study[1] of more than 140,000 people treated at rehabilitation centres across the United States found that misuse by injection, snorting or smoking declined by two-thirds in the two years after the reformulation. In light of these results, in 2013, Purdue won the right from the US Food and Drug Administration (FDA) to describe the misuse-deterrent benefits of OxyContin on the drug's label and to make marketing claims accordingly. The FDA said at the time that any future generic versions of OxyContin would have to incorporate equivalent misuse-deterrent protection. (In April 2015, the FDA released a guidance document outlining the types of study needed to establish misuse-deterrence, but the report stopped short of addressing generic opioid products.)

Other painkillers that now have FDA-approved misuse-deterrent labelling include Embeda, an extended-release morphine from New York-based pharmaceutical firm Pfizer, and Targiniq, another long-acting preparation of oxycodone from Purdue. Both contain antagonist agents — offsetting ingredients that remain largely inactive when the drugs are taken as directed, but that will annul the opioid's effects if the drugs are snorted or injected.

"These new technologies are showing some positive results," notes Robert Jamison, a pain psychologist at the Brigham and Women's Hospital Pain Management Center in Chestnut Hill, Massachusetts. In Australia, for example, OxyContin users accounted for more than 60% of the visits to the Medically Supervised Injecting Centre in Sydney. After the tamper-resistant version of OxyContin hit the Australian market in April 2014, a team led by Louisa Degenhardt, a drug-addiction researcher at the University of New South Wales in Sydney, found[2] that the number dropped to 5%. In the United States, levels of opioid misuse have decreased from their peak in 2010, when the new formulation of OxyContin arrived on the market. Rates of opioid dispensing and overdoses have dropped appreciably, too.

These public-health benefits come with an economic bonus. According to calculations from Noam Kirson and his colleagues at Analysis Group, a consulting firm in Boston, Massachusetts, the reformulated OxyContin has reduced misuse-related medical expenses and indirect societal costs by more than US$1 billion per year in the United States[3]. "These are substantial savings," Kirson says.

OLD HABITS DIE HARD

Despite the gains, the misuse-deterrence field still has a long way to go. Drug users who have been thwarted by one technology can switch to another prescription medicine that lacks anti-tampering defences. That is what happened in rural Appalachia following the introduction of reformulated OxyContin. Opioid misusers simply started snorting and injecting the less potent immediate-release preparations of oxycodone, most of which lack misuse-deterrence characteristics. "It's kind of a whack-a-mole situation," says Jennifer Havens, an epidemiologist at the University of Kentucky Center for Drug and Alcohol Research in Lexington.

Plus, even with the latest physical defences it is still possible to get high by swallowing lots of OxyContin or Embeda pills at once. Preventing oral misuse requires a different approach — which a company called Signature Therapeutics, based in Palo Alto, California, is pursuing.

> ***"It behooves us to make a greater effort at creating unabusable formularies."***

Signature Therapeutics' technology uses prodrugs, which are inactive until they undergo the appropriate chemical conversion in the body. When these pills are taken by mouth as directed, a digestive enzyme in the gut called trypsin releases part of the prodrug, initiating the process of opioid drug release. But because trypsin is not found elsewhere in the body, the prodrug remains inert when injected, snorted or smoked. Signature Therapeutics has already tested its painkilling hydromorphone prodrug in a phase I trial of healthy volunteers; the company plans to begin evaluating its oxycodone prodrug in human studies later this year.

Prodrugs alone do not prevent excessive pill-popping, but scientists at Signature Therapeutics have another trick up their sleeves. If the prodrugs look promising in the clinic, the company will add a second compound that blocks trypsin activity. This might seem counterintuitive, but it is all about threshold levels. The amount of trypsin inhibitor found in one or two pills will not interfere with the prodrug modification, but a handful of pills collectively contain enough inhibitor to shut down the conversion process. With this approach, Signature Therapeutics can create either extended-release or immediate-release opioids. Bill Schmidt, chief medical officer at the company, says that the potential of these drugs is "maximum therapeutic benefit with very low abuse liability".

New formulations such as these could ultimately prove to be almost addiction-proof, but they are not cheap. And their benefits might not be fully realized unless authorities require drug companies to include them. "The problem with abuse-deterrence right now is the lack of incentives," Cohen says.

