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Psychedelics For CNS Disorders: Understanding The Opportunity

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Executive Summary

Investigational uses of psilocybin and MDMA – two illicit drugs associated with recreational use and abuse in the US – will soon enter the later stages of clinical development for the treatment of CNS disorders including depression, addiction and post-traumatic stress disorder. Janssen's experiences marketing Spravato, an inhaled form of ketamine indicated for severe forms of depression, may be instructive for companies working to bring other psychoactive compounds into mainstream use as therapeutics.

Source: Shutterstock

An expanding community of clinical researchers, academic institutions, nonprofit organizations and drug developers are working to bring old psychoactive drugs – or medicines, to use the preferred term of psilocybin advocates – into new therapeutic uses. Early clinical successes with MDMA and psilocybin have now transitioned into large, late-stage trials, with the potential to upend psychiatric treatment standards for conditions including major depressive disorder (MDD), treatment-resistant depression, anxiety and depression associated with cancer, post-traumatic stress disorder (PTSD) and addiction.

In depression specifically, the rapid onset of drugs like ketamine and psilocybin provide a crucial benefit to traditional therapies like selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of anti-depressants, which can take four to six weeks to start working. Side effects common to SSRIs, including weight fluctuation, sexual dysfunction and sleep disruption, are absent from the clinical profiles emerging for psilocybin and MDMA, and in FDA labeling for Spravato (esketamine), Janssen's (a Johnson & Johnson company) inhaled version of ketamine. These psychoactive substances bring new risks, however, along with new safeguards for administration and patient monitoring. If approved, they may also have to overcome a reticence among psychiatrists and patients to use drugs previously associated with the 1960s counterculture or dance clubs and raves in the 80s and 90s.

Breakthrough Approval

Ketamine, a drug capable of producing hypnotic, analgesic and amnesic effects all at once, was developed by Parke-Davis and first approved by the FDA for use as an anesthetic called Ketalar, in 1970. Since then, it has been used for anesthesia and pain relief during surgery, and is considered a safer option for patients with lung and heart conditions. It has been used widely in veterinary medicine, and more recently, as an off-label treatment for severe depression. By 2018 – prior to the approval of Spravato on 5 March, 2019 – an estimated 300 clinics in the US were offering ketamine off-label to depressed patients willing to pay out of pocket for treatment.

Esketamine, the active ingredient in Spravato, is the s-enantiomer of ketamine, which is considered more potent than the ketamine molecule's mirror image, known as r-ketamine. Unlike older formulations of ketamine, esketamine is patent protected, and delivered via nasal spray. "Esketamine is more potent, and so a lower amount of the compound can be included in the nasal spray, which leads to the same effects you would see from an intravenous treatment," Michelle Kramer, vice president, US neuroscience and medical affairs at Janssen, told *In Vivo*.

DR. MICHELLE KRAMER, VICE PRESIDENT, US NEUROSCIENCE AND MEDICAL AFFAIRS, JANSSEN

Spravato received Breakthrough Therapy designation from the FDA in 2013, and was approved for treatment-resistant depression in 2019. The FDA awarded Janssen a second Breakthrough Therapy designation in 2016, and approved a second indication for MDD with acute suicidal ideation or behavior, on 31 July, 2020. (Also see "US FDA Opens Door For J&J's Spravato To Another MDD Population" - Scrip, 3 Aug, 2020.) The FDA has also granted Breakthrough Therapy designations to three other psychoactive substances in the last three years, all of which are making progress in clinical trials (see Exhibit 1).

Exhibit 1.

FDA Breakthrough Designations For Psilocybin And MDMA

Sponsor	Product	Indication	Supporting Data	Status	Date Ann
Usona Institute	Psilocybin, a psychedelic agent administered by facilitators under a Set and Setting (SaS) protocol with post-dose integration sessions	CNS - Treatment of major depressive disorder (MDD)	Undisclosed	Clinical - Phase II PSIL201 trial started 2019-10	201
Compass Pathways	Psilocybin therapy combining a dose of the psychoactive agent (the active ingredient in 'magic mushrooms') with psychological support	CNS - Treatment-resistant depression	Undisclosed, but sponsor notes a 2015 Imperial College London study of 19 patients and early phase studies funded by the Heffter Research Institute	Clinical - Phase IIb started 2018-08	201
Multidisciplinary Association for Psychedelic Studies (MAPS)	MDMA (methylenedioxymethamphetamine), a hallucinogen used in drug-assisted psychotherapy	CNS - Post-traumatic stress disorder (PTSD)	Phase II data	Clinical - Phase III MAPP1 and MAPP2 trials in severe PTSD ongoing, with completion expected in 2021; FDA agreed to expanded Access program 2020-01-17 limited to treatment-resistant patients with moderate	201

