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Preventing the Gaps in Psychedelic Research from Becoming Practice Pitfalls: A Translational Research Agenda

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Abstract

The reemergence of psychedelic medicines as clinical treatments has generated considerable interest in both professional and popular arenas. Although evidence is promising for psychedelic-assisted therapy (PAT), there is much that is not yet known and needs to be researched so as to understand how to safely and effectively utilize PAT in clinical populations and to most effectively deploy PAT to patients. In addition, non-clinical stakeholders introduce interests and agendas that may differ from those of clinicians. This article reviews the history of how psychedelics were initially outlawed and then introduces research questions that will help to fill these gaps in knowledge.

Keywords: psychedelics, PAT, psychotherapy, research gaps, research agenda

Introduction

The findings emerging from clinical trials of 3,4 methylenedioxymethamphetamine (MDMA)-assisted therapy for Post Traumatic Stress Disorder (PTSD) and the use of psilocybin-facilitated therapy for major depression have generated excitement within the field of mental health and in the culture at large.[1] Psychedelics, including psilocybin, were made illegal in the United States with the enactment of the Controlled Substances Act in 1970. MDMA was added in 1985.

These two drugs are now poised for approval by the US Food and Drug Administration (FDA). Other countries around the world, such as Australia, Canada, Israel, the United Kingdom, and others, are also considering steps toward legal approval for psychedelic therapies. For the many who have worked tirelessly to re-engage society's interest in these substances, the likely approval of these drugs for clinical use will likely feel like an enormous validation of the therapeutic value of psychedelics and a repudiation of the sullied reputation of these compounds.

It is, indeed, remarkable that these drugs, half a century ago, were deemed to have considerable risks with no medical benefits but are now being heralded as novel approaches for the treatment of intransigent and common mental health conditions.

As FDA approval in the United States becomes more imminent, it is important to be clear about what such approval does and does not mean. It is also essential to distinguish between FDA approval of psychedelics and the adoption and integration of psychedelics and psychedelic-assisted

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therapy (PAT) into the armamentarium of existing treatment options for patients.

The FDA approval in one country only represents a starting point from which to begin conversations about the long-term viability of psychedelic therapies. It is not the finish line. Typically, drugs are approved by the FDA after a lengthy process of small Phase 1 and 2 studies to assess for safety and early indications of efficacy, that are then repeated in Phase 3 trials in which the efficacy and safety is confirmed in a larger, more diverse population of patients.

Once the FDA approves a drug for a specific clinical indication, it is up to clinicians, advocates, payers, consumers, and larger health care systems (such as the Veteran's Administration) to determine whether or how the new drug can be integrated into existing clinical treatment infrastructures and/or adopted into wider practice. The FDA approval of a drug for a specific medical indication does not imply permission to use the drug for other purposes, particularly if the FDA imposes a risk evaluation mitigation strategy (REMS) plan, as it is likely to do with PAT.[2]

Other countries will undergo their own regulatory processes that may be influenced by FDA decisions, and the implications on regulations in other countries will vary. Although clinicians in the United States will have some discretion when it comes to off label prescribing of approved medicines, the FDA/REMS will carefully monitor use of new drugs and can rescind or modify the conditions of approval if warranted.[3]

This article will discuss some of the upcoming challenges facing psychedelic treatments for mental health as they gain more traction in a post-approval environment. Many of these challenges can be anticipated by carefully reviewing the history of how the perception of psychedelics went from novel, mind-expanding compounds that could be potential therapeutic agents in psychiatry to villainous drugs that posed a threat to users.

One of the biggest contributors to the US federal government's scheduling of psychedelics and other drugs in 1970 was the lack of compelling scientific data from rigorous clinical trials before the widespread use and abuse of these drugs occurred in the mainstream population.[4] There is currently a feeling of déjà vu for many observers, as the interest in psychedelics rises once again, leading to financial investment and political action to legalize these drugs for the mainstream without ample scientific foundation for the use of these compounds for conditions beyond the indications for which they were studied.

