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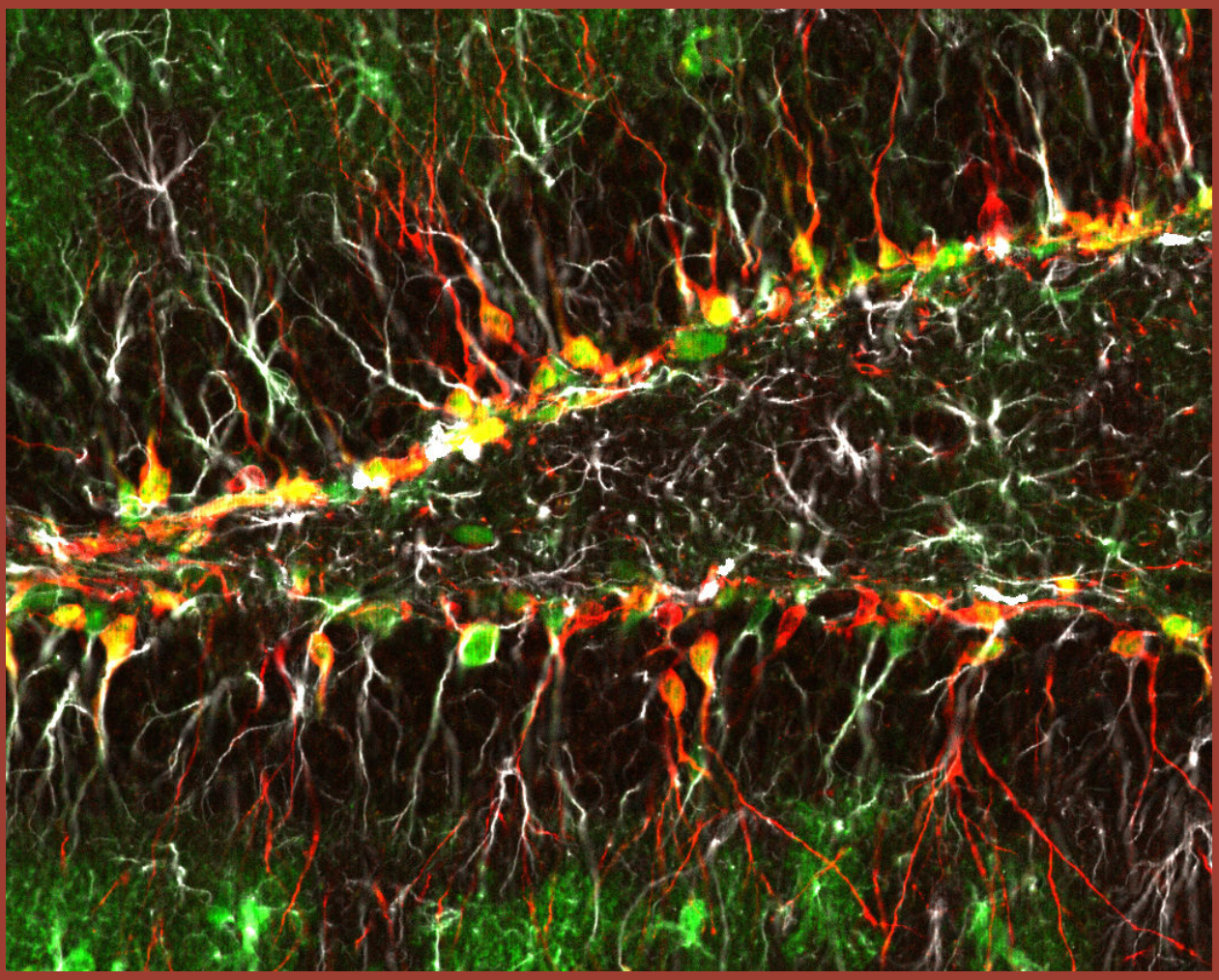

