Next-generation psychedelics: should new agents skip the trip?

Companies attract venture funding for redesigned psychedelic drugs and notch clinical trial milestones.

By Mark Peplow

'Magic mushrooms', the name commonly given to mushrooms containing the substance psylocibin, have therapeutic potential.

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When Boston-based biotech Seaport Therapeutics launched in April with $100 million in venture funding, it joined a growing cadre of biotech companies that are fine-tuning psychedelic drugs to treat a range of mental health problems. These 'next-generation psychedelics' aim to overcome some of the limitations of using classical psychedelics as therapeutic drugs for conditions such as depression and substance use disorder.

In May, Gilgamesh Pharmaceuticals, another company working on next-generation psychedelics, announced that it would collaborate with pharma giant AbbVie to develop new therapies for psychiatric disorders. Gilgamesh will receive an up-front payment of $65 million from AbbVie, with the potential for up to $1.95 billion in option fees and milestone payments, a clear sign of the growing interest in this area.

Classical psychedelics – including psilocybin, found in 'magic mushrooms'; dimethyltryptamine (DMT), the active ingredient in the South American psychoactive brew ayahuasca; and the 1960s counterculture stalwart lysergic acid diethylamide (LSD) – are already being tested as mental health treatments. "This was very much fringe science even five years ago," says Sam Banister, co-founder and CSO of Psylo, a biotech with labs in Sydney, New South Wales, Australia, and Boulder, Colorado, working on next-generation psychedelics. "Now you have billions of dollars of funding pouring into these initiatives and literally hundreds of companies developing psychedelics."

The resurgent interest in psychedelics is partly driven by huge unmet need. The World Health Organization estimates that about 280 million people worldwide have depression, yet the most common antidepressants – selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine) – often show limited efficacy. Investor interest has also been buoyed by the recent success of Spravato (esketamine), a single enantiomer of the anesthetic ketamine, which induces trance-like states. The drug won US Food and Drug Administration (FDA) approval for treating depression in 2019, and last year racked up $689 million in sales for Johnson & Johnson.

But the psychoactive effects of such compounds pose some major challenges. It can be difficult to find a reliable placebo for a blinded clinical trial, for example – there's no way a patient can mistake a sugar pill for a dose of LSD. And patients typically need close supervision for many hours while under the influence of the drugs, making it burdensome, expensive and impractical for many patients.

To avoid these problems, some companies are tweaking psychedelic drugs to induce shorter or milder 'trips' that will not require such intensive patient oversight from clinicians. Others, including Seaport, are redesigning the molecules to erase their psychedelic effects altogether while retaining their treatment efficacy (Table 1). "Some patients are terrified when they go through these trips, and it's not something they ever want to do again," says Aaron Koenig, chief medical officer at Boston-based biotech Delix Therapeutics.

Although some researchers argue that a psychedelic experience is essential for a long-term improvement in mental health, nobody knows for sure whether it will be possible to retain therapeutic benefit while avoiding the trip. "That's the billion-dollar question of the field," says Andrew Kruegel, CSO and co-founder of Gilgamesh.

Banister notes that biotechs working on next-generation psychedelics all seem to be pursuing distinct strategies to fine-tune their molecules. "Every company in this space, as far as I can tell, is taking quite a different approach," he says. In part, that may reflect the lack of scientific consensus about the role of the psychedelic trip in the classical drugs' therapeutic effects. But it also demonstrates the breadth of opportunity in an area that has seen relatively little pharmaceutical progress since the SSRIs of the 1980s and 1990s.

Psychedelics are a broad and somewhat ill-defined class of compounds. The psychoactive effects of these drugs, including

Table 1 | Selected companies working on next-generation psychedelic therapeutics

Name	Location	Founded	Pipeline: strategy	Conditions	Progress
Cybin	Toronto and Dublin	2019	CYB003: deuterated psilocybin analog with a shorter psychedelic experience	MDD	Phase 2 complete, phase 3 imminent
			CYB004: deuterated DMT analog with a longer psychedelic experience	Generalized anxiety disorder	Phase 2 imminent
Gilgamesh Pharmaceuticals	New York	2019	GM-1020: ketamine analog with no dissociative effects	MDD	Phase 2 underway
			GM-2505: psilocybin analog with shorter psychedelic experience	MDD	Phase 2 recruiting
Reunion Neuroscience	Toronto	2019	RE104: psilocybin analog with shorter psychedelic experience	Postpartum depression	Preparing for phase 2
Delix Therapeutics	Boston	2018	DLX-001: non-hallucinogenic analog of MDMA and DMT	MDD	Phase 1
Lophora	Copenhagen	2018	LPH-5: a potentially non-hallucinogenic cousin of phenylethylamines	Depression	Preparing for phase 1
Psylo	Australia	2021	PSYLO-100X: non-hallucinogenic 'psychedelic adjacent'	Depression	Preclinical
Seaport Therapeutics	Boston	2024	SPT-348: non-hallucinogenic LSD derivative	Depression, anxiety	Preclinical

MDD: major depressive disorder.

hallucinations and feelings of dissociation from the body, vary dramatically depending on the compound and the dose. "It ranges from feeling a buzz similar to having a cup of coffee to a full-blown LSD experience where you're shaking hands with God," says Jesper Kristensen, a medicinal chemist at the University of Copenhagen, whose spinout company Lophora is developing next-generation psychedelics.

