AN AUDIENCE WITH…

Will psychedelics be ‘a revolution in psychiatry’?


Credit: David Nutt

Mind-altering drugs such as psilocybin and MDMA could transform the treatment paradigm for mental health disorders, says neuroscientist David Nutt. But trial design considerations, regulatory hurdles and economics still pose problems for psychedelic-assisted therapies.

When David Nutt started working as a psychiatrist and neuropsychopharmacologist in the 1970s, the glow of the first psychedelic era was already fading. Despite evidence that LSD, psilocybin and MDMA might work wonders in mental health, the perceived dangers of mind-altering agents — and their use by counterculture groups — had spooked the medical establishment. When governments made these compounds illegal, research into their potential therapeutic uses ground to a near halt.

Nutt, now at Imperial College London, has been advocating for these rules to be lifted ever since. He and others have been working to rehabilitate the reputation of these agents. And a growing body of evidence again supports the view that psychedelics could yet help address staggering unmet needs in psychiatric medicine.

In May, for example, the non-profit organization MAPS reported first phase III results for MDMA in post-traumatic stress disorder (PTSD) in *Nature Medicine*, showing that the drug combined with talk therapy improved outcomes. Nutt’s own phase II trial of psilocybin plus psychotherapy in depression missed its primary end point, he reported in the *New England Journal of Medicine* in April, but still showcased the maturation of the psychedelic-assisted therapy space. And Compass Pathways — the scientific advisory board of which is chaired by Nutt — is one of several firms advancing this approach through the clinic for depression and other psychiatric indications.

Hopes are high again for psychedelics, but there are also plenty of pitfalls ahead.

You started dosing individuals with psilocybin in the 2000s. What were your expectations for this work then?

Our work with psychedelics is to understand the psychedelic state, and to understand what these receptors are doing. The human cortex is loaded with these 5-HT receptors. There are people who believe these receptors led to the evolution of the human brain, and are why it is so big. Why are these receptors there? That’s a fundamental question.

I was not thinking about therapeutic uses, to be honest. I just wanted to understand the effects of these drugs on these receptors and the psychedelic state, which is a very important state of mind. It was when we consistently saw these features of psychedelics — that you can turn off parts of the brain that relate to depression — that we began to think about therapeutic uses. But this is translational science. I never expected in 2005 to be doing anything therapeutic.

And now?

I think psychedelics are going to be a revolution in psychiatry.

Our recent trial showed that psilocybin is a completely viable alternative to current antidepressant medication, for example. It works faster, it works better on most measures, and it has a very different and slightly better side-effect profile.

But I want to point out that this trial was not a superiority or a non-inferiority trial of psilocybin versus escitalopram in depression. It was a study of the brain mechanisms of these agents. It was powered for brain imaging data that are being analysed now.

We believe there are fundamental differences in the way these drugs work. Briefly, SSRIs work on 5-HT_{1A} receptors in the limbic subcortical systems to dampen down stress sensitivity. They allow the brain to heal from the effects of chronic stress. It’s like putting a plaster cast on a broken leg, to support the bone until it heals. You shield the limbic system, the limbic system heals. The psychedelics work in the cortex, via the 5-HT_{2A} receptors rather than 5-HT_{1A} receptors, and they basically disrupt repetitive negative thinking in depression. They actually reset the brain’s thinking processes. We set up our latest study to compare the brain effects of these two different approaches.

This is an interesting point because although your depression study — as well as the MAPS’s study of MDMA in PTSD — showcases the maturation of this field, these trials raise regulatory red flags. Patients are unblinded, for example, by the effects of the psychedelics. Variability in treatment sites matters. And your trial missed its primary clinical efficacy end point. How big a challenge is trial design for psychedelic approvability?

Psychedelic therapies are seriously different from other types of therapy, because of the blinding. If regulators want to find any excuse not to allow them, it won’t be difficult. We tried to get equipoise in our trial by giving everyone psilocybin: one group got a low 1-mg dose and the other a high 25-mg dose. But people generally know the difference.

If you absolutely insist that the blind is vital, you could argue you could never run psychedelics in a way that would meet with a full traditional regulatory approval. Now, that would be folly. But it is something we’ve got to think about.

Someone once said that the only way to prove they work is to give them under anaesthesia. And to my mind, that is a completely absurd statement. Because people misunderstand that these aren’t drugs in the traditional sense. These are drugs that facilitate psychotherapy.

Regulators aside, are industry and health-care systems ready to embrace a model of psychedelic-assisted psychotherapy?

There are companies that are interested because it’s novel, and because there’s nothing else novel in psychiatry. There’s a little bit of a gold rush at present, actually, and lots of interest and people trying to find compounds other than psilocybin.

But the interest is not from big pharma. I know they’re watching it, but none of them have actually bitten the bullet. There are several reasons for that. For one, it’s such a novel approach that no one has a clue, really, whether it’ll get regulatory approval. And part

of that is also because you'd have to regulate the therapy as well as the drug.