Lawmakers in the US House of Representatives previously proposed legislation that would have barred the approval of any new pharmaceuticals that did not use formulas resistant to tampering. That bill died in committee, but, according to Cohen, revised legislation should be introduced again "soon". Individual US states have also begun to pass laws that compel pharmacists exclusively to dispense, and insurers to cover, misuse-deterrent versions of opioids unless instructed otherwise by a physician.

Ultimately, the success of long-term efforts to rein in opioid addiction could depend on the regulations surrounding generic painkillers. In December 2014, Australia allowed the sale of a generic long-acting oxycodone without misuse-deterrence characteristics. Degenhardt, who is monitoring the drug-misuse data, worries that many of the gains of OxyContin's reformulation will now be lost. By contrast, US authorities have already said that they will not approve such a product.

All of these efforts should help to bring down the number of overdose deaths and also prevent experimentation with prescription pills. In her study population in rural Appalachia, Havens has met so many young people like Marcuccio's son — for whom easily misused opioids were the gateway to addiction — that she has reached a simple, but absolute, conclusion: "The only way that abuse-deterrent formulations are going to work is if they're all abuse-deterring," she says. "It can't just be piecemeal. It's got to be all or nothing."

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PERSPECTIVE

Behavioural addictions matter

More research, and dedicated funding, is needed to understand and successfully treat compulsive habits, says **Marc Potenza**.

YALE UNIV.

What behaviours can be considered addictions? Gambling, gaming, Internet use, sex, shopping and eating can become excessive, but whether they should be labelled as addictions is an ongoing debate.

In the most recent, fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*) — a book published by the American Psychiatric Association in 2013 that defines and classifies mental health conditions — gambling disorder was moved from its category of 'Impulse-control disorders not elsewhere classified' to 'Substance-related and addictive disorders'. This represents a significant shift from a view that has prevailed since the 1980s that addictions are disorders involving compulsive drug use, and multiple non-substance-related behaviours may now be considered addictions[1].

Gambling disorder is currently the only non-substance condition that is listed as an addiction in the *DSM–5*, although a work group proposed that Internet gaming disorder (IGD) warrants additional research. Multiple aspects of IGD remain controversial, including to what extent the Internet may be the vehicle versus the focus of a disorder, and, if a broader 'Internet-use disorder' is to be accepted, the extent to which use represents an addiction. The work group focused on gaming because it was the most well studied and arguably problematic form of Internet use at the time[2], but behaviours such as social networking and pornography viewing are also under scrutiny. Such uses of the Internet also appear clinically relevant: problematic online social networking, for example, has been linked to poor emotional regulation and problems with alcohol use among university students[3]. Given that more people are growing up with digital technology, considering a broader range of Internet-related activities as potentially addictive seems important for addiction researchers.

PROBLEMATIC ONLINE SOCIAL NETWORKING HAS BEEN LINKED TO POOR EMOTIONAL REGULATION AND PROBLEMS WITH ALCOHOL USE.

DEFINING BIZARRE BEHAVIOUR

But even if such diagnoses were to be accepted, the question of where to draw the line between abnormal and normal behaviours is still up for debate and has contributed to wide variations in prevalence estimates for problematic Internet use[2]. Currently, the *DSM–5* uses a more stringent threshold for diagnosing gambling disorder (it must meet 4 or more inclusionary criteria out of 9) or Internet gaming disorder (5 or more out of 10) than it does for diagnosing substance-use disorders (2 or more inclusionary criteria out of 11); we must take care not to underestimate how widespread such non-substance behaviours are and the negative impact that they can have on public health.

Another controversial topic is sex addiction. Formal criteria for hypersexual disorder have been proposed and tested[4], but the condition was not included in the *DSM–5*. As with the other behavioural addictions, debate exists about where to set the threshold between normal and abnormal levels of sexual activity. Nevertheless, similarities in cognitive and biological changes involving craving and reward circuitry have been noted between compulsive sexual behaviours and substance and gambling addictions, and scales assessing addiction-like features such as craving seem relevant to aspects of sexual behaviours. A better understanding of aetiological and associated factors, such as to what extent psychological and biological determinants linked to gambling and substance addictions also relate to hypersexuality, should help classification efforts and promote the development of targeted treatments.