Many psychedelics share similar molecular structures based on a tryptamine or a phenylethylamine core. Most are agonists of a serotonin receptor called 5-HT_{2A}, which seems to be crucial to their effects. Ketamine, in contrast, is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, a common target for anesthetics.

For all psychedelic agents, the sector is booming. "We have identified nearly 150 drug development programs based on different types of psychedelic drugs," says Jasparam Kaur, a senior business analyst at Roots Analysis, a market research company headquartered in Chandigarh, India. A recent report by Roots calculates that companies in this area have collectively raised over $3.5 billion since 2017 and estimates the market for therapeutic psychedelics could grow to $6.7 billion by 2030.

One of the leading companies working on classical psychedelics is Lykos Therapeutics in San Jose, California. It has completed two phase 3 trials using 3,4-methylenedioxymethamphetamine (MDMA) in drug-assisted psychotherapy to treat post-traumatic stress disorder (PTSD) and has an Investigational New Drug application pending with the FDA. The agency is holding its first advisory meeting to discuss the application on 4 June. (MDMA is not considered a classical psychedelic, but it is often treated as such.)

Close behind Lykos is Compass Pathways in London, which is testing psilocybin in two phase 3 trials for treatment-resistant depression; and Mind Medicine, a New York-based biotech that unveiled positive phase 2b results in March for its LSD D-tartrate compound MM120 in treating generalized anxiety disorder. Compass and Mind Medicine have both received FDA 'breakthrough therapy' designations for these drugs.

"I am excited about the therapeutic possibilities of these substances, but I think there's a lot of hype," cautions Robert Malenka at Stanford University. Much of the science underpinning these approaches remains unknown, and, he adds: "The actual evidence of therapeutic efficacy is relatively limited."

There are also questions about their cost effectiveness, given that patients require close supervision by psychotherapists during the drug experience. "In Australia, the cost per patient of MDMA or psilocybin therapy is likely to be around AUS$20,000 to AUS$30,000 for a treatment course lasting several months [US$13,000 to US$20,000]," says Banister.

Psilocybin faces similar challenges because a therapeutic trip can last for 8 hours. This is partly because the drug must first be metabolized in the body to form psilocin, the compound that targets the 5-HT_{2A} receptor.

Cybin, a biopharmaceutical company headquartered in Toronto, has shortened that trip with its psilocybin analog CYB003, which does not require metabolic activation in the liver and intestines. To fine-tune the drug's pharmacokinetics, the company also replaced some of the molecule's hydrogen atoms with its heavier isotope deuterium, which slows its metabolic breakdown. The result of this tinkering is a more manageable psychedelic experience: although it still requires psychological support, the trip lasts for only 4–6 hours.

Cybin has completed a phase 2 trial of CYB003 for major depressive disorder, using a lower dose than classical psilocybin. In March, the company unveiled data showing that CYB003 achieved strong antidepressant effects that were more durable than those of SSRIs. "After four-and-a-half months, we are seeing the vast majority of patients still responding and staying in remission," says Amir Inamdar, Cybin's chief medical officer. CYB003 has breakthrough therapy designation from the FDA and is due to start a phase 3 trial in the next few months, assisted by $150 million raised in March.

Cybin's pipeline also includes CYB004, a deuterated analog of DMT. When given intravenously, DMT itself is rapidly metabolized and causes an intense trip that lasts less than 20 minutes, which may be too brief to

be an effective therapy. In contrast, a single intravenous injection of CYB004 produces a 90-minute trip, and Cybin is about to start recruiting patients to a phase 2 trial of the drug to treat generalized anxiety disorder.

Another problem is that some classical psychedelics are also agonists of the 5-HT_{2B} receptor, which is expressed in heart tissue and can cause long-term cardiac problems. Kristensen's company Lophora aims to solve that with its lead compound LPH-5, a phenylethylamine derivative with an extra molecular ring that makes it less flexible. LPH-5 has a 60-fold higher selectivity for 5-HT_{2A} over 5-HT_{2B}.

Lophora plucked LPH-5 from a large library of analogs that the company has screened against various receptors. Other experiments in rats suggest that it could have a persistent and robust antidepressant effect, and the company is now preparing for a phase 1 trial of LPH-5 for treatment-resistant depression, which will use electroencephalogram readings and other measures to assess the drug's effects. Kristensen expects that a therapeutic dose will not induce a trip in humans, based on standard experiments that involve measuring head-twitching behavior in mice, a good proxy for their psychoactive effects in humans.

