ROUNDTABLE REPORT

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Psychedelics In CNS Therapeutics: Why Interest Is Surging And What To Expect Next

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Celia Morgan, Head of Psychology, Professor of Psychopharmacology, University of Exeter
Jo Neill, Professor of Psychopharmacology, University of Manchester
Gideon Shapiro, VP of Discovery, Bright Minds Biosciences
Varun Renjen, MD, Associate Principal, Blue Matter Consulting (Moderator)

KEY TAKEAWAYS

- FDA approval of Spravato paves the way for commercialization of additional psychedelic drugs.
- Psychedelics have the potential to treat multiple diseases.
- Patient access to psychedelics will be limited until scientists develop a safer, less toxic second generation of drugs.
- Looking ahead, FDA breakthrough designation is likely for new psychedelics.
- As companies commercialize psychedelics, they must incorporate the entire patient experience into their go-to-market strategies.

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OVERVIEW

Psychedelics are undergoing a 'renaissance' in central nervous system (CNS) therapeutics. The Food and Drug Administration (FDA) has granted breakthrough designation to three psychedelic drugs: Spravato as an add-on to oral antidepressants, synthetic psilocybin for severe depression and MDMA for post-traumatic stress disorder (PTSD). Investors, biopharma companies and other stakeholders are conducting more research into the potential benefits of psychedelics. To generate a return on investment, drug developers must develop the next generation of these drugs that are safer, less toxic and more efficacious with better dosing regimens for patients. They must also evaluate other key aspects of their go-to-market strategies, such as the payer perspective, clinician training and more.

CONTEXT

An expert panel from the investment community, the biopharma industry and the medical field shared their thoughts about psychedelics and offered perspectives on how the field may evolve in the next three to five years.

KEY TAKEAWAYS

FDA approval of Spravato paves the way for commercialization of additional psychedelic drugs.

In March 2019, J&J's esketamine-derived nasal spray, Spravato, became the first FDA-approved psychedelic treatment for a psychiatric disorder. The FDA has given the drug breakthrough designation. Spravato was approved as an add-on to oral antidepressants to treat adult patients with treatment-resistant depression or with major depressive disorder with suicidal thoughts or actions.

Prior to Spravato's approval, patient access to ketamine was limited. It was administered via an intravenous drip. This resulted in an off-label status so payers didn't reimburse for the drug. In addition, many psychologists/psychiatrists weren't accustomed to giving patients IV infusions in their offices. Spravato has the potential to widen patient access. Patients take the drug under supervision at certified facilities. They are monitored for two hours to ensure that they can leave the clinic safely.

Spravato is quite costly, with a list price of $590 to $895 per treatment session. However, the product is doing well commercially. By 2024, annual sales are expected to reach $1.5 billion. Earlier this year, Spravato received European Commission regulatory approval. However, the UK's National Institute for Health and Care Excellence (NICE) hasn't approved the drug, citing a lack of clinical evidence and the high cost.

> We can't deny that Spravato is one big step toward paving the way for a wider psychedelics industry. It's also giving us insight into how regulators are approaching approvals for these new drugs. These drugs will most likely only receive approval if they are rolled out under clinical supervision.
>
> *Clara Burtenshaw, Neo Kuma Ventures*

Psychedelics have the potential to treat multiple diseases.

Several clinical trials are underway to explore the use of ketamine to treat eating disorders and personality disorders. Evidence is also emerging that ketamine and other psychedelics can be used to treat bipolar disorder, social anxiety, generalized anxiety, PTSD, obsessive compulsive disorder, addiction and more. The participants shared findings from several research studies:

- **Ketamine and alcohol use disorder.** Last year, Dr Morgan's team conducted a Phase II clinical trial which found that ketamine can increase abstinence among people with alcohol use disorder. The study had four arms. In two arms, study participants used ketamine. One of the arms included therapy and one did not. Study participants in the ketamine/therapy arm received three doses of ketamine and seven therapy sessions. The other two arms used a placebo, one with therapy and one without. The strongest treatment effects occurred in the group given both ketamine and therapy. Awakn Life Sciences is advancing to Phase III.
- **MDMA and PTSD.** The Multidisciplinary Association for Psychedelic Studies recently conducted a Phase III trial using MDMA to treat PTSD. The double-blind, placebo-controlled, randomized trial included 90 people with severe PTSD who did not respond to talk therapy and SSRIs. The trial participants had three eight-hour sessions with MDMA spaced four weeks apart. They also had three preparatory sessions and nine integration sessions. The primary endpoint was a CAPS-5 score for PTSD. The effects of MDMA were significant. Eighteen weeks after baseline, 67% of the patients no longer met the criteria for PTSD, compared to 32% in the placebo group. There were also very few adverse effects.
- **Citalopram vs. psilocybin.** This trial was published in the *New England Journal of Medicine*. It was a Phase II, double-blind randomized controlled trial. It included 59 people with severe to major depressive disorder. The researchers compared citalopram with psilocybin for severe depression. Participants took two doses of psilocybin, three weeks apart. One group got a high dose and one group got a low dose. Everyone got psychological support. The primary outcome measure was a quick inventory of depressive symptomatology. The two drugs came out the same. For all the secondary outcomes measures, psilocybin performed a lot better than citalopram.

