Duke | MARGOLIS CENTER for Health Policy

Duke-Margolis and FDA Convening: Development and Regulation of Psychedelics for Therapeutic Use

Virtual Private Meeting

April 12-13, 2021

Meeting Summary

Introduction

In recent years, there has been a resurgence in the investigation of psychedelic drugs to treat various conditions in clinical settings. This renewed interest in the therapeutic applications has led to the exploration of psychedelics for treating conditions such as major depressive disorder (MDD), anxiety, post-traumatic stress disorder (PTSD), and substance use disorders among others. However, the Schedule I categorization of many of these substances has complicated their use in clinical settings. Additionally, significant challenges exist in both clinical trial design and conduct when studying psychedelic therapeutics, hampering progress on finding promising clinical applications.

The The Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), held a private meeting on April 12 and 13, 2021 that brought together a range of stakeholders to discuss the development and regulation of psychedelics for therapeutic use. In this meeting, participants identified specific challenges associated with clinical trials investigating the therapeutic use of psychedelics and discussed emerging best practices for the development and regulation of these drugs.

The Research and Regulatory Landscape for Psychedelics

Psychedelics have historically been grouped together due to their hallucinogenic properties. However, psychedelics is an umbrella term that encompasses a number of different substances with varied mechanisms of action, some of which are more well-characterized than others. Neurobiological mechanisms, such as serotonin 5-HT2A receptor downregulation, inflammatory mechanisms, or increasing functional connectivity between limbic and paralimbic networks are thought to be at play during psychedelic use. Psychological mechanisms, such as alterations to self-concept or renewed life outlook, may need to be better characterized as they are considered a major part of the psychedelic treatment experience by many researchers but little is known about these mechanisms. Of note, psychospiritual or mystical mediators may be particularly hard to quantify and are not explored much in western medicine. Research into these mediators may be important for gaining a better understanding of different psychedelics and their potential for various therapeutic applications.

Non-clinical psychedelic use, such as for religious or recreational use, has a long history tracing back thousands of years. Observations with uses outside of clinical practice has led to research on potential therapeutic applications in more recent decades. Scientific publications about drugs such as lysergic acid diethylamide (LSD) were recognized by traditional medical and scientific journals as early as the 1940s, with the 1950s and 1960s being an active time of psychedelics research. In the 1970s, legal and societal factors caused a downturn in psychedelics research interest. However, there has been a renewed interest in the past two decades to explore potential therapeutic uses for conditions that have proven difficult to treat through more conventional interventions. Potential therapeutic applications have been

mostly for chronic psychiatric disorders such as treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD), but researchers have explored other applications for psychedelics such as for treatment of cluster headache, smoking cessation, and end-of-life care.

Investigational New Drug Applications (INDs) for psychedelic drugs have been increasing year over year, potentially driven in part by recent breakthrough therapy designations received by some investigational psychedelic applications. FDA first granted 3,4-methylenedioxymethamphetamine (MDMA) breakthrough therapy designation in 2017 for treatment of PTSD, then granted the designation to psilocybin for treatment-resistant depression in 2018 and major depressive disorder (MDD) in 2019. MDMA and psilocybin are the only psychedelics with publicly acknowledged drug development programs at this time. However, other psychedelics, including ayahuasca and LSD among others, are currently under consideration. Preliminary randomized controlled trials supported the breakthrough therapy designations and will help future investigators fine-tune trial designs to support regulatory decision-making.

A number of investigational products are currently under development for use exclusively in psychedelic-assisted psychotherapy, and therefore many of the clinical trials and considerations discussed in this meeting reflect the unique concerns around products for use in conjunction with psychotherapy. Psychedelics trials investigating products for use in conjunction with psychotherapy typically have three components: preparatory psychotherapy sessions, drug treatment sessions, and integrative psychotherapy sessions. Preparatory psychotherapy sessions allow patients and clinicians to discuss meaningful life experiences, establish goals for treatment, and build rapport. During drug treatment sessions, monitors offer gentle guidance and help reduce adverse psychological reactions. Integrative psychotherapy sessions allow patients to talk through novel thoughts and feelings that arose during the drug treatment sessions.

Barriers to Psychedelic Research and Clinical Trial Conduct

Many challenges remain in psychedelic drug development related to identifying the risks, benefits, and key considerations for the therapeutic use of psychedelic drugs. Additionally, while clinical trials for psychedelic drugs may vary slightly in design by substance and therapeutic area, these trials tend to experience the same common challenges. Important trial design components, such as the selection of appropriate controls, blinding, the influence of extra-pharmacological factors, and outcome measurement were key topics of discussion at the meeting.