Other companies are confident that they can further reduce or even erase those effects without losing therapeutic efficacy. Gilgamesh, for example, is taking that approach with ketamine, DMT and psilocybin. In the case of ketamine, says Kruegel, the dissociative side effects require that the subjects remain under supervision. So Gilgamesh designed a ketamine analog called GM-1020 that has no dissociative effects and that also has better oral bioavailability than ketamine itself. After completing a phase 1 trial last year, the company began dosing patients with GM-1020 in a phase 2 trial for major depressive disorder in March. "The hope is that the psychoactive effects will be limited enough that this can eventually be taken at home," says Kruegel.

Gilgamesh has been using machine learning algorithms to study videos of mice in head-twitch experiments, to accurately quantify the animals' movements. They are also using Neuropixels probes to directly monitor how hundreds of individual neurons respond to the drugs, offering a much higher resolution than conventional electroencephalograms.

Gilgamesh is also working on GM-2505, a 5-HT_{2A} agonist that is structurally related to psilocybin and DMT. GM-2505 completed a phase 1 trial late last year and should enter phase 2 for major depressive disorder this year. Its psychedelic effect lasts 60–90 minutes – long enough for patients to "explore the altered state of consciousness that might be needed for long-term durable efficacy," says Krugel, yet within a timeframe that is manageable for healthcare systems. "Personally, I believe that the hallucinogenic effects *are* an important component, as multiple hallucinogenic compounds have demonstrated durable, transformational changes from a single dose in human studies," he adds.

Nevertheless, the company is also screening non-hallucinogenic drug candidates for their neuroplastic effects. Neuroplasticity is the brain's ability to grow and reconfigure its synaptic circuits, and the company hopes that its 'neuroplastogen' compounds will retain the efficacy of classical psychedelics while eliminating their hallucinogenic effects. "If it has efficacy, even if it's not remission after a single dose, the uptake of such a therapy would be much higher," says Kruegel. "It could be taken with no monitoring, at home, as often as needed, just like any other pharmaceutical."

Such non-hallucinogenic psychedelic analogs could also be safely taken by patients with schizophrenia or dementia, says Kurt Rasmussen, CSO at Delix. A phase 1 trial of Delix's DLX-001, a neuroplastogen molecule related to both MDMA and DMT, has shown that it is non-hallucinogenic in people. In rodents, DLX-001 and other neuroplastogens in Delix's pipeline can stimulate the regrowth of damaged dendritic spines, key structures that help to connect neurons. Animal experiments also show that DLX-001activates 5-HT_{2A}, but not the cardiac-risk-related 5-HT_{2B}, and the drug is on course for a phase 2 trial for major depression in 2025.

Delix's Boston neighbor Seaport is also developing neuroplastogens, along with other compounds, to treat depression and anxiety disorders. "Our particular play is based on the notion that you don't need a psychedelic trip experience to gather the beneficial effects of these psychedelic agents," says founder and board chair Steve Paul.

One of the company's preclinical antidepressants is a non-hallucinogenic LSD analog called SPT-348. LSD itself is a 5-HT_{2A} agonist, but there is a lot of variation between patients in how quickly it is metabolized in the liver, making it challenging to determine the optimal dose. So Seaport has tethered its LSD analog to a novel drug delivery system called Glyph that helps the drug to circumvent the liver. The drug is attached via a linker to a triglyceride, which is absorbed through the gastrointestinal lymphatic system just like dietary fats and passes directly into the bloodstream before breaking down to release the drug.

Classical psychedelic drugs are challenging to blind with a placebo in a clinical trial, but SPT-348 should be able avoid that difficulty. "Since we don't have a psychedelic experience, the idea is you could do a real placebo-controlled trial, which I think is helpful," says Paul.

In Australia, Psylo has made extensive use of computational modeling to study how hundreds of millions of different molecules fit into the crucial 5-HT_{2A} receptor and designed thousands of potential drug candidates based on the results. Its non-hallucinogenic lead compound PSYLO-100X is not derived from any classical psychedelic, and Banister prefers to call it "psychedelic adjacent." The company is still carrying out toxicology studies on the compound, but Banister is hopeful that it will enter a phase 1 trial next year.

Banister notes that regulators have become much more receptive to supporting clinical trials involving psychedelic drugs in recent years, as more evidence emerges that these therapies might help patients. "We've seen an enormous growth in mental disorders, exacerbated by the COVID-19 pandemic," said Steffen Thirstrup, chief medical officer at the European Medicines Agency, during an online Q&A session on 7 May. "I believe psychedelics deserve a second chance."

In the next couple of years, many of these companies' clinical trials may begin to answer that crucial question of whether psychedelic drugs can deliver therapeutic benefit without the trip. Positive results could mark a major advance in neuropharmacology. "If it works, the reward there is tremendous," says Kruegel.

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