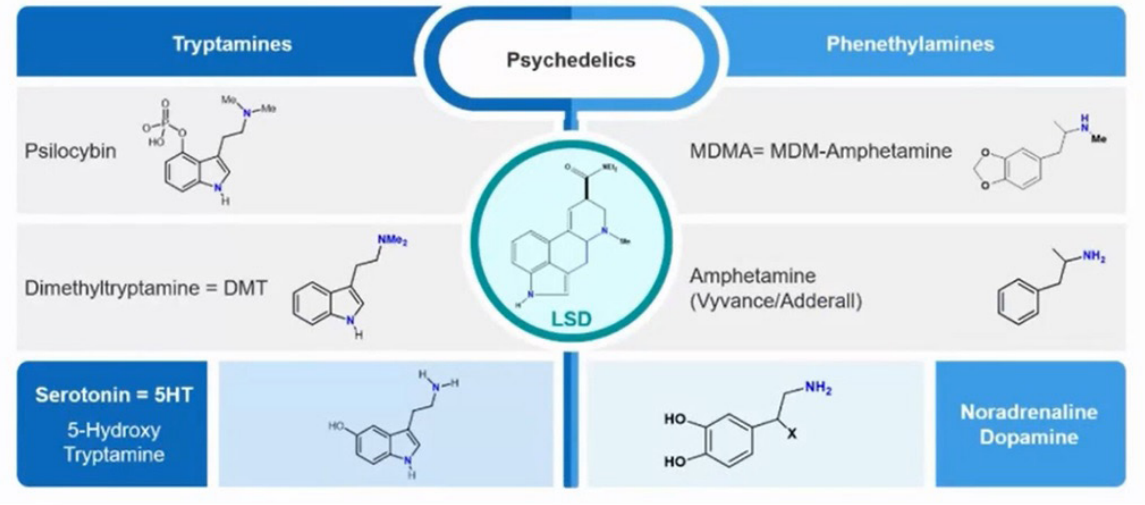
> The potential of ketamine to enhance therapy goes back to how it works neurobiologically. We found in the hours and days following ketamine, the brain goes into a very plastic state where people are able to learn.
>
> *Celia Morgan, University of Exeter*

Patient access to psychedelics will be limited until scientists develop a safer, less toxic second generation of drugs.

The first generation of psychedelics that are now being pursued clinically were first discovered 70 years ago. Now that scientists understand the biology of psychedelics at the molecular level, they can develop safer, less toxic second-generation drugs.

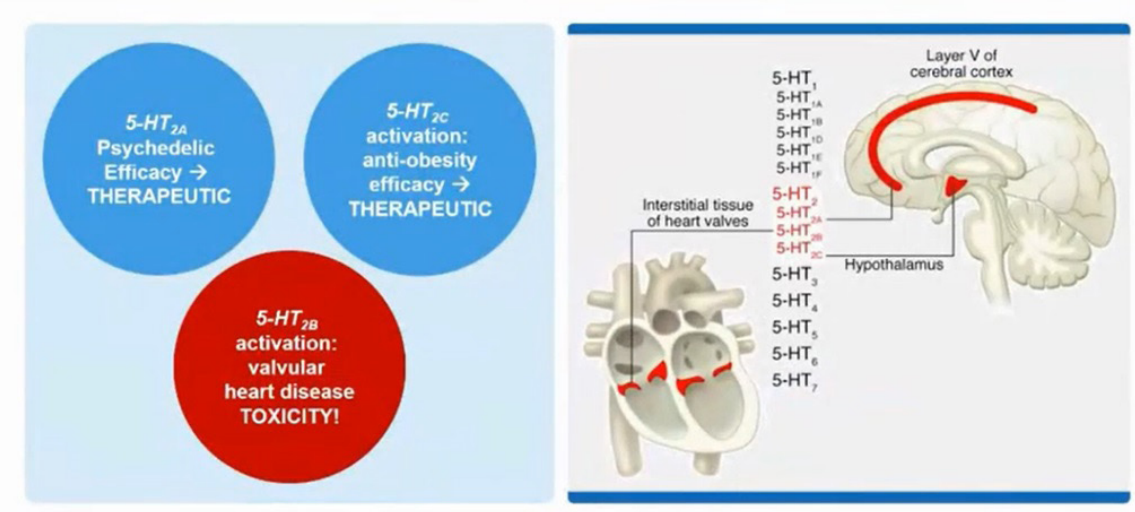
With the exception of ketamine, psychedelics bifurcate into two categories: tryptamines and phenethylamines.