Selection of Controls and Blinding

The selection of appropriate controls is a major concern in psychedelics trials. Some studies use inactive controls while others use active controls, such as low doses of psychedelics or substances like niacin and diphenhydramine. Meeting participants stressed that both inactive and active controls present methodological challenges. For example, inactive controls can result in functional unblinding of patients, session monitors, and clinicians, while some active controls may cause unintended treatment and/or adverse effects depending upon the dose or substance selected. Meeting participants suggested that randomized crossover trial design or comparative effectiveness studies should be considered to overcome challenges with inactive placebo use in psychedelic clinical trials. However, participants also stressed the need to maintain methodological rigor whatever the selected trial design.

Researchers noted that the psychedelics dose-response relationship is not well-understood, so determining proper dosing for trials has been a challenge. Trialists have had difficulty determining what doses produce therapeutic effects and what a proper dose should be for general patient populations. In addition, the parameters for patient retreatment have not been well-explored. Overall, determining proper dosing continues to be an obstacle in psychedelics trial design.

Blinding in trials of psychedelics may be compromised by strong and novel psychedelic effects, which may be perceptible to both patients and session monitors – even if participants are psychedelic-naïve. Patients may experience self-unblinding if they have previously had a psychedelic experience or by having high treatment expectations surrounding psychedelics. Of note, popular culture descriptors depicting psychedelic experiences as self-evident or as highly meaningful life events may substantially impact a patient's expectations. Such expectations may lead to self-unblinding in the event the participant does not experience any significant effects during the treatment session. In addition, session monitors may experience unblinding due to the stark difference in patient experience between active and placebo treatments.

Meeting participants also noted that patients may experience the "nocebo effect." The nocebo effect is a negative outcome that can occur while a participant is on placebo or active control and is tied to expectations the participant may have related to the therapeutic intervention. The nocebo effect in psychedelics can cause desperation in patients who had high expectations for a preconceived drug effect, but ultimately didn't get that effect. Nocebo effect can lead to patient safety concerns, particularly in the vulnerable populations currently under study in many psychedelics trials, as well as potential unblinding of session monitors.

Considerations for "Set" and "Setting"

Extra-pharmacological variables, such as "set" and "setting," are important considerations for the development and therapeutic use of psychedelics. "Set" includes components of a patient's experience such as personality structure, mood, expectations, and intention. "Setting" includes the physical treatment environment, the presence of trained session monitors, and safety protocols implemented during the session. Developing and maintaining a proper set and setting during psychedelics trials promotes patient safety and increases the likelihood that patients will experience a treatment effect, as appropriate external and internal environment can improve patient comfort and focus on session and treatment goals rather than extraneous factors.

Session monitors play an important role in the safe and successful conduct of psychedelics clinical trials. Formalized session structure optimizes safety for patients, and session monitors can prevent dangerous or harmful actions, making them crucial to patients' safety and wellbeing during psychedelics trials. Streamlining session monitor requirements was a major topic of discussion at the meeting. Session monitors must be well-trained and have a background in clinical treatment, although there are no widespread, standardized requirements for training or expertise. Some researchers have called for stricter standards around session monitor training and credentials. In addition, researchers have stressed the need for modernized safety standards surrounding psychotherapy that occurs in concert with psychedelic drug treatment.

Outcome Measurement and Generalizability Concerns

Currently, psychedelic clinical trial investigators do not have a well-defined and reliable method of assessing treatment response for many of the conditions for which these drugs are being studied. Complicators of efficacy assessment include the level of practitioner engagement during treatment sessions, the hyper-suggestibility of patients exposed to psychedelics, patient expectations of treatment efficacy, and the elaborateness of the intervention (which may lead to the placebo effect), all of which could introduce bias and impact outcome measurement. Establishing a causal relationship between drug treatment and the adverse event becomes more difficult as more time passes. Meeting participants noted that adverse event attribution may occur in studies in which follow-up takes place weeks or months after treatment sessions. Patients who perceive that they received the control may also seek out other treatments, which may confound long-term safety assessments of psychedelic therapies. Additionally, researchers noted that another challenge in outcome measurement is the common clinician use of varied scales in ongoing clinical trials that have not been deemed fit-for-purpose.

Highly selected patient populations limit the generalizability of the therapy to broader audiences. Meeting participants noted that there are strict screening guidelines for current psychedelics trials, including limitations on individuals with certain underlying medical or psychiatric vulnerabilities. Additionally, these trials have typically excluded children, teenagers, and the elderly. These restrictive eligibility criteria raise questions about how patients in other groups may respond to treatment compared with the population under study and whether patients who could ultimately benefit from such treatments may be inappropriately excluded from access. In addition, meeting participants shared that ensuring accessibility for patients who are eligible to participate in trials is a major challenge, further limiting the patient population who may be able to benefit from psychedelics trials.

Characteristics of Ongoing Clinical Trials with Psychedelics

During the meeting, participants considered trial design and future directions in two areas of active investigation on psychedelics: the use of MDMA for the treatment of PTSD and the use of psilocybin for the treatment of TRD.