Scientific data, both clinical and translational, are necessary precursors for investment in drug development, policy change, and mental health advocacy. We, therefore, identify fundamental research questions that will increase acceptance of these treatments in the clinical arena and protect against a potential backlash that may occur in reaction to unanticipated adverse consequences of psychedelics. We further discuss how interests of nonclinical stakeholders in the psychedelic arena may affect the viability of psychedelics as mental health treatments.

History

Psychedelics are compounds that promote a change in consciousness, perception, and acuity of senses. Often, people report that the psychedelic induces a sense of revelation or transpersonal (mystical) experience. The term ''psychedelic'' is a Greek neologism meaning mind-manifesting. These compounds typically engender temporary changes in emotion, perception, cognition, and personal narrative.

Most psychedelics under the current study are not novel drugs *per se*. Compounds such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT) are typically referred to as *classical psychedelics*. MDMA and ketamine, though subject to some debate among pharmacologists because of their different mechanisms of action from these classical psychedelics, will be included in the term *psychedelics* for the purposes of this article.

An extensive discussion of the pharmacology of these compounds is beyond the scope of this article and has been discussed elsewhere.[5] MDMA has been described as an entactogen or an empathogen, suggesting it occasions the experience of ''touching within'' and/or increasing empathy for self and others that is useful in the treatment of trauma.[6]

At this time, there is no clear consensus definition of psychedelic drug, nor is their agreement about whether the salient feature of the psychedelic should be its subjective effects, mechanisms of action or type of pharmacologic compound, or ability to facilitate a shift in perspective.

Certainly, psychedelics are compounds that have historically garnered significant interest by scientists, clinicians, countercultures, and the public at large, because of their unique subjective properties, until their unregulated use and the threats this posed contributed to the banning of these substances, even in cases where they may have had clinical utility.[7]

Psychedelic studies, beginning in earnest in the early 2000s, appear to have been conceived by stakeholders seeking to remediate these drugs from their historical sullied reputation and to prove their utility as clinical treatments.[8]

Positive results from treatment outcome studies create a counterweight to the narrative that psychedelics were banned because there were not enough data to support their therapeutic use when compared against the potential for their abuse. However, even with such studies, there are still considerable gaps in knowledge.

Gaps in knowledge can lead to unanticipated consequences and are best addressed through objective

research that is without bias or agenda. Failure to address important unknowns about psychedelics through systematic research may threaten the future clinical use of these drugs in practice, particularly if unanticipated adverse events cannot be identified and prospectively explored.

In the late 1940s, when articles about psychedelics—mostly LSD—began appearing in the scientific literature, and through the next decade and a half, there were no explicit prohibitions against physicians administering compounds to people and examining their subsequent effects.[9] Experimental compounds, including psychedelics, could be used as a treatment by physicians and administered to patients without adequate informed consent.[10]

LSD could be obtained from the Sandoz corporation for research purposes.[11] Thus, many reports—hundreds, according to PUBMED—were published of clinicians reporting what happened when psychedelics were administered as part of an ''experimental'' clinical treatment of a patient for conditions such as alcohol dependency or anxiety.[9]

By contemporary research standards, these studies were poorly constructed, almost always unblinded, and used non-standard outcome measures, or sometimes, no outcome measures other than qualitative clinical descriptions of the patients.[12] There were some attempts at prospective research studies on the effects of psychedelics in normal volunteers.[13] Although these studies were better designed, they were not necessarily informative about the efficacy of psychedelics in patients with psychiatric conditions. In some reviews, it is asserted that there is a wealth of knowledge in the scientific literature produced in the 1950s to early 1970s and that these should provide a sufficient reassurance for the safety and promising efficacy of these compounds.[14] However, only a handful of the studies in the literature would meet today's standards and some published reports from that period identify significant concerns or adverse effects.[7]

The practice in the 1950s and early 1960s of administering experimental drugs to patients and reporting anecdotal outcomes was not limited to psychedelic medicines. In that sense, the standard of the psychedelic literature was no better or worse than the standard in psychiatry or medicine, where anecdotal reports about the use of unapproved compounds were plentiful. By 1959, several physicians noticed that the over-the-counter drug thalidomide, used largely in Europe to treat anxiety and insomnia in pregnant women, was later associated with birth defects in the offspring of women who took this drug.[15]

Many thousands of women had taken thalidomide before actions were taken to stop the drug's distribution. Although thalidomide was not widely used in the United States, the risks of not having a clear process for vetting pharmaceutical agents was evident and in 1962, congress passed the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act of 1938 requiring evidence that prescription drugs were both safe and effective.