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Viewpoint

Enhancing Methodological Rigor in Controlled Trials of Psychedelics

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Abstract:
There has recently been a resurgence in the clinical development of pharmacologic treatments for psychiatric disorders, exemplified by a renewal of psychedelic research. Given the unmet need for new therapies in psychiatry and encouraging positive results from initial psychedelic clinical trials, there is tremendous enthusiasm and promotion of their potential for a variety of indications. Though promising, this enthusiasm has been ahead of a general acceptance of rigorous clinical trial methodology and optimization of study designs to show treatment effects and sufficient characterization of safety. Importantly, although psychedelics are largely considered to have a favorable safety profile, their pharmacology is complex, and their use is not without risk. Only recently have clinical trials in major depression, treatment-resistant depression, post-traumatic stress disorder, and other indications been undertaken in efforts to replicate earlier proof-of-concept trials. These well-controlled clinical trials in larger patient samples are needed to further characterize which patients might be predisposed to adverse reactions, which patient characteristics might predict response, and the optimal treatment setting. This paper outlines the need for conducting psychedelic clinical trials with more rigor, not only to substantiate efficacy but also to characterize their safety. As there is increasing demand for sites that can conduct these trials, this paper also summarizes considerations for implementing psychedelic trials with rigor and efficiency while accounting for site and patient practicalities, including a discussion of appropriate patient enrollment, the ideal site profile, and suggested safety

We are fortunate to be in the midst of a "renaissance" in neuroscience drug development characterized by a renewed interest in pharmacotherapies aimed at the central nervous system (CNS) [1]. This revitalization has been driven by increasing knowledge of the pathophysiology of neuropsychiatric diseases, encouragement from regulatory agencies that are inspiring innovative approaches to drug development, and funding sources for development that have been both diversified and increased. This resurgence of CNS clinical trials should ultimately improve the quality and extent of life for those afflicted with mental health disorders, particularly given the tremendous unmet medical need in psychiatry specifically, which has only been exacerbated by the COVID-19 pandemic [2].

This recent resurgence in psychiatry is exemplified by an ever-growing interest and renewal of psychedelic clinical research. The psychedelic market is expected to grow from an estimated $2 billion in 2019 to $10 billion by 2027 [3], with over 70 organizations with psychedelic drug development programs underway and beginning to advance toward larger Phase 3 trials. Several distinguished academic institutions globally have dedicated psychedelic research centers or programs; some examples include Yale and Johns Hopkins in the United States and Imperial College and King's College in the United Kingdom, with a growing number of research sites entering the space. Psychedelic research efforts were initially funded primarily by non-traditional sources such as philanthropic gifts and non-profit organizations—a shift in

traditional psychiatric drug development once heavily reliant on industry, although industry and federal agencies are now also heavily invested [4]. Regulatory agencies are encouraging psychedelic development efforts as well. The US Food and Drug Administration (FDA) granted breakthrough designation for MDMA-assisted therapy for post-traumatic stress disorder (PTSD) in 2017, followed by similar designations for two psilocybin-based compounds in 2019, one for treatment-resistant depression and one for major depressive disorder (MDD). Similarly, the UK Medicines & Healthcare products Regulatory Agency (MHRA) granted fast-track status for dimethyltryptamine (DMT)-assisted therapy for major depressive disorder in 2021, and in 2022 the Minister of Health in the Netherlands endorsed more research in psychedelic therapy [5]. Further, the US Drug Enforcement Agency (DEA) has accelerated the once onerous process of granting licenses for research with Schedule 1 compounds [6] and reversed its decision to categorize five different psychedelic substances as Schedule 1 after considerable public and researcher pushback [7].

These efforts have helped give rise to an abundance of encouraging data from recent psychedelic research across several psychiatric indications. In one study, a single dose of psilocybin produced substantial and clinically meaningful decreases in depressed mood and anxiety and increased quality of life in 51 patients with cancer-related distress[8]. Further, treatment effects were durable, with an overall rate of clinical response at 6 months for depression and anxiety of 78% and 83%, respectively. In a pooled analysis across six Phase 2 trials of MDMA in patients with chronic PTSD who had previously failed to respond to pharmacotherapies or psychotherapies, 54.2% of patients no longer met PTSD diagnostic criteria one to two months after two experimental sessions, compared to 22.6% in the control group, with a large effect size (Cohen's *d* of 0.8) [9]. After a third dose, symptoms on average improved further. In patients with moderate or severe MDD, psilocybin-assisted therapy produced robust, rapid, and sustained antidepressant effects after two sessions; 71% of patients continued to show a clinically significant response for up to 8 weeks, again with very large effect sizes (Cohen's d =2.6) [10]. Psilocybin has also shown promise for addiction, specifically in smoking cessation and alcohol use disorder [11,12]. Results have also been encouraging with ayahuasca, as seen in a preliminary report from a small sample of patients with a current depressive episode, noting clinically meaningful reductions in depressive symptoms three weeks after a single dose [13]. These studies, however, have mainly been in a small number of patients, but efforts to replicate results in larger samples are underway.