Use of MDMA for Treatment of PTSD

MDMA increases the presence of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) by blocking its reuptake, resulting in the release of oxytocin, prolactin, vasopressin, and cortisol. Classified as an “entactogen” or “empathogen,” MDMA enhances feelings of empathy and connectedness, along with well-being, extroversion, and euphoria. MDMA may increase interpersonal trust, making the substance useful when combined with psychotherapy as patients can form more productive relationships with their practitioners. MDMA may also reduce feelings of fear and perceived loss of control compared to other psychedelics such as LSD or psilocybin.

The Multidisciplinary Association for Psychedelic Studies (MAPS) has staged multiple clinical trials for MDMA-assisted therapy for PTSD treatment. Current Phase III trial design elements include three sessions of MDMA-assisted therapy with dose titration across sessions, with the option for patients to increase the dosage. The trial is blinded using an independent rater pool for outcome assessments. Treatment efficacy is measured by comparing the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) scores between MDMA and placebo groups at the primary endpoint. Patients participate in a two-

month and twelve-month follow-up, which is thought to be a greater predictor of treatment efficacy. Dose titration sessions are complemented with nine sessions of integrative psychotherapy as well as three preparatory sessions. The therapeutic approach in the MAPS trial uses a co-therapy team of licensed health providers with trauma experience that focuses on trauma memory and emotional processing.

Risks Associated with the Use of MDMA in Clinical Trials

Researchers identified several possible risks with MDMA therapy that warrant further consideration. While MDMA has a low to moderate abuse potential in non-medical settings, there is limited data on the abuse potential of MDMA in clinical settings. The effects of repeated use in clinical settings remain unknown. Two studies found that MDMA users had reduced serotonin transporter (SERT) densities, and the effects of repeat and frequency of dosing are unknown beyond three clinical sessions.[1,2]

MDMA facilitates trauma memory and emotion processing, and this may leave patients in clinical trials particularly vulnerable and result in safety concerns that present challenges for the informed consent process. Of note, MDMA induces feelings of bonding and openness, which may create power differentials between patients and session monitors or other involved clinicians. Meeting participants stressed that patients may experience suicidal ideation or significant distress during or after MDMA sessions, and it is unclear if trials allow for enough patient-provider contact to ensure patient safety immediately following sessions. Patients also may feel distressed after the abrupt termination of patient-provider relationships following the end of their participation in the study given the intensity of the psychotherapy sessions, and there are no widespread guidelines that address patient follow-up or transition to other care after trial participation is complete.

Risk is also tied to biological responses to MDMA, which include elevated blood pressure, heart rate, and body temperature. Due to the risk posed by these responses, patients with underlying cardiovascular conditions are typically excluded from trials. Additionally, some patients may experience hallucinogen-persisting perception disorder (HPPD), which is understudied but has been found to greatly affect some patients following psychedelics intervention.

Some patients that do not see PTSD symptom reduction following MDMA treatment may experience feelings of hopelessness and despair – in patients from this vulnerable population, this presents further safety concerns. Meeting participants emphasized that clinicians should incorporate information into the informed consent process about the possibility of being a non-responder, meaning patients who receive a psychedelic dose but do not have a psychedelic experience. Clinicians should also ensure adequate aftercare for non-responders.

Considerations for Future MDMA Clinical Trials

One meeting participant noted that some children and teens may benefit from MDMA-assisted therapy and that lowering the age floor to 15 could be beneficial to patients with applicable conditions such as PTSD. Another participant added that trials should see a more diverse pool of participants and a bigger range of sources of PTSD to be truly representative. Clinicians need to continue considering the number and length of integrative sessions, MDMA-assisted sessions, follow-up sessions, and qualifications of session monitors are appropriate or necessary to support the optimization of future MDMA trials.

Use of Psilocybin for Treatment-Resistant Depression

There is substantial unmet treatment need for many individuals experiencing clinical depression. About seven percent of U.S. adults had a major depressive episode in 2017, with 64 percent of those having severe impairment. Of note, most patients do not experience full resolution of symptoms with existing antidepressant treatments.[3] Psilocybin studies represent a different psychiatric paradigm compared with more traditional treatment interventions for depression, as the drug is applied in conjunction with a small number of sessions and may have long-term benefits beyond cessation of the treatment. Trials for therapeutic applications of psilocybin have shown promising results, particularly through large reductions in depression and related symptoms. Meeting participants in this session discussed key studies and concerns in this developing area of psychedelic research.

