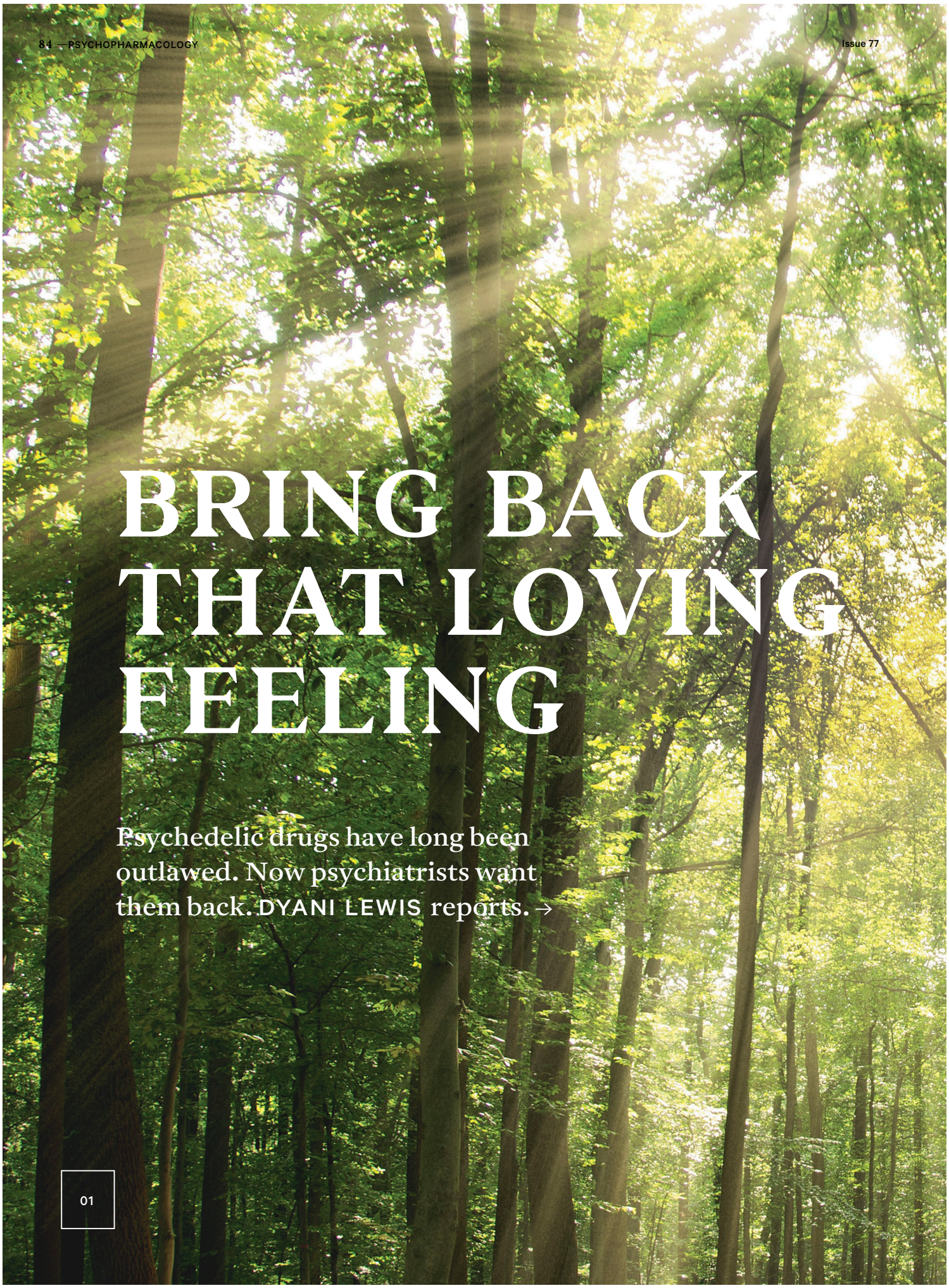

BRING BACK THAT LOVING FEELING

Psychedelic drugs have long been outlawed. Now psychiatrists want them back. DYANI LEWIS reports. →

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ON A SWELTERING NEW YORK EVENING in August 2016, Jesse Noakes finally found relief from years of mind-numbing depression. As he sat on the sofa facing the therapist his gloom melted away, replaced by feelings of clarity, warmth and enthusiasm. "It was magical," he says, "something that I was so, so desperate for."

THE AUSTRALIAN WRITER HAD SPENT his 20s cycling from one antidepressant to the next without relief. The therapy session that finally sliced through his mental miasma came at the end of a months-long global quest that took him to the Netherlands, Switzerland, and finally the US. It also took him to the wrong side of the law. That's because his therapy session was boosted by a dose of MDMA, the active ingredient in the illegal party drug ecstasy.