	to severe PTSD

Source: Pink Sheet FDA Performance Tracker

Esketamine is a Drug Enforcement Administration (DEA) schedule 3 controlled substance, a classification for drugs with moderate to low potential for physical and psychological dependence, according to the DEA. Other schedule 3 drugs include anabolic steroids, testosterone and products containing less than 90 milligrams of codeine per dosage unit. Psilocybin and MDMA, on the other hand, are schedule 1 substances, the most restrictive DEA classification, defined as having no currently accepted medical use and a high potential for abuse. Other schedule 1 drugs include heroin, LSD and cannabis.

Access Challenges

Psychiatrists who want to prescribe Spravato, and pharmacies that want to stock it, must be trained and certified, according to Spravato's Risk Evaluation and Mitigation Strategy (REMS). Patients are required to self-administer Spravato, in the presence and under the direct supervision of a health care provider. The standard dosage is twice a week, for four weeks, and patients must be monitored for two hours after administration.

The process and procedure involved in treating patients with Spravato has caused health care facilities "to pause, appropriately pause, and really think about it, because it's not just as easy as filling out papers and then starting to prescribe," said Kramer. "They really need to think about how they're going to educate patients, educate staff, how they're going to manage this controlled substance, where they'll store it, how they'll dispense it, how they'll process it through their facility." Once a practice has firsthand experience using Spravato, and seeing a patient's response, however, they are very likely to use it again, Kramer believes.

For MDD patients with acute suicidal ideation or behavior, symptoms can be expected to improve in 24 hours, and for some patients, a reduction in symptoms happened in just four hours, said Kramer. "Being able to get some glimmer of hope that your symptoms are going to be improved as early as 24 hours is a big difference," compared with other antidepressants. Spravato's most common side effects are sedation (48%-61% of patients) and dissociation (61%-84% of patients), which is described in the product labeling as "perceptual changes (including distortion of time, space and illusions), derealization and depersonalization, based on a Clinician-Administered Dissociative States Scale. "That is what the REMS is intended to monitor for and to prevent the possibility that a bad outcome happens, because of those symptoms," said Kramer. "We do see [these side effects] in a large number of people, but it's transient," and usually occurs in the treatment session or soon after. "We certainly did not see the sexual dysfunction that has occurred with other antidepressants; the profile is very different compared to oral antidepressants," she said.

Craig Chepke, a board-certified psychiatrist and Fellow of the American Psychiatric Association, has been prescribing Spravato to patients for more than a year. Chepke founded his private practice, Excel Psychiatric Associates, with his wife Tiffany Chepke, a social worker, in 2012, and became a certified Spravato treatment center soon after the launch in 2019. The biggest unmet need in treating patients with depression, Chepke told *In Vivo*, was the speed at which the response to treatment occurred. "The response to our traditional antidepressants is four to six weeks, and that's not fast enough. In almost any other field of medicine, patients don't have to wait that long to see responses. So patients can just suffer and suffer for such a long period of time that it becomes unbearable."

Products like Spravato and other novel therapies derived from psilocybin or MDMA had presented a quandary for practicing psychiatrists, for several reasons, explained Chepke. "There's not enough curiosity, not enough of a desire to break out of the traditional molds that we've had for decades."

Chepke asks his new patients to check off medications they have used from a comprehensive two-page list of psychotropic drugs. "The percentage of patients who come in having checked off either five out of six, or all six out of the six SSRIs, is just so disheartening to me."

DR. CRAIG CHEPKE, A BOARD-CERTIFIED PSYCHIATRIST AND FELLOW OF THE AMERICAN PSYCHIATRIC ASSOCIATION, HAS BEEN PRESCRIBING SPRAVATO TO PATIENTS FOR MORE THAN A YEAR.

Psychiatrists may also be reluctant to prescribe products historically associated with illicit uses. "We're going through an opioid epidemic in this country, and no one wants to be a part of a next wave of any sort of controlled substance epidemic," said Chepke. "With Spravato, the REMS makes it almost impossible for that to happen, everything is locked down so tightly, but still there's that stigma." Some psychiatrists may also balk at patient monitoring requirements – in addition to the two-hour observation period, physicians prescribing Spravato must also monitor blood pressure and co-morbidities. Chepke said his residency at Duke University, which has a combined internal medicine and psychiatry program, taught him to be a doctor first, and a psychiatrist second. "Not every psychiatrist was trained like that, so they may not be comfortable with a lot of the medical monitoring that has to be put in place."

