Report: Clinical Trials of Psychedelic Drugs for Psychiatric Indications

Researched by Cell Trials.org

Promoted by Rising Consciousness Community

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Chapter 1. Background to this Report

Goals of this Report

This report is a companion summary to go with an excel file that provides a database of clinical trials which use psychedelic drugs to treat psychiatric conditions. To the best of our knowledge, we have produced the only up-to-date (through the end of 2022) database of clinical trials of psychedelic compounds which is available for anyone to purchase. There are probably similar reviews compiled by companies that are active in this field, but they are for in-house use only. There are good reviews of clinical trials using psychedelic drugs published in the peer-reviewed medical literature. However, the delays inherent in academic publishing ensure that those summaries are out-of-date by the time that they appear, and this is especially true in a field like psychedelic research that is moving quickly. For example, the number of clinical trials using psilocybin for psychiatric indications increased over five-fold from 2019 to 2022.

The primary goal of this report is to summarize the clinical trials data available for psychedelic drugs and point out noteworthy trends. The second goal in this report is to identify potential opportunities for researchers and investors in this field. Within the community that follows psychedelic drug research, there has been a lot of media attention focused on a handful of companies. Those companies are getting attention because they appear to be close to achieving FDA market approval for a specific psychedelic product for a specific psychiatric indication. But where is the next market opportunity for each psychedelic compound? This report endeavors to answer that question.

Definitions

We first must define what we mean by drugs that are psychedelic, psychoactive, or entheogenic. The term “psychedelic” derives from the Greek words “mind manifesting.” But almost any ingested chemical can alter perceptions and mood, including the caffeine in a cup of coffee. Another definition of psychedelic drugs is that they have the ability to bring aspects of the subconscious mind into conscious awareness (Inserra, De Gregorio & Gobbi 2021). The user of a psychedelic drug may experience the symptoms as primarily hallucinogenic, dissociative, or empathogenic in nature (NIDA, Jikomes 2021). Researchers are discovering that these drugs are valuable to psychiatry, even though their short-term effects may resemble psychosis (loss of contact with reality), because they offer long-term improvements in mental health for diagnoses which are considered to be intractable with conventional psychiatric treatments. Another critical advantage of psychedelic drugs is that their effects are rapid onset, whereas for many of these challenging diagnoses the existing standard of care may require weeks to show

an impact. For some diagnoses, there is by now little doubt that psychedelic drugs show beneficial effects (Andersen et al. 2020). The biggest outstanding questions for this class of drugs is how long do their effects last, and how best to harness them as a companion or replacement for conventional therapy.

A clinical trial, by definition, is a medical study in which an intervention is tested in humans (NIH). Typically, human trials they are preceded by pre-clinical research to determine if a drug works in a laboratory dish, and if it works in animals. Even once the drug makes it into clinical trials, it usually progresses down a pipeline, from phase 1 to phase 2 and phase 3. Higher phase number trials are not just bigger, they also add more confirmations in the form of control groups, randomization of patient assignment to groups, and blinding of both the participants and the researchers conducting the trial. At CellTrials.org, we are experts at compiling databases of clinical trials and publishing reports about their trends, but we normally report on therapy with living cells (also called biologics), and this is our first report on chemical drugs.

Expectations for Psychedelics

To illustrate the potential of psychedelic drugs for psychiatry, we cite the case of the somewhat famous clinical trial NCT03181529 that was launched by Johns Hopkins University in 2017 and was published in JAMA Psychiatry by Davis et al. 2020. In this study, 24 patients diagnosed with major depressive disorder (MDD) received two doses of psilocybin in the context of therapy to provide psychological support. The patients' level of depression was measured on the GRID-Hamilton Depression Rating Scale. The study found that at the four-week evaluation, depression symptoms had decreased by 50% or more for 17 (71%) of the patients and for 13 (54%) of the patients the depression score was so low that they were in remission from depression. This was a small study with only one month of follow up, but it spurred a lot of excitement because "The magnitude of the effect we saw was about four times larger than what clinical trials have shown for traditional antidepressants on the market", according to lead investigator Alan Kooi Davis, PhD, of Johns Hopkins.

This clinical trial and its publication illustrate what is called the "expectancy" effect of psychedelics. Obviously, any drug that performs four times better than the current standard of care could become a blockbuster in the pharmaceutical industry. The early excitement about the potential of psychedelic drugs for the treatment of depression has been so great, that it has led to push back from some psychiatrists, who argue that the clinical trial results are being influenced by the "expectancy" of both the patients and the researchers (Butler, Jelen & Rucker 2022). Basically, "expectancy" is a new name for the well-known placebo effect. In theory, double-blind randomized controlled trials (RCT) are supposed to remove this effect. But in

practice, patients can often guess whether they are getting the active drug or placebo, and psychiatrists are concerned that expectations for psychedelic drugs are running so high that extra care must be taken to guard against bias in their clinical trials.

Mechanism of Action

The mechanism of action by which psychedelic compounds influence the neurobiology of the brain is a complex subject, and this is covered in both the public medical literature and on websites for patients (Garcia-Romeu, Kersgaard & Addy 2016, Inserra, De Gregorio & Gobbi 2021, Erowid.org, Baltimore Psychedelic Society). In this report we will not attempt to explain how the psychedelic drugs work, or which existing drugs they mimic. We will focus on a comprehensive review of clinical trials to identify trends of which drugs have been tested for which diagnoses, under what treatment protocols.