While the body of literature surrounding the use of psilocybin for TRD is still growing, the most robust research in this area surrounds patients with terminal cancer. One promising study for patients with life-threatening cancer and depression and/or anxiety disorder at Johns Hopkins University had patients participate in two psilocybin sessions that were five weeks apart, with either one (or three) mg or 22 (or 30) mg doses. Patients in both treatment groups saw reductions in depression and anxiety that lasted at least six months after treatment.[4]

While researchers may determine a favorable risk-benefit ratio for some patients with TRD to participate in psychedelics trials, there is a degree of risk with such an elaborate intervention. Meeting participants stressed that it is important that stakeholders across the drug development lifecycle appreciate the risk to patients that are participating in psychedelics trials. TRD is a heterogeneous disorder. Researchers emphasized that the study design should account for the differences between patients, and exclusion criteria should be carefully examined to promote patient safety and methodological rigor.

Next Steps in Development and Regulation of Psychedelics

Addressing regulatory challenges and exploring the development of new trial designs to better measure treatment efficacy will be important next steps for stakeholders involved in psychedelic drug development. In addition, clinicians must continue to ensure patient safety in clinical trials through improving and enforcing standards for session monitors, designing and modifying trial conduct to promote safety given the condition and specific drug being studied, and assuring potential risks of trial participation are clearly conveyed to subjects in the informed consent process. Stakeholders may be able to look at past successes, such as the development and regulation of esketamine, for further guidance throughout the drug approval process.

Regulatory hurdles, such as scheduling and labeling, will be important to address as psychedelic drug development progresses. Meeting participants noted that scheduling will likely be a significant challenge for regulators and clinicians because most psychedelics currently being studied, such as MDMA, are classified as Schedule I drugs. Scheduling can create restrictions on clinical access, which may become burdensome on investigators and may eventually restrict therapeutic use as well. Rescheduling of some psychedelic drugs could be considered with adequate data on abuse potential. Additionally, FDA does not regulate the practice of medicine or psychotherapy, so the combination of a psychedelic drug with

psychotherapy poses questions for regulators about proper drug labeling. Challenges with labeling must be addressed to further clinical applications of psychedelics.

Clinicians should continue to evaluate whether traditional scales for depression are applicable in psychedelics trials for treatment of depression. Alternative scales may provide further insight into the clinical benefits of investigational psychedelic therapies. Some meeting participants pointed to the mystical experience scale as an example of a measure that may be additive to other measures in use for clinical trials investigating psychedelic-assisted therapy. The mystical experience scale measures unity, positive mood, transcendence of time and space, and other factors for patients using psilocybin, and has been correlated with therapeutic effects of psychedelics in some studies. However, it is critical that any measures selected for psychedelic clinical trials ultimately reflect real and meaningful clinical benefit for patients with depression.

Current psychedelic trials lack adequate diversity of patients, which impacts the generalizability of these studies. Psychedelic trials need a greater diversity of investigators and session monitors to encourage a greater diversity of participants, improve the patient experience for individuals from diverse populations, and ultimately increase the generalizability of psychedelics trials. There is an opportunity for more women as well as Black, Indigenous, and People of Color to become investigators and session monitors. Investigators should also prioritize recruiting more socioeconomically diverse participants, as past trials have been fairly homogenous in this respect.

The role of session monitors is to aid the therapeutic process and ensure patient safety. To better support patient safety, session monitors need to be accountable for unethical behavior and steps must be taken to prevent future harm. Session conduct and monitoring standards are key areas to optimize in support of future studies, and in time for supporting clinical use as well. For example, identifying the ideal behavioral platform (cognitive behavioral therapy, motivational interviewing, etc.) will be important for streamlined trial design and optimization. In addition, patient safety must be a priority when considering further development of session monitor standards.

It will be important to continue prioritizing patient safety during psychedelic trials. Clinicians can work on managing patient expectations before sessions and include more robust informed consent processes in their trial protocols, including briefing patients on the potential of being a non-responder. Reconsidering guidelines for adequate re-treatment, follow-up, and aftercare at the end of patient participation in a trial may better support vulnerable patients under study. Meeting participants stressed the importance of maintaining patient safety and high clinician standards beyond clinical trials if psychedelic drugs are approved for more widespread use.

There are opportunities to learn from past successes and by leveraging existing data to support progress in psychedelic drug development. Lessons from the development and approval of esketamine, a product derived from the dissociative drug ketamine, may apply to psychedelic drug regulation. The Risk Evaluation and Mitigation Strategy (REMS) program associated with esketamine may be relevant to future regulation of psychedelic drugs. In addition, real-world evidence may help further support efforts to establish safety and efficacy for psychedelic therapies.

Conclusion

Psychedelic drug research is an area of renewed academic interest after showing preliminary evidence of clinical benefit for certain patients with unmet treatment needs. However, the many challenges that arise throughout psychedelics trials make it difficult to use more traditional clinical trial designs to demonstrate safety and efficacy. Academic researchers, clinicians, and regulators must work together to further clarify trial designs that will produce adequate data to support regulatory review of psychedelic products while being sensitive to unique patient safety concerns.

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