Given such results, it is not surprising that public interest and enthusiasm for using psychedelics to treat mental health disorders has grown at a staggering speed, albeit with some healthy skepticism toward pharmaceutical industry involvement, given that the drug class is deemed natural and used by Indigenous people for millennia. While it would be foolish not to both respect and learn from those with generational knowledge of these compounds, formal, rigorous testing is necessary, especially for (although not limited to) psychedelic substances that have been manipulated or are manufactured synthetically to minimize potential adverse effects.

Need for Rigorous Clinical Trial Methodology

Although psychedelics are considered to have a favorable safety profile, their pharmacology is complex, and their use is not without risk. Classic psychedelics including psilocybin, lysergic acid diethylamide (LSD), mescaline, and DMT, act as agonists at the

serotonin 2A receptors (5-HT_{2A}), which is similar to the mechanism of action for many antipsychotics and antidepressants. Serotonin (5-hydroxytryptamine, 5-HT) mediates a wide range of bodily functions, the more well-known being regulation of emotion/mood and memory, but also platelet aggregation and wound healing, gastrointestinal function, sexual function, and bone health. There are 14 distinct mammalian 5-HT receptor subtypes, which are divided into seven families (5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7) distributed mainly in the central nervous system but also heavily expressed in the liver, kidney, heart, and fundus of the stomach [14]. LSD primarily acts on the 5-HT family of receptors but has non-specific interactions across several receptor types. Both psilocin (the active metabolite of psilocybin) and LSD are potent 5-HT_{2B} agonists; activation of 5-HT_{2B} receptors can cause cumulation of potentially serious side effects such as valvular heart disease with chronic use over time. Other psychedelics such as ibogaine and MDMA act on different pathways; for example, MDMA is an analog of phenethylamine and works via serotonin release rather than 5-HT_{2A} agonism, which causes psychoactive effects that only partially overlap with classic psychedelics [15].

Psychedelics also vary in their duration of action. LSD, for example, dissociates from the receptor very slowly and its effects are relatively long-lasting—12 to 36 hours depending on dose, with subjective effects not necessarily correlating with pharmacokinetics and lasting much longer. Conversely, DMT has a much shorter duration of effect, 30 to 90 minutes. Ayahuasca and psilocybin also have an intermediate duration of action (6 to 8 hours) and, along with LSD, are challenging to scale and control dose, thus limiting the ability to end a negative adverse reaction should one occur.

Serious adverse effects after using psychedelics in unsupervised settings are well documented. For example, MDMA toxicity has been associated with seizures, hyperthermia, acute kidney injury, and rhabdomyolysis, with some cases leading to death [16]. LSD and psilocybin commonly cause nausea, vomiting, headaches, agitation, and tachycardia [17]. Some patients may also experience heightened anxiety or panic, mood volatility, or psychosis-like symptoms during a "bad trip" that can linger or even exacerbate suicidality. Well-controlled clinical trials in larger patient samples are needed to help identify which patients might be predisposed to adverse reactions, what patient characteristics might predict response, and what the durability of response may be, at what dose, duration of treatment, and importantly, what kind of therapy (if any) should accompany dosing. It is also imperative to determine which medications may interact with psychedelics to make more informed risk/benefit judgments at the individual patient level. The purpose of performing such clinical trials is not only to substantiate the efficacy of putative compounds but to address these types of questions and ultimately to protect patients who would otherwise be exposed to undue risk. It should be noted, however, that although rigorous clinical trials are necessary, there remains the need for balance with expeditious patient access to potentially beneficial treatments; it is precisely for that reason that regulatory agencies have created fast-track programs.

Given the public enthusiasm to use these substances, there is some urgency to both initiate and expand larger studies in the psychedelic space. In the US, states are already beginning to legalize access to psilocybin for mental health treatment, despite insufficient evidence supporting the practice [18]. Research with ketamine for mood disorders began much the same way and there are applicable similarities in terms of cautions and pitfalls. Small academic studies of ketamine for treatment-resistant depression were

completed then followed by a National Institute of Mental Health study in 2006; about 300 clinical trials have since been conducted and the first "ketamine clinic" was opened in the US in 2012 [19]. Although ketamine has been approved by the FDA as an anesthetic for nearly five decades, the lack of patent protection and prolific off-label use makes it unlikely that larger Phase 3 trials required for approval in a psychiatric indication or post-marketing surveillance studies that would address longer-term safety and effectiveness will ever be completed [20]. There are likely now 800 to 1000 ketamine clinics in North America alone using off-label or "proprietary blends" of ketamine for depression, with wide-ranging inconsistencies in screening patients, medical oversight, dosing, and frequency of infusions [21].