Clandestine therapy sessions like these may soon be a thing of the past. For years now a band of dedicated scientists has been quietly building a case to redeem the reputation of MDMA and a raft of other psychedelic drugs – LSD, psilocybin, mescaline and ketamine – hoping to deliver them into the hands of mainstream psychiatry. They claim that when it comes to some of our most debilitating mental illnesses – depression, anxiety, post-traumatic stress disorder (PTSD), addiction, obsessive-compulsive disorder (OCD) – the therapeutic cupboard is close to bare. Psychedelic drugs might provide a radical new answer.

The efforts of the psychedelics champions are paying off. In August 2017, the US Food and Drug Administration (FDA) gave the green light to a phase 3 clinical trial of MDMA-assisted psychotherapy for treating PTSD. It also designated MDMA a 'breakthrough therapy', clearing the path for a speedy approval process.

If successful, it will be the first psychedelic to be approved since a clampdown on mind-bending drugs swept the world in the early 1970s.

PSYCHEDELICS WEREN'T ALWAYS on the wrong side of the law. In the 1950s dozens of Hollywood stars including Esther Williams and Cary Grant were taking LSD as part of their psychotherapy regimen.

Lysergic acid diethylamide – a derivative of lysergic acid from the ergot fungus – had been first synthesised in the late 1930s by Swiss chemist Albert Hofmann working for the pharmaceutical company Sandoz. He discovered its mind-bending properties in 1943; while making a batch, he must have touched his face – his lips or eyes, perhaps – and inadvertently absorbed some.

The accidental dose brought on a "dreamlike

state" during which he experienced "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours". As he glided back to reality, he knew he had stumbled upon a potent psychoactive drug. By the end of the 1940s LSD was being sold under the trade name Delysid to relieve anxiety and "obsessive neuroses" in conjunction with psychotherapy.

There was significant scientific interest in LSD and other psychedelics throughout the 1950s and 1960s. At Harvard University, however, that interest got out of hand. More than just academic curiosity drove psychologists Timothy Leary and Richard Alpert to want to research psilocybin, LSD and mescaline.

First patented in 1913 by German chemical company Merck for its potential to staunch internal bleeding, it never ended up being tested on humans and was largely forgotten until 'rediscovered' in 1965 by a chemist with Dow Chemical Company. It gained a small following among psychiatrists as a psychotherapeutic aid in the 1970s and early 1980s until governments around the world banned it in line with its Schedule 1 listing.

BUT NOT EVERYONE GAVE UP on psychedelics. Psychiatrists who had experienced the drugs for themselves, or read the smattering of pre-prohibition reports on their use, were left wondering whether a potentially beneficial therapy had been shelved for

02 | Ecstasy, which contains MDMA

03 | LSD blotter tabs

They took the drugs themselves and distributed them to others. By 1964 both had been dismissed. They continued ad hoc experiments that were more wild parties than any form of rigorous scientific enquiry.

As psychedelics became inextricably linked with the 1960s counterculture, governments cracked down. In the US, president Richard Nixon branded Leary "the most dangerous man in America". The US Congress passed the Controlled Substances Act in 1970. A year later came the United Nations Convention on Psychotropic Substances, which bound signatories to follow its proscriptions. LSD, psilocybin and mescaline (among others) were put on its 'Schedule 1' – prohibited drugs deemed to have no therapeutic value. Research on most psychedelic drugs ground to a halt.

MDMA (3,4-Methylenedioxymethamphetamine) was added to the convention's Schedule 1 in 1986.

political reasons. Michael Mithoefer, in particular, was intrigued by the possibility that MDMA offered something new for the burgeoning and largely intractable problem of PTSD. "I really felt strongly that we needed to do careful research," says the Charleston, South Carolina-based psychiatrist.

In the late 1990s he turned to the Multidisciplinary Association for Psychedelic Studies for advice. MAPS, founded by American psychologist Rick Doblin in 1986, was one of a number of philanthropic organisations that cropped up in the wake of the global clampdown. Their mission was to re-educate a suspicious public, and lobby for carefully controlled research into psychedelics.

Mithoefer was convinced he would have to conduct his MDMA study outside of the US. But MAPS got behind the project, sourcing funding and helping

to develop the hefty 500-page protocol that was submitted to the FDA in late 2001. With almost no pushback, the trial was approved a month later.

Academia was not so welcoming: not a single institution was game enough to be associated with the groundbreaking trial. Delays also came from the Drug Enforcement Agency. It took two and a half years, and the intervention of a US senator on Mithoefer's behalf, before the DEA issued a licence to trial the drug.