Figure 1: Psychedelics Overview



Tryptamines act on 5-HT$_2$ receptors that are localized in the cerebral cortex. For the first generation of psychedelics, the biggest issue is patient safety. The 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors have therapeutic effects, while the 5-HT$_{2B}$ receptor can activate valvular heart disease. The FDA and other regulators are very sensitive to the potential toxicity of drugs that may interact with the 5-HT$_{2B}$ target. Although most first-generation psychedelics can be dosed on a limited basis, their cardiotoxicity liabilities represent a serious regulatory hurdle.

Figure 2: 5-HT2 Receptor Targets



In addition to toxicity concerns, the duration of action for some psychedelics like LSD and psilocybin is long. With a 10-hour duration of action, for example, it is impractical to keep a patient in the clinic until the drug wears off.

Figure 3: First-Generation Psychedelics & Cardiotoxicity Liabilities

Compound/ Indications	Liabilities	$5HT_1$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$D_{1,2,3}$
Psilocybin	• Tryptamine • Unselective vs 5-HT2B receptor cardiotox subtype • Restricted Frequency of Administration • Duration of Action ca. 6hrs	+	++	++	++	
MDMA	• Amphetamine • Unselective vs 5-HT2B receptor cardiotox subtype • Noradrenaline & Dopaminergic Activity • Restricted Frequency of Administration	+++	+++	+++	+++	
DMT	• Tryptamine • Unselective vs 5-HT2B receptor cardiotox subtype • Restricted Frequency of Administration • Not orally active/insufflation	++++	+++	++	++	
LSD	• Ergot • Unselective vs 5-HT2B receptor cardiotox subtype • Dopaminergic Activity • Duration of action ca. 10hrs	+++	++++	++	+	++

First generation psychedelics -> $5HT_{2B}$ cardiotoxicity liabilities

There is a definite need for second-generation psychedelics that don't have cardiovascular safety issues, have a short duration of action and are orally active. This would enable clinicians to reach more patients with a safer class of drugs. Since many diseases like depression are recurring, doctors need medications with unlimited dosing to prevent patient relapses.

> To reach millions of patients with no limitations, you must focus in on the psychedelic receptor. If you can make your next-generation drug specific to 5-HT_{2A} and eliminate 5-HT_{2B}, you will have an easier time and be able to treat many more patients without dosing frequency limitations.
>
> *Gideon Shapiro, Bright Minds Biosciences*

Looking ahead, FDA breakthrough designation is likely for new psychedelics.

Over the last couple of years, the FDA has selected three psychedelics for breakthrough designation: Spravato, synthetic psilocybin for severe depression and MDMA for PTSD. As more psychedelics pass through clinical trials, the FDA will most likely grant breakthrough designation to additional drugs. Since the FDA's top priority is patient care and safety, it is unlikely however that a psychedelic drug will ever be approved that is taken by patients at home.

> Psychedelics have four key features. They heal people with severe mental illness. In psychiatry, we normally manage symptoms, rather than heal. In addition, the dosing is different, the side effect burden is much lower than taking a daily medication and the effects are long lasting.
>
> *Jo Neill, University of Manchester*

As companies commercialize psychedelics, they must incorporate the entire patient experience into their go-to-market strategies.