The popularity of ketamine clinics was at least partially fueled by the approval of intranasal esketamine (SPRAVATO®) in the US, UK, and Europe for treatment-resistant depression in March of 2019. Though esketamine is derived from racemic ketamine, they are not the same drug—there is no FDA-approved dosing regimen, no data supporting the conversion of esketamine nasal spray and compounded ketamine nasal spray, and compounded ketamine is often used at different doses and higher frequency than currently approved for SPRAVATO®. It should be noted that SPRAVATO® was also approved with a required Risk Evaluation and Mitigation Strategy (REMS) due to its potential for sedation, dissociative properties, and abuse and misuse. This program requires certification of pharmacies and healthcare settings and administration only in a medically supervised healthcare setting with appropriate monitoring. The FDA has more recently issued a health alert after a concerning number of case reports of psychiatric adverse events associated with off-label use of ketamine, and after becoming aware that some pharmacies compound nasal spray formulations of ketamine either alone or in combination with other ingredients [22].

Optimizing the Conduct of Clinical Trials of Psychedelics

Given the tremendous interest in psychedelic drugs, the need for rigorous clinical trial methodology, and the increasing demand for sites that can conduct controlled psychedelic clinical trials, the remainder of this paper will summarize considerations for optimizing study conduct. While clinical trials in psychiatry are by nature complex, psychedelic trials in psychiatric indications can be even more complex and there is no uniform approach to follow. Logistically, conducting large, global clinical trials of psychedelics intended for registration can be challenging but is quite achievable. Considerations follow for implementing psychedelic trials with rigor and efficiency while accounting for site and patient practicalities, including a discussion of appropriate patient enrollment, the ideal site profile, and suggested safety monitoring for psychedelic clinical trials. It should be noted that some of these considerations vary by compound and the treatment model employed; this discussion is intended to be broad and may not apply to all psychedelic compounds and treatment models.

Enrolling the right patient population

There are always indication-specific considerations in psychiatric trials to ensure proper diagnosis of the condition under study, exclusion of comorbidities, history of response (or lack thereof) to previous treatments, and requirements for symptom severity and stability over time. All of these are equally relevant in psychedelic trials and should be contemplated in terms of individual patient safety and to help ensure trial assay sensitivity (i.e., the ability of a trial to detect treatment differences if they actually exist). For example,

although the literature is not clear on how previous experience with psychedelics may influence subsequent experiences and treatment response, careful determination of a patient's previous psychedelic use pattern is warranted prior to enrollment in a clinical trial and whether that use was recreational in nature or part of a medical treatment plan. It is also important to characterize their subjective experience. Patients who did not respond to prior psychedelic use in a medical treatment setting, who experienced worsening symptoms or significant anxiety during treatment, or who developed active suicidal ideation after treatment should be excluded from participating in a clinical trial of a similar drug. Patients who used psychedelics recreationally within the last few years should also be excluded if their use patterns are consistent with substance abuse.

Patients with mood disorders and other mental health conditions are vulnerable by nature. Psychedelic studies perhaps draw an even more vulnerable patient population—patients have often tried many other treatment options unsuccessfully and see participation in a psychedelic trial as a "last resort." Patients are also becoming increasingly savvy "consumers" and are acutely aware of the clinical trial space and what is required for enrollment. Some may feign or deny specific symptoms or even purposefully achieve certain scale scores to qualify for enrollment. In the face of such expectations or behavior, it is challenging for the research site staff to strike the right balance in managing patient expectations of benefit and providing therapeutic support required within the study protocol with the ability to objectively determine if study medication is efficacious and maintaining clinical equipoise.