The study was small – just 20 survivors of childhood sexual abuse and rape – but the results were encouraging. Of 12 people who underwent two MDMA-assisted psychotherapy sessions, 10 showed improvements, compared with only two out of eight in the placebo group. Mithoefer and his colleagues have since completed a similar study on 24 army veterans, firefighters and police officers. They found positive and enduring effects in both trials.

A phase 3 trial is set to start in 2018 and will enrol a larger number of people at institutions across the US, Canada and Israel. MAPS has fielded more than 20,000 requests from patients wishing to participate in the trial; and more than 4,000 psychiatrists have been clamouring to get a spot on a training course on how to conduct MDMA therapy. "It's quite striking how much interest there is," Mithoefer says.

When Swiss psychiatrist Peter Oehen got wind of Mithoefer's first MDMA trial, he and his wife, psychotherapist Verena Widmer, jumped on a plane to the US. Their aim was to convince MAPS to collaborate on a small trial in Switzerland.

Meanwhile Oehen's colleague Peter Gasser was eager to conduct more research into LSD-assisted psychotherapy. Both had trained during a brief window of permissiveness in Switzerland starting in the late 1980s. But in 1993 a patient with an undiagnosed heart condition took the psychedelic drug ibogaine and died. Switzerland fell into line with other countries.

So things stood for 13 years till 2006. Switzerland celebrated the centenary of Albert Hofmann's birth. Gasser saw an opportunity to push for the resurrection of LSD research. With MAPS backing, the Swiss government gave permission for a small trial of LSD-assisted therapy to treat people with terminal cancer. Oehen's pilot study of MDMA was also approved.

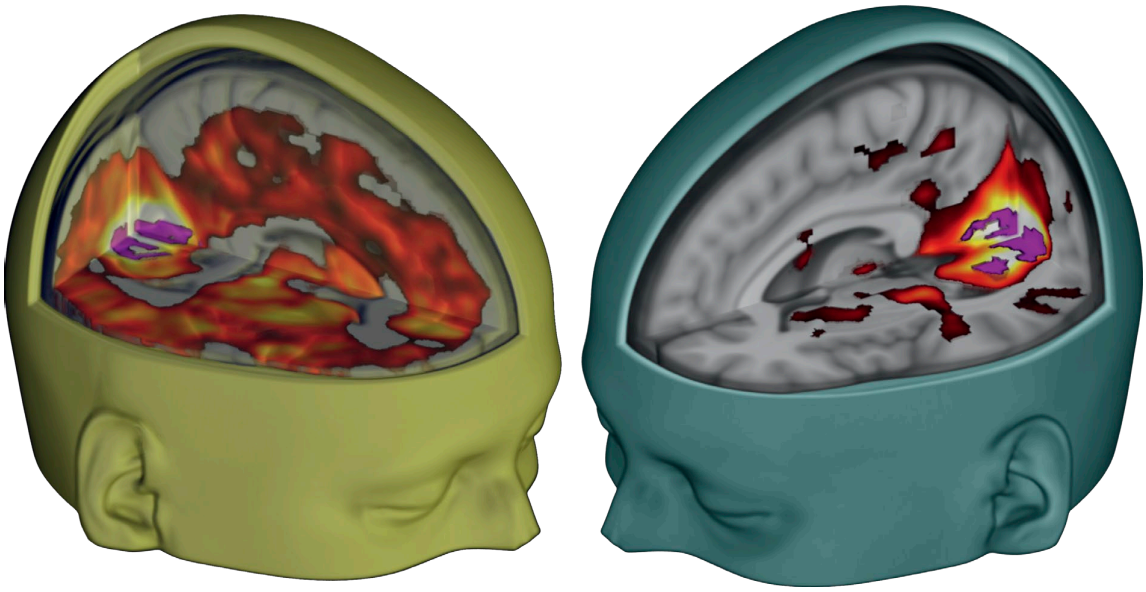
04 | Mushrooms, the source of psilocybin

05 | Ketamine – see breakout pg 90

Today Oehen and Gasser share the distinction of holding the world's only two licences to treat people with LSD and MDMA outside of a formal clinical trial. Only Swiss patients are eligible – ruling out someone like Noakes – and only the hardest cases qualify. People with heart conditions or at risk of psychosis are barred.

'MIND-ALTERING' IS AN APT description for psychedelic drugs. While antidepressants and anti-anxiety drugs need to be taken continuously for months or years, studies suggest that in some cases just one or two trips on a psychedelic – in conjunction with psychotherapy sessions – can be enough, though two or three sessions a year is more typical. Psychedelics enrich and deepen the therapy process, Gasser says.