Legal Status of Psychedelic Drugs

Dispensing psychedelic drugs in the United States is supposed to be subject to strict regulatory requirements, but these regulations have some problematic loopholes. Under the federal Drug Enforcement Administration (DEA) drug schedule of controlled substances, psychedelics fall into "category 1", which means substances "with no currently accepted medical use and a high potential for abuse". For many years this category 1 status was a big deterrent to research on psychedelics drugs. The DEA provides an alphabetic list of controlled substances.

The tide turned pretty dramatically in March 2019 after the FDA gave approval to Spravato as therapy for treatment-resistant depression. Spravato is a specific chemical form of ketamine, a drug that has been approved for use in anesthesia since 1970. Spravato is manufactured by Janssen Pharmaceuticals, a part of Johnson & Johnson. It is also notable that Spravato is delivered by intranasal inhaler, whereas the traditional use of ketamine for anesthesia relies on intravenous administration. The development and approval of Spravato is described in more detail in our chapter on ketamine. The FDA published a perspective in the New England Journal of Medicine in July 2019 stating that this was the "first FDA-approved antidepressant in a new class".

However, the FDA approval of Spravato has led to waves of unexpected consequences. Because of the risk for ketamine addiction and abuse, the FDA approved Spravato subject to a Risk Evaluation and Mitigation Strategy (REMS). Spravato may only be dispensed in a medically supervised healthcare setting. Pharmacies and healthcare settings that dispense Spravato must become certified participants in the Spravato REMS.

But, in the United States, once the FDA has approved a drug for one indication, medical doctors can use their discretion to prescribe that drug "off-label" for other indications. This is because ***the FDA does not regulate the "practice of medicine."*** The consequence is that off-label prescribing of drugs is very common. In 2015 it was estimated that 1 in 5 prescriptions were written off-label. There are still numerous restrictions on how physicians can prescribe controlled substances, many of which were developed in response to the ongoing epidemic of opioid abuse (CDC, Preuss, Kalava & King 2022).

The upshot is, right now in the US there is a thriving market for off-label sales of ketamine. Enterprising healthcare providers have set up "ketamine clinics" where they offer patients doses of ketamine that are delivered under questionable levels of medical supervision (Das 2023). Some ketamine providers are marketing direct to consumers on social media, claiming that they can cure depression (Grose 2023). An investigation by the NYTimes has revealed that healthcare providers took advantage of the pandemic-era relaxation of regulations to prescribe ketamine via telehealth appointments (Hamby 2023). The telehealth pathway allowed patients to self-dose at home, with no medical supervision. Yet none of these freelance purveyors of ketamine cures is dispensing the ketamine product Spravato that was actually approved for depression. The clinics are delivering generic intravenous ketamine, and/or other ketamine products manufactured in compounding pharmacies. This too is a loophole: ***compounding pharmacies are not regulated by the FDA*** (APhA, FDA). It had been hoped that the FDA approval of Spravato would make legal ketamine more available and less expensive for patients than the off-label ketamine prescriptions, but so far that has not come to pass (Roxas et al. 2021). Journalists have described the current situation as a "Wild West" of ketamine treatment (NYTimes 2023-03-05).

So far, the ketamine Wild West has not been repeated for other psychedelic drugs, but it is undeniable that there is some risk of that happening. ***Unlike ketamine, none of the other psychedelic drugs have an existing FDA approval that can be exploited to prescribe it off-label.*** But on the other hand, some psychedelic drugs that are labelled Schedule 1 by the federal DEA have been decriminalized at the state level. Since January 2019, researchers identified 74 bills and referendums in 25 US states that sought to expand access to psychedelics, especially psilocybin, the key ingredient in "magic mushrooms" (Siegel, Daily & Perry 2022). As of Dec. 2022, those measures have become law in 11 states (Burton 2022). These legalization trends mean that even if the FDA approves a special formulation of a psychedelic drug for prescription by psychiatrists under controlled conditions, that pharmaceutical product may end up competing against knock-offs manufactured in compounding pharmacies and prescribed off-label by medical entrepreneurs.

In summary, the preliminary clinical results of several psychedelic drugs for psychiatric diagnoses have been so good that they have triggered great expectations among researchers, patients, and investors. This excitement must be tempered against a realistic understanding of the steps needed to bring a new drug to market, and the manufacturing approaches that can make the drug more resistant to competition.

Classic SWOT Analysis of Psychedelic Drugs

STRENGTHS	**WEAKNESSES**
• Psychedelic drugs have been around for decades; they have well established safety profiles that make it straightforward to launch clinical trials with these drugs. • Psychedelic drugs are chemical compounds that are easy to manufacture, unlike personalized medicine using living cells and/or gene editing.	• There is no profit motive to run clinical trials on generic versions of psychedelics. Only new formulations of old psychedelics will have patent protection. • FDA requirements that psychedelic drugs be prescribed subject to risk mitigation plans will restrict patient access and raise costs.
OPPORTUNITIES	**THREATS:**
• Psychedelic drugs are already known to provide rapid onset relief from depression, which is a “paradigm shift” because the standard of care takes weeks to be effective. • Psychedelic drugs may fill the unmet medical needs of patients suffering from intractable disorders which have a high cost to society, such as Treatment-Resistant Depression, PTSD, and Addiction. • The FDA offers expedited approval pathways for drugs which fill “unmet needs” or perform much better than the standard of care.	• Any FDA-approved psychedelic drugs will face competition from knock-off versions that are manufactured in unregulated compounding pharmacies and distributed outside official medical channels.