Clara Burtenshaw discussed several key considerations for go-to-market models:

The payer perspective	Psychedelic-assisted therapy is based on the use of drugs in combination with therapy visits. Insurers are unlikely to reimburse for every aspect of psychedelic-assisted therapy.
Patient monitoring	Clinicians may want to monitor patients with digital tools or wearables to track their symptoms.
The clinic environment	The setting where psychedelics are administered is important. Clinics must be designed with a bespoke look and feel that attracts intellectual property such as literacy and artistic works.
Add-on devices and services	A company called Wavepaths, for example, is creating digital tools that enable patients to select their own music during sessions. Based on biometric data, the music could also change during therapy.
Psychiatrist training	One of the biggest barriers to success is psychiatrists' comfort with administering drugs. This can be addressed through education. Although new training platforms are emerging, they are expensive.

BIOGRAPHIES

Clara Burtenshaw

Partner, Neo Kuma Ventures

Clara Burtenshaw is a partner at Neo Kuma Ventures, Europe's first investment fund dedicated solely to psychedelic healthcare. Prior to founding Neo Kuma, she served as General Counsel and senior management at a PE-backed major retail group, growing annual revenue to £365m through M&A, international rollouts and restructuring. Clara began her career at Slaughter and May, a magic circle law firm, and has significant transactional, VC, IP and operational experience.

Celia Morgan

Head of Psychology, Professor of Psychopharmacology, University of Exeter

Prof Celia Morgan is head of ketamine-assisted psychotherapy for alcohol use disorder practice at Awakn Life Sciences, a biotechnology company with clinical operations researching, developing and delivering psychedelic medicine to treat Addiction. Prof. Morgan completed her undergraduate degree and Ph.D. at University College London (UCL) and completed a scholarship program at Yale University. After working at University of Melbourne, Australia, as a visiting research fellow, she returned to UCL for Lectureship before joining University of Exeter as a Senior Lecturer in 2013; and was given a Chair in Psychopharmacology in 2015. Prof Morgan holds an Honorary Readership at University College London, is the academic lead for Exeter Translational Addiction Partnership and is the head of psychology at the School of Psychology, Exeter.

Jo Neill

Professor of Psychopharmacology, University of Manchester

Jo Neill is Professor of Psychopharmacology at the University of Manchester (Division of Pharmacy & Optometry). She is Chair of the Medical Psychedelics Working Group for Drug Science, a scientific advisor for Heroic Hearts UK, the Conservative Drug Policy Reform Group, Beckley Psytech and Albert Labs. She is co-founder of b-neuro, a University based Contract Research Organization developing new treatments for mental illness through animal models. Jo is past President of the British Association for Psychopharmacology (President 2016-2018). She served on the Research Excellence Framework panel for Unit of Assessment 3 (Allied Health Professions, Dentistry, Nursing and Pharmacy) in 2014. Jo is working with Policy at Manchester to educate the public about the urgent need for drug law reform and suspension of Schedule 1 restrictions to enable research into the medicinal properties of currently illegal drugs.

Dr Gideon Shapiro

VP of Discovery, Bright Minds Biosciences

Dr Gideon Shapiro, trained as an organic chemist at the University of North Carolina, the University of California, Berkeley and the Federal Institute of Technology (ETH), is a seasoned drug hunter. He has a 30+ year professional career in drug discovery, development and drug program management. Early in his career, Dr Shapiro served as the head of the Alzheimer chemistry group at Sandoz, the company first responsible for discovering LSD and marketing psilocybin. He has also held senior roles at various other companies, including Novartis, developing novel CNS drugs. Later, he transitioned his career to founding and leading biopharmaceutical ventures including EraGen Biosciences (later acquired by Luminex) and Somatocor Pharmaceuticals. Over the last 15 years, Dr Shapiro has had a central role in drug discovery, development and corporate partnering efforts at Fidelity venture-backed companies, including EnVivo Pharmaceuticals, and played a leadership role in the invention and advancement of numerous CNS drugs that entered late-stage clinical trials. Dr Shapiro spent the last several years as the Chief Science Officer at Rugen Therapeutics, a leading drug discovery company with a therapeutic goal to correct synaptic dysfunction using a form of ketamine.

Varun Renjen, MD (Moderator)

Associate Principal, Blue Matter Consulting

Dr Varun Renjen is an Associate Principal with Blue Matter Consulting, where he leads the firm's CNS Center of Excellence. Blue Matter is a strategic consultancy focused on the life science industry. For more than a decade, Dr Renjen has provided strategic guidance to a wide range of pharmaceutical and biotech companies with heavy focus on neurological and psychiatric diseases. Prior to joining Blue Matter, he held strategic consulting roles at Navigant and IQIVIA. Varun is a MD with a neuroscience research background.