Other behaviours, including excessive eating and shopping, are also sometimes considered addictions. Of note, patients receiving dopamine-boosting treatment for Parkinson's disease have sometimes developed excessive eating, shopping, sex and gambling habits, suggesting that there may be a biological link that drives all of these behaviours. But there are nuances: although obesity has been found to share biological features with substance addictions, the variety of ways that the condition manifests itself suggests that only a subset of individuals with obesity may be characterized by food addiction. In particular, individuals with binge-eating disorder are likely to meet food-addiction criteria, suggesting similarities with gambling disorder and substance-use disorders. If foods are demonstrated to have addictive potential, it would be important to identify the specific foods or food components and implement relevant public-health policies and interventions.

While experts debate which non-substance disorders may constitute addictions, people continue to exhibit problematic behaviours. Thus, more research is needed to better understand the epidemiological, clinical, neurobiological, genetic and cultural features to help prevent and treat behavioural addictions. Research was paramount in compiling the *DSM–5*, and a similar process should be used in writing the 11th edition (due in 2017) of the World Health Organization's *International Classification of Diseases*. But for this to happen, funding agencies must prioritize research into non-substance addictions. In the United States, the National Institutes of Health includes departments focusing on drugs and alcohol, but none that target behavioural addictions. The creation of a national institute on behavioural addictions would help to advance research in this area. In France, the government requires addiction treatment centres to provide care for people with behavioural addictions. Thus, how we classify these behaviours has direct clinical implications, and there is an important need to understand how best to prevent behavioural addictions and help people who experience harm related to them. ■

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NIK SPENCER

ADDICTION

4 BIG QUESTIONS

Research into addiction explores many aspects of how and why this disease develops. Here are four of the toughest questions.

BY DAVID HOLMES

	QUESTION	WHY IT MATTERS	WHAT WE KNOW	NEXT STEPS
1	***How broadly should we define addiction?***	We often think about addiction in connection with the misuse of substances such as alcohol, heroin and cocaine. But should compulsive behaviours that involve sex, video games and gambling also be treated as addictions?	Gambling is the only officially recognized behavioural addiction. But there is increasing evidence that other behaviours resemble substance misuse in their underlying neurobiology, and the way in which they respond to treatment (see page S62).	Researchers want to move from a system that classifies addiction according to clinical symptoms to one more rooted in a mechanistic understanding of the disease, with a greater role for genetic imaging and cognitive science.
2	***How is addiction affected by our genes?***	A better understanding of the genetic factors that influence the risk of addiction could revolutionize the way that addiction is diagnosed, treated and prevented.	Numerous adoption and twin studies have shown that the risk of addiction is about 50% heritable. But identifying the genetic factors and the extent to which they interact with each other and the environment has been more tricky (S48).	Researchers are looking in ever-finer detail at potential sources of genetic variations (such as gene copy-number or the existence of rare genes) and epigenetic changes in the way that genes are expressed.
3	***If addiction rewires the brain, can we short the circuit?***	Scientists know that the use of addictive substances causes physical changes in the brain that can lead to addiction. What they are just beginning to understand is how those changes can be reversed to treat the disease.	Using optogenetic-guided brain surgery in mice, researchers have been able to identify a type of dopamine receptor that seems to have a crucial role in addiction. Blocking this receptor has reversed the symptoms of cocaine addiction in mice (S50).	For practical and ethical reasons, optogenetic methods cannot be used in humans, but their increasing use in the lab could speed the discovery of drugs to target and reset the reward circuits that are overloaded in addiction.
4	***Can we get from the 12-step recovery programme to one shot?***	One of the biggest hurdles in treating addiction is preventing relapse: people can fall off the wagon after years of abstinence. A vaccine that neutralizes a substance before it reaches the brain could prevent people from returning to old habits.	Researchers have been developing anti-drug vaccines for more than two decades and have a candidate that tricks rats' immune systems into thinking injected heroin is a pathogen, so the drug is quickly neutralized before it reaches the brain (S53).	Without a trial of an effective vaccine in humans, concerns over whether a vaccine could lead to drug users taking ever-higher doses cannot be addressed, but few, if any, pharmaceutical companies look likely to stump up the cash.

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