Another reason is that Janssen's fingers have been burnt a bit with esketamine [a fast-acting antidepressant approved by the FDA in 2019]. Certainly in Europe, the view is that it works, but it is expensive and insurers don't want to pay for it. Now, the advantage of psychedelics over ketamine is that the effects are more enduring. But, there's still a question about cost-effectiveness. What can you charge for two doses of psilocybin, 3 weeks apart? And how would that compare with SSRIs, which cost peanuts?

My own view is that these drugs may turn out to be quite economical, because depression is actually a very debilitating disorder. But until the economics are sorted and the regulators have shown some interest, I think big pharma are just going to sit back and watch.

But esketamine is approved as a stand-alone drug, rather than for psychedelic-assisted psychotherapy.
Correct, it was approved as a drug. But there are people who believe that if you did some psychotherapy with it as well, you might get better results. I'm open-minded.

Multiple companies tried to chase Janssen, developing NMDA antagonists of their own for depression. These all failed. What implications does that hold for follow-on work with 'next-generation' psilocybin and MDMA analogues?
The story here is that people generally tried to make compounds that would not be psychedelic, because it was thought that was a bad thing and because there is this legacy of ketamine dependence and abuse. People were looking for ketamine light. But, it didn't work.

My view is that it's very likely that the therapeutic effect of ketamine/esketamine are due to its psychedelic-like effect. It fragments cortical function in the same way as psychedelics.

The difference is that it works on the NMDA receptor, and the NMDA receptor doesn't particularly generate neuroplasticity. The 5-HT_{2A} receptor seems to be very powerful in terms of driving neuroplasticity. We think that under psilocybin, if you come up with new insights into why you are depressed or into how to avoid being depressed, you can learn those and they can be laid down as a new pattern of thinking and behaviour. Whereas under ketamine, you might get these wonderful insights, but then your brain can't change to adapt to use them.

Researchers recently reported progress with non-hallucinogenic psychedelics. What are your thoughts on those?
I'm open-minded, but skeptical. For one, I don't think you can really interrogate the psychedelic experience in mice. For another, even if you can get antidepressant effects in mice, these don't necessarily translate well to humans. Third, our experience tells us that the people who don't have a psychedelic experience on treatment don't do as well when psychedelics are used as therapeutics.

Compass Pathway's trial of psilocybin in treatment-resistant depression is testing a 1-mg dose, a 10-mg dose and a 25-mg dose. I'm almost certain they are going to find that the 25-mg dose is a hell of a lot better than the 1-mg dose. Now, you could say that's just the dose effect. But I'm going to say that it's quite likely it's a psychedelic effect. The mechanism of recovery with psychedelics is, we believe, a disruption of thinking processes. If you don't disrupt those, then you haven't got a treatment effect.

Given the gold rush in this space from smaller companies, do you worry that lack of scientific rigour could push this field back underground?
The last thing we want is people breaching protocols and doing things that they shouldn't do, or harming people through a failure of due diligence or proper control. That would be so unfortunate.

I don't think this field is going to be the gold mine that many people think it is. I sense that quite a lot of the companies in this field have got residual money from the cannabis explosion, and cannabis is a very, very different kind of medicine. Psychedelics are much more complex, trial methodology is very different, the regulatory approach is challenging. And it may be very difficult for most of these small companies ever to generate convincing data that can get through the regulators.

Overall, there's a lot of hype and I don't see a lot of innovation. Let's put it that way.

What's your take on the value of genetics in psychiatry?
A waste of space, totally, for all sorts of reasons.

The idea that you can knock out a gene and replicate a psychiatric disorder, when we know that these disorders are polygenic, just seems to me naive and innocent. I was so amused 7 years ago when a whole-genome analysis came up with around 100 genes for schizophrenia. That's probably because it's multiple disorders. But someone said, "Oh, look, the dopamine gene is there". And I think, "Well, I kind of knew dopamine was involved in schizophrenia a very long time ago, because I've been prescribing drugs that block it for 50 years".

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I think it's been a fascinating example of a giant dead end. That said, the cytochromes are quite interesting genes, and unquestionably there are people who would benefit from having their cytochrome analysis done so that we could actually titrate the right dose of a psychiatric drug to them. But in psychiatry, at present, genetics has virtually no utility.

I think it has deflected people a lot. It has re-enforced this model that a disorder can be defined by a single target in a single cell type. Whereas more and more we see psychiatric disorders as disorders of brain systems and networks, rather than just simply of transmitters.

Psilocybin still works on a transmitter.
Yes, but it's about disrupting a network, rather than the more traditional model of stopping an overactive neurotransmitter from working or stimulating a dysfunctional neurotransmitter. The conceptualization of psilocybin's mechanism of action is at the network level, rather than at the level of the synapse.

Beyond the need for more clinical efficacy data, what other outstanding questions does this field face?
How do you sustain wellness after a psychedelic? Okay, so people get better. But do they stay well? And how do you maximize staying well? Do you keep giving psychedelics or do you put people on an SSRI, or in psychotherapy?

No one knows the best way of maximizing output for the long-term goals.

Interviewed by Asher Mullard

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