The FDA began requiring drugs to be tested, for a defined indication (which would become part of the drug label), utilizing clear protocols, informed consent, and randomized clinical trials.[16] Previously, only safety was regulated.[16] The patent on LSD was soon expiring in 1965, and Sandoz had no incentive to complete such studies.[4]

The FDA also began to monitor the safety of existing drugs more closely and, over the next 20 years, began to remove drugs from the historic pharmacopeia that had no evidence for efficacy under the Drug Efficacy Safety Investigation (DESI) program.[17] Thus, an important contributor to the end of psychedelic research were greater restrictions and a higher standard of evidence for the use of any drug in clinical treatment.

Although the FDA was trying to improve the safety and efficacy of all drugs, LSD slipped from the laboratory and the clinic, and became a libation for the counterculture. LSD proselytizers, such as the one-time Harvard professors Timothy Leary and Richard Alpert, and the California writer Ken Kesey are often credited with promoting the use of psychedelics among members of the younger generation.[18,19]

This led to Sandoz stopping the distribution of LSD in 1965 to researchers as well as the rise of underground chemists such as Owsley Stanley and Nick Sand creating illicit LSD known as ''purple haze'' and ''orange sunshine,'' respectively.[20,21] A popular historical narrative is that the mainstream conservative culture was fearful of the influence of Leary, who encouraged both the widespread use of psychedelics and the rejection of mainstream values, including participation in military service and conventional careers.[22]

Leary's rise in popularity and provocative edicts, in turn, are often linked to the general lack of self-restraint in some sectors of the psychedelic community of the 1960s contributing to the backlash and prohibition of these compounds.[23] Popular anecdotes, such as the suicide of the daughter of television host Art Linkletter, were questionably linked to LSD.[24] These anecdotes became apocryphal, leading to a polarized perception of the risks of psychedelics. Although psychedelics can certainly carry risks, the decision to prohibit psychedelics appears to have been based more on political considerations than scientific evidence.

On the other hand, the absence of rigorous studies (at that time) demonstrating therapeutic benefit limited the ability to mount a counterargument that psychedelics should be retained in the pharmacopeia. Therefore, LSD was federally criminalized in 1968 and formally classified by the Controlled Substance Act in 1970 as a schedule 1 compound.[25,26] This effectively rendered the possession and use of psychedelics illegal, even when used in biomedical research, except under the most highly regulated conditions.

In a coda to the psychedelic 1960s, the reputation of psychedelics as potentially dangerous compounds soon reached new heights as details of the government's secret, and by today's standards, unethical research on psychedelics became known. In 1977, the US Senate Select Committee on Intelligence heard testimony on Project MKULTRA that involved secret governmental projects in which psychedelic drugs were administered, unbeknownst to individuals, documenting serious adverse effects.[27]

Indeed, since the administration of psychedelics requires intention and preparation for being in an altered state, providing psychedelics to people who are not aware that they are ingesting these substances will not allow them to properly interpret perceptual distortions, and may amplify the fear attendant to losing control of one's faculties.

The convergence of the Controlled Substance Act of 1970 restricting research and the general increase in FDA oversight of drug development eventually added to a radical diminution of interest in the therapeutic potential of psychedelics.[10] Research into psychedelic compounds was still possible, although extremely challenging, requiring adherence to strict regulatory standards. As such, most research into the clinical uses of psychedelics ended during this time. But the end of the research was not specifically the result of governmental regulation prohibiting such activities.

From the 1970s through the early 2000s, most published papers on psychedelics examined the emergence of newer compounds, such as MDMA, and generally reported on the adverse consequences of these drugs on brain and behavior when taken recreationally, or when administered to animals.[28–30] The studies were often funded by the National Institutes on Drug Abuse (NIDA) and served as a *posthoc* justification for the banning of these drugs.

More importantly, they were instrumental in perpetuating the idea within mainstream science and medicine that psychedelic compounds could engender physiological and psychological harm in recreational users. It was the formation