MDMA is not a so-called 'classical' psychedelic; unlike LSD or psilocybin it doesn't cause



06 | The mind-expanding effects of LSD: MRI scans show the increase in brain connectivity, especially in the visual processing centres, after taking LSD (left) compared to a placebo (right). This may explain hallucinations.

hallucinations. It is often referred to in the medical literature as an 'empathogen', due to its ability to induce feelings of empathy and compassion – including self-compassion.

Brain imaging studies show MDMA decreases activity in the brain's emotion centre – the amygdala. However, at the same time it increases activity in the higher processing regions of the prefrontal cortex. This dialing down of the emotional output, while ramping up the activity of the reasoning centre, may explain the therapeutic effects for PTSD, where patients simply cannot forget their emotional trauma. For Mithoefer, this jibes with what he sees in his patients. "If you can decrease fear and bring on higher processing, you can try to get a new perspective and process the trauma in a different way," he says.

It also jibes with Jesse Noakes' experience on that sweltering New York evening in 2016. He recalls how MDMA cut through the emotional haze, giving him a sense of clarity about his turmoil. "If for a few hours you can turn the fear off completely – and that seems to be what MDMA can offer in the right environment – the picture comes into focus and you can go, 'oh, that's what's going on, time to make some changes'," he says.

He describes it as like opening a window into his mind. "The MDMA session shows you what it's like when you're relaxed, and confident, and open," he says. "It shows you that you're able to process very difficult things and confront things you thought were too terrible to confront."

MDMA's ability to strengthen a person's sense of connection to others is also crucial, Oehen says: "It helps to get people in touch with other people again, especially for victims of interpersonal trauma."

Though brain scans give us some idea of how MDMA achieves its far-reaching effects, pinning down the molecular mechanism is a major challenge.

MDMA creates a minor snowstorm in the brain, showering it with serotonin, dopamine and norepinephrine, chemicals known as neurotransmitters because they carry signals from neuron to neuron. Commonly prescribed antidepressants also raise the levels of these neurotransmitters, but MDMA also causes the release of stress hormones like corticosteroids as well as oxytocin, associated with social bonding.

For some researchers, this snowstorm of brain chemicals raises a red flag. "MDMA is a very messy drug," says Luke Downey, a drug and alcohol researcher at Swinburne University of Technology in Melbourne. He describes the evidence from MDMA trials as "less than compelling" and says proponents are ignoring the negative consequences of taking MDMA. Studies of long-term users of ecstasy, for instance, have shown problems with memory, reduced serotonin levels and neuron damage. "Utilising a drug with known negative effects does outweigh the benefit," he says.

Mithoefer concedes that "like any drug, MDMA has risks" but long-term use is not what psychedelics advocates propose.

ANTIPODES ANTIPATHY: A MISSED OPPORTUNITY

IN AUSTRALIA ATTEMPTS TO establish a trial of MDMA have proven difficult. Sandy McFarlane, a PTSD researcher at the University of Adelaide, reflects the cautious mood. "It's important not to get overly excited," he says. "It has to be 95% science, 5% hope, and I think at the moment it really is a little too early."

But for addiction psychologist Stephen Bright this is a missed opportunity. He is is vice-president of PRISM – Psychedelic Research in Science and Medicine – set up in 2011 to mirror the work of MAPS in the US. "In psychiatry, there hasn't been a revolutionary drug since Prozac came out," he says; that was in the 1990s.

Melbourne-based psychiatrist Nigel Strauss has also been agitating for research into MDMA and psychedelics. "There is an element of the new paradigm in these drugs and it's exciting," he says.

In 2015, he and others put together a proposal to study the use of MDMA to treat PTSD at a university in Melbourne. The night before it was due to be reviewed by the ethics committee, the university's vice-chancellor of research deemed the study too controversial.

After that, Strauss says, "I had lots of discussions around town and realised that pretty much every university was going to adopt that attitude." Strauss now focuses his efforts on educating people about the research that's happening elsewhere, hoping that destigmatising the drugs will clear the path for research in the future.

Such resistance perplexes Mithoefer. "We're not saying this is the best thing since sliced bread," he says. "We're saying we should do careful research."

"The fact there's resistance to doing careful research is disturbing because we're talking about finding better treatments for people who are committing suicide. So it's not a trivial matter."

WHEN IT COMES TO LSD and other 'classical' psychedelics, the clinical story is similar. Gasser's study of LSD-assisted psychotherapy for people with end-of-life anxiety found that LSD reduced anxiety in 12 participants with effects lasting for a year. Studies using the milder psychedelic psilocybin have been even more promising. In 2016 two studies – with a combined 80 participants – found that anxiety and depression were alleviated and attitudes towards death improved. For 60-80% of people who took the drug, the positive effects were felt six months later.