Of note, not all research sites are equally skilled in diagnosing psychiatric conditions and relevant comorbidities. Incorporating a structured clinical interview (e.g., the SCID or MINI) can be useful not only for diagnostic specificity, but also for standardizing diagnostic methods across investigative sites and correctly identifying salient comorbid disorders in an individual patient. Adequate severity and stability of symptoms should also be considered formally in protocol entry criteria. For example, in trials for MDD or treatment-resistant depression (TRD), there are typically minimum severity requirements as measured by the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS), or similarly with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) in PTSD trials to avoid ceiling and floor effects and enhance the ability to detect change with treatment. It is not enough to have adequate symptoms, but they should also be relatively persistent. Stability of symptoms can be guaranteed by assuming that there should not be significant changes (improvement or decline) in key symptoms over relatively short periods of time on successive measures, which could be accomplished by excluding those with more than a 20% or 30% change in a severity score (e.g., HAM-D, CAPS-5, MADRS, etc.) between screening and baseline. Patients with higher levels of variability are more likely to have external sources driving this instability and are more likely to respond to non-specific effects independent of treatment and therefore heighten "placebo" response.

Other sources of non-specific treatment effects include rater inflation or exaggerated judgment of symptom severity by the clinician (subconsciously or overtly) to qualify a potential patient to meet study entry criteria. Rater inflation can result in an artificial improvement of symptoms post-baseline reflecting regression to the mean. For example, when using a high HAM-D score for inclusion purposes, a decrease in score the next time the scale is administered would be expected even with no treatment. This decrease is because statistical regression to the mean

acknowledges that severe or higher scores are more likely to have positive measurement error, while less severe or lower ones are more likely to have negative measurement error. As measurement error is, by definition, uncorrelated with the true measurement of the underlying construct, the measurement error of any two independent measures of the same construct should be zero. There are several ways to help avoid rater inflation, including the use of one scale for entrance purposes (e.g., the Hospital Anxiety and Depression Scale for Depression [HADS-D] or even a Clinical Global Impressions [CGI]) followed by a separate independent scale for baseline (e.g., the HAM-D) and then using change scores from that baseline measure as an efficacy outcome, which ultimately helps reduce placebo response. Alternatively, using a combination of self-report and investigator-reported measures with some measure of congruence has been shown to be helpful. Additionally, blinding patients (as well as site staff) to all cardinal entry criteria can decrease the possibility of rater inflation of scores for inclusion purposes; appropriate and efficient randomization can be accomplished through the use of an algorithm via an automated system. When blinding these entry criteria, sites are merely informed that there will be a minimal level of severity and stability during the screening period and that sites will be notified if the patient is eligible for randomization or not. Finally, the use of independent centralized raters blinded to the study visit of individual patients can prevent biased inflation of ratings.

A history of treatment resistance should also be carefully evaluated, with the definition of treatment resistance clearly defined in the study's protocol, typically operationalized as less than a 30 to 50% response to at least two treatment agents of different classes taken over an adequate period with ostensible compliance. Patients with a current or lifetime history or family history of any psychotic disorder, bipolar disorder, or personality disorder should also be excluded from participating in a psychedelic trial for both safety and efficacy reasons. Additionally, unless there are strong data indicating that there are no drug-drug interactions of consequence with other serotonergic agents, the use of serotonergic medications is generally discontinued prior to study entry.

Practically Managing "Placebo" Response

Control groups in clinical trials allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors (e.g., natural progression of disease, patient expectations, or other treatment) and are required by regulatory agencies for the evaluation of safety and efficacy [23]. An adequate and well-controlled trial, as defined by regulatory agencies, could utilize a placebo control, no treatment, a different dose or regimen of the study treatment, or a different active treatment. Given the extensive and recognizable effects of psychedelics, these trials often do not include a true "placebo" control and instead often employ a very low dose of the test treatment or even a different active control that causes some physiologic response (e.g., niacin or methylphenidate) that is intended to aid in blinding. Regardless of the control used, patient and site expectations of benefit can have substantial impact on assay sensitivity of the overall trial. Most psychedelic study protocols incorporate preparatory sessions for trial procedures as well as the overall psychedelic experience (what to expect, what patients may or may not experience), which are critical. This training should also be extended to family members/caregivers, as family members can influence the response of the patient on efficacy measures. The requirement for caregivers in a psychedelic study varies,, depending on the compound and local country requirements. Competent authorities in some countries

mandate patient caregivers so that they are aware of worsening of patient symptoms during the washout period of SSRIs, for example, and to accompany the patient home after their dosing day. In addition, some study protocols also include caregiver assessments for an independent observer review of how the study drug has affected the patient.