Insurers can also create barriers to treatment with Spravato. "There have been a lot of patients who are really good candidates for Spravato, but they just cannot get the medication covered by their insurance," said Chepke. "It's absolutely heartbreaking to have someone who by definition is suffering from treatment-resistant depression, who have not had success from so many different medications."

Spravato was sometimes covered under medical benefits, said Chepke, and that worked for integrated delivery networks, "but for a private practice like me, I can't afford to buy and bill thousands and thousands of dollars worth of Spravato ahead of time, and try to get it back through medical benefits on the back end. That's frustrating, because an insurance company will say it's covered, but it's not covered under something where we can actually access it for this patient in my office, and that's what really matters. I would have hoped that a year and half after launch, coverage would have improved, but I'm still having to turn away way too many people who may not have any other viable options left."

Growing Interest In Psychedelic Therapies

There are currently over 50 active clinical trials investigating therapeutic uses of psilocybin, an entheogenic hallucinogen naturally produced in certain mushroom types, known popularly as "magic mushrooms." Documented uses of psilocybin go back centuries, to Central and South American rituals and ceremonies. Timothy Leary famously dosed students at Harvard with psilocybin, during a renaissance of psychedelic research in the 1950s and 60s. Growing numbers of recreational users, and abuse of drugs like cannabis, psilocybin, lysergic acid diethylamide (LSD), cocaine and heroin led to the passage of the Controlled Substances Act in 1970. President Nixon established the DEA in 1973. As a result, research on the therapeutic uses of psilocybin and other psychoactive substances – which were placed in the DEA's schedule 1 category – was halted for decades.

In the late 1990s, scientists and clinicians began to conduct new studies on psychedelic drugs, to better understand their therapeutic potential. "There are several studies now showing that people that are struggling with very significant anxiety and depression, whether they are medically healthy, or whether they are suffering with cancer, appear to

Social Media And The Psychedelic Research Community

Facebook – surprisingly, perhaps – has been a positive and useful meeting place for physicians treating patients with Spravato, an inhaled esketamine product marketed by Janssen. Craig

get a significant and long-lasting improvement in their symptoms from a single treatment of psilocybin when it is administered in a safe, supportive clinical setting," said Chuck Raison, director of clinical and translational research, in a video on the Usona Institute's website.

The Usona Institute was founded in 2014 by Bill Linton, CEO and founder of Promega Corporation, a supplier of enzymes, regents and other equipment supporting the life sciences industries. The Usona Institute is a nonprofit medical research organization supporting clinical research on the therapeutic effects of psilocybin. Created on the concept of "open science" and collaboration, the Usona Institute's goal is to help carry psilocybin research forward to Phase III clinical trials, using endowment funds to support psilocybin research. The Institute is currently involved in three psilocybin clinical trials, one of which is a two-year, noninterventional follow-up study. In November of 2019, the FDA awarded Breakthrough Therapy Designation to Usona for psilocybin as a treatment for MDD.

The Heffter Research Institute is another nonprofit organization focused on supporting and funding psilocybin clinical research. Named after German research pharmacologist Alfred Heffter, who identified mescaline as the active principle in the peyote cactus in the late 1890s, the Heffter Research Center is currently involved in 10 active clinical trials studying psilocybin for a variety of uses including demoralization in long-term AIDS survivors, obsessive compulsive disorder, smoking cessation, alcohol dependence, cluster headache, depression and anxiety in cancer patients, and MDD.

Chepke, a board-certified psychiatrist, said that when he decided to incorporate Spravato into his practice, he wanted to engage with other physicians with experience treating patients with ketamine. "Facebook has actually been amazing for this – there are several closed groups that are for physicians and other providers that was initially called the ketamine psychiatry group," said Chepke. The name of the group was changed to psychedelic psychiatry six or eight months ago, said Chepke, because physicians realized that psilocybin and MDMA are on the horizon, and people who are interested in one are likely interested in the others. "I'm a member of that group, and I've been reading from people who are much more actively involved in either that research or looking to integrate those products into their practices as soon as possible."