The specifics of how classical psychedelics produce their therapeutic benefits – or how they cause hallucinations – are still not fully understood. Compared with MDMA, the effects on the brain are less scatter-gun. They activate a single serotonin 5-HT2A receptor that studs neurons found in the brain's outer layer, or cortex.

Brain-imaging studies show psychedelics literally "expand the mind", says pharmacologist David Nichols, at the University of North Carolina at Chapel Hill. A 2016 study from Imperial College London and the Beckley Foundation in Oxford, which funds psychedelic research, used MRI scans to show a dramatic increase in the connectivity of different brain regions in subjects taking LSD. This increased connectivity was particularly evident in the visual cortex, which may explain hallucinations.

Normally neurons fire and communicate with other cells in their local neighbourhood, and only rarely reach out to communicate with distant parts of the brain. "When you take a psychedelic," Nichols says, "all the internal structure of these local networks seems to break down and they all reach out and everything starts globally connecting."

For Gasser, the mind-expanding effect of classical psychedelics underpins their therapeutic effect. "It's not a kind of Alice in Wonderland fantasy land," he

KETAMINE'S SPECIAL LEGAL LOOPHOLE

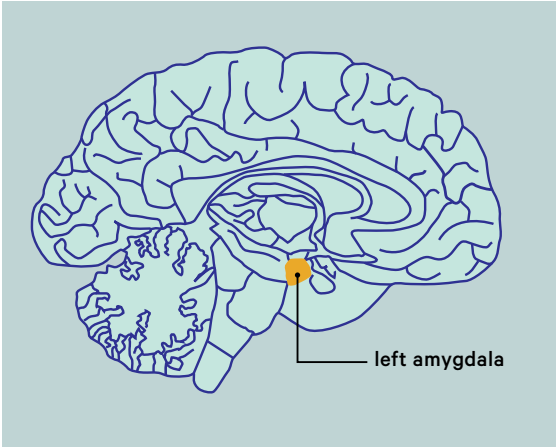
UNLIKE LSD OR MDMA, the hallucinogen ketamine – aka the party drug Special K – is already a recognised pharmaceutical; it has been used as an anaesthetic as well as an animal tranquiliser since the 1960s.

It works primarily by blocking the receptor for the neurotransmitter glutamate in nerve cells, but its interaction with numerous other brain cell receptors makes it hard to know which activities are responsible for its effects.

Because it is a controlled but not illegal drug, doctors are able to prescribe ketamine 'off label' – to treat conditions for which it hasn't officially been approved – such as chronic pain, depression, alcohol addiction and OCD. The drug is usually given intravenously, and not necessarily paired with psychotherapy, according to Colleen Loo, a clinical psychiatrist responsible for the first randomised controlled trials of ketamine in Australia.

Loo, who works at the University of New South Wales, was initially sceptical about ketamine's effectiveness against depression. She changed her mind, however, when she saw it work. "The first person I treated, I was just astounded," she says. "The speed of the powerful effects was unlike any other treatment I've seen for depression." Pooled data from three separate studies support Loo's experience. Two thirds of people with treatment–resistant diagnoses improved with ketamine infusions.

One drawback of ketamine is that, while its hallucinations are reminiscent of classical psychedelics, its effects don't last and people can become desensitised over time. "Just because one dose works for a few days doesn't mean that giving five or 10 doses is going to lead to a long-term benefit," Loo says. She and her team are conducting a trial of 200 people with depression – the largest of its kind so far – to see if repeat dosing of ketamine is safe and leads to lasting remission.



MDMA decreases activity in the amygdala, the brain's emotion centre, while increasing activity in the prefrontal cortex, the reasoning centre. This may explain its therapeutic benefit.

says. Sessions can be challenging but his patients' problems come to the surface in an LSD session. The drug, he explains, brings about a feeling of connectedness – to nature, to friends and loved ones, and to the deep-seated issues that remain buried during the hustle and bustle of everyday life.

MAPS' GOAL IS TO HAVE MDMA reclassified as a pharmaceutical drug by 2021, with psilocybin close on its heels. If the legal landscape in the US changes, other countries may follow.

For Jesse Noakes, the mainstream acceptance of psychedelics can't come soon enough. Having now found a trusted therapist in Australia, his therapy no longer requires traipsing to the other side of the world, though it still takes him to the wrong side of the law. But he's confident the psychedelic tide is turning. "I think it's inevitable," he says.

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