During the consent process, patients are routinely told they may or may not receive active study drug and that if they do receive active treatment, it is uncertain whether it will work—and that this is the purpose of studying it in a clinical trial. For psychedelic studies in particular and given the profound mystical experience that can accompany psychedelic use, it should be further explained that change may occur in the absence of a complete mystical experience. Further, sites should encourage a "research" and, as much as possible, not a "therapeutic" partnership with patients in order to establish a true sense of clinical equipoise at the site in which site staff does not have a predisposition to study drug effect (i.e., the purpose of a patient's participation is to help determine if a treatment is efficacious, rather than to themselves improve). An assessment of site staff beliefs and expectations regarding clinical practice versus research should be incorporated, as well as a standardized training program on practical methods of standardizing patient interactions that will limit non-specific treatment effects. Site staff also need training on managing their own expectations of treatment success. Demanding that site staff interactions with patients be controlled and not inappropriately and unintentionally create a nonspecific supportive treatment environment that heightens placebo response is especially tricky in the psychedelic setting because in many instances therapy is by design part of the treatment. For this reason, the therapist (sometimes referred to as a facilitator, supporter, or moderator) providing support during and after dosing should be a separate clinician from the one providing efficacy ratings for the study. An independent rater, blinded to the patient's experience during dosing sessions, should complete efficacy assessments in these trials. Those raters should be evaluated on their qualifications to rate and have experience both with the patient population and the assessments used and undergo specific training on using those assessments in the context of the protocol for that specific study. Using remote centralized raters through phone or video contact with subjects is an alternative option that can be more efficient and further decrease variability in study outcomes.

Proper Safety Monitoring

Proper safety monitoring in a psychedelic clinical trial is multifaceted and should be in place both during and after dosing sessions. Prior to dosing sessions, careful preparation of patients regarding the session is essential. During dosing sessions when patients are most vulnerable, the setting should provide a safe environment that can accommodate privacy, particularly in the event of a difficult experience. Real-time access to an on-call physician or clinician (often a psychiatrist) responsible for safety should be maintained in case the patient requires rescue medication or additional psychiatric support. Anxiety can often occur and can be significant but transient; sustained psychotic reactions or loss of reality are rare. Participant consent permitting, sessions should be videotaped and reviewed in a timely manner by independent reviewers, which protects both the patient and the therapists/facilitators. Of note, regulatory agencies may also request a review of videotaped sessions. Physiologically, safety monitoring by qualified, trained staff that can provide medical oversight should include an evaluation of cardiovascular effects (QT prolongation, tachycardia), respiratory depression, sedation or impairment, and

although rare, serotonergic toxicity, seizures, or hallucinogen persisting perception disorder. Frequent acute physiologic effects also include nausea and vomiting. Patients with valvular heart disease, uncontrolled hypertension, or arrhythmias or who are taking other serotonergic agents, MAOIs, lithium, atypical antipsychotics, or tricyclic antidepressants should not participate in earlier phase trials. Psychiatric adverse events of interest include psychosis or delirium and suicidal ideation, and those with a prior history or familial history of psychosis or severe mental illness should not participate. Nearly all psychiatric clinical trials have been required to formally and prospectively assess and actively monitor the occurrence of treatment-emergent suicidal ideation [24]. For psychedelic trials, this should also include a formalized, written plan of action (e.g., hospitalization, initiation of other treatment, referral, etc.) at the individual site level in the event suicidal ideation occurs. Data alerts should also be established for suicidality measures included in the protocol (Columbia-Suicide Severity Rating Scale [C-SSRS], MADRS, HAM-D scores) with active surveillance of those data by either the sponsor or study medical monitor.

Following dosing, patients can remain vulnerable for an extended period, and therefore post-dose integration sessions are important--crucial depending on the type of psychedelic. Sites should also be aware of the potential disappointment and worsening of symptoms if patients report feeling "no different" after treatment. Follow-up contact with patients should occur between clinic visits, with any symptom worsening documented along with whether those changes are due to the treatment itself, patient expectations of treatment, or if related to the natural course of illness. Once the clinical trial has concluded, adequate aftercare needs to be in place, whether with the established therapist or referral elsewhere. Therapy may come to an abrupt halt from the patient's perspective after the last study visit, which is of particular importance in psychedelic trials as patients have likely formed a bond with their therapist after many hours of partnership for the trial. Offering an open-label extension where all patients can access active study drug for an extended period is helpful in these cases and is also a successful way of aiding recruitment and mitigating against potential drop-outs of patients who were not randomized to active treatment. Ethics committees and Institutional Review Boards may also look favorably on offering patients extended open-label treatment as it not only allows patients access to active study drug but also permits more extensive safety evaluation.