Separately, Rick Doblin, founder of the Multidisciplinary Association for Psychedelic Studies (MAPS) collaborated with Tim Ferriss, an American entrepreneur self-help author and blogger, to successfully raise $30m in funding for a phase III clinical trial testing MDMA-assisted psychotherapy as a treatment for post traumatic stress disorder (PTSD). The Capstone Campaign was announced during an interview with Rick Doblin on The Tim Ferriss Show podcast. The podcast led to a flood of donations, including a $2m donation from GoDaddy and PXG founder Bob Parsons, and a $1m donation from Alan Fournier, founder of Pennant Investors, both of whom heard about the campaign on the podcast.

A third nonprofit research organization, the Multidisciplinary Association for Psychedelic Studies (MAPS), announced on 20 August this year that a fundraising campaign raised $30m in three months, for the purposes of funding a Phase III trial studying MDMA-assisted psychotherapy for the treatment of PTSD. That clinical program received an FDA Breakthrough Therapy Designation in 2017. MAPS was founded in 1986 by Rick Doblin, a researcher and advocate for beneficial uses of psychedelics and marijuana. MAPS is involved with 22 active or completed MDMA interventional trials among the over 60 studies listed by clinicaltrials.gov.

Elite academic institutions, such as Yale University, New York University and Johns Hopkins University, are also participating in psychedelic research and conducting clinical trials. A behavioral pharmacology research group at Johns Hopkins University was first to obtain regulatory approval in the US, in 2000, to reinitiate research with psychedelics in healthy, psychedelic-naive volunteers. A member of that group, Roland Griffiths, is now the founding director of the Johns Hopkins Center for Psychedelic & Consciousness

Research, a new center launched in September of 2019, with $17m in private funding, including funding from the Heffter Research Institute.

The Johns Hopkins Center for Psychedelic & Consciousness Research is studying psilocybin as a treatment for depression and addiction, as well as mystical and religious effects of the drug, including a clinical study investigating the "effects and possible utility of psilocybin-facilitated experiences for professional religious leaders," according to clinicaltrials.gov documentation. At a talk about psilocybin clinical trial results, Griffiths ended by saying: "What I really want to underscore is that because these mystical experiences give rise to these trait-level changes in spirituality, in altruism, gratitude, forgiveness, interpersonal closeness ... they really appear to be foundational to our very deepest ethical and moral understandings, this prosocial impulse for mutual caretaking. And therefore further research into the causes and consequences of these absolutely extraordinary experiences is very likely to be crucial ultimately to the very survival of our species."

Biopharma Industry Support Lagging

In reading through listings for psilocybin and MDMA clinical trials, biopharma industry participation is conspicuously absent. One exception is COMPASS Pathways, a UK-based biotech founded in 2016. Compass is recruiting over 200 patients into a Phase IIb clinical study testing its lead product candidate, a synthetic form of psilocybin called COMP360, for treatment-resistant depression. (Also see "Can COMPASS Bring Psilocybin's 'Magic' To Depression?" - Scrip, 12 Dec, 2019.) COMP360 received an FDA Breakthrough Therapy Designation in 2018. The Phase IIb study, which paused recruitment in March due to COVID-19 but has begun to reopen at trial sites, will be the largest psilocybin study ever conducted. Trial completion is expected to be completed in December 2021. In April, Compass raised $80m in a Series B funding round.

If Compass does eventually receive FDA approval for its psilocybin treatment – the company predicts this will happen by 2025 – the DEA will have to either downgrade psilocybin from schedule 1 status, or carve out an exception, as it did following the approval of GW Pharma's cannabidiol drug Epidiolex, in 2018. Cannabidiol, an extract from the marijuana plant, does not cause intoxication or euphoria. The DEA determined that Epidiolex would be a schedule 5 drug, the safest scheduling classification. Psilocybin, with its hallucinogenic and dissociative properties, is not likely to follow in the footsteps of Epidiolex. But an FDA approval of psilocybin or MDMA would force the DEA to move those drugs out of schedule 1, since approval would confirm a medical use.

Psychedelic treatments like psilocybin or MDMA were likely to work best when used in concert with psychotherapy and physician observation, said Chepke. "One thing I look for now, a year and half in to treating patients with Spravato – in terms of predictors of success – is that patients who engage in psychotherapy have a much better chance of getting better with Spravato than someone who is just hoping that the medication is going to do it all for them," he said. "All psychiatrists are trained in what we call the bio-psycho-social model, that there are biological components, psychological components, and there are social factors that determine a person's [now illness] and then their treatment, we have to attend to all of this. Every patient receiving a psychedelic for the treatment of mental illness, I think it should be standard of care that they are engaged in psychotherapy in some form."