Choosing the Right Sites

In addition to having the competencies related to appropriate safety monitoring, sites should have experience in the psychiatric indication under study, as well as experience in running clinical trials intended for registration in a "good clinical practice" setting. Ideally, sites would also have experience in psychedelic research (even better in a range of psychoactive agents), but this is infrequent. Aside from the requirements for traditional psychiatric clinical trials, psychedelic trials also require:

- Adequate resources, with few overlapping, competing trials. The main source of competition is often for scarce resources and capacity within a given site, although competing for the same patient population should also be considered,
- Sites with specialized, qualified, and trained therapists (or facilitators, moderators) that are separate from the investigator responsible for overall patient safety. Two therapists, one male and one female, are ideal.

- Additional independent efficacy raters, qualified and trained to rate scales being used in the study. Alternatively, centralized raters not on staff at the site may be used, which is often a more efficient approach that aids in minimizing unwanted variance in assessments.
- Recent experience with a range of Schedule 1 (or comparable) controlled substances, with adequate and secure storage. A separate pharmacist may be required if the drug storage location is off site.
- Suitable space for dosing rooms, with the ability to adjust the setting (furniture, lighting, audio) to specific protocols or to handle group dosing, if required.
- Importantly, the ability to recruit patients with established patient referral pathways in place, ideally ones who are well known to the investigator or referring physician. Sites that have a combination of their own clinic patients and additional patients through referrals tend to be the most successful. A tailored approach for each site is the most helpful way to boost recruitment, and establishing the patient recruitment pathway early on is key. Site-based referral pathways are more productive than broad direct-to-patient outreach campaigns for finding suitable patients whilst also mitigating the potential to overload sites with ineligible patients.

The geographic location of the site can also be important from a regulatory and timeline perspective. In some countries, the lengthy and cumbersome controlled substance licensing process can be started in parallel with ethics committee submissions as soon as sites are selected.

Given the tremendous increase in psychedelic trials, many more competent sites are needed. Of note, it is easier to train sites established and experienced doing regulated clinical trials which may not be experienced with psychedelics than to upskill those experienced with psychedelics on regulatory requirements conforming to International Conference on Harmonization Good Clinical Practice standards. One possible solution is to select known sites or site networks experienced with Phase 1 psychiatric trials that have an inpatient unit and infrastructure already in place and train them in the methods specific to psychedelic compounds and research setting. Having a blend of sites will greatly improve recruitment because experienced sites have clear and established patient pathways at the outset. Sites with previous psychedelic experience mitigate the risk of delays to site activation due to Schedule 1 licensing complexities and therapist recruitment, ultimately leading to delayed start-up timelines.

Summary

One clear illustration of the renewed interest in drug development for psychiatric disorders is the tremendous growing interest in psychedelics, hailed as potential treatments for anxiety, depression, and addiction – indications that have exhibited a recent rise in prevalence but with available treatments characterized by only modest efficacy with significant side effects. Recently both regulatory and funding agencies have demonstrated their willingness to both support and speed the approval of psychedelic treatments. Many pharma/biotech companies have taken advantage of these events and now find themselves in possession of promising albeit limited initial safety and efficacy data in small proof-of-concept studies. This encouragement for further development and the accompanying demand for more sites that can reliably and systematically conduct controlled clinical trials of psychedelics makes it imperative that drug

developers optimize study parameters. Specifically, sponsors should drive best practices surrounding proper patient and site selection, appropriate safety monitoring, training on apposite efficacy assessments and drug-related subjective effects, and management of "placebo" response in a rigorously controlled trial setting -- all while ensuring assay sensitivity and clinical equipoise. Only with the application of these effective and practical clinical trial methodologies can the conduct of large, global clinical trials of psychedelics intended for registration be ensured.

AUTHOR INFORMATION

Conflicts of Interest:
All authors are salaried employees of Worldwide Clinical Trials, an international, full-service, contract research organization that specializes in clinical research activities in support of the pharmaceutical industry. Relationships exist with multiple (>100) pharmaceutical companies as part of the company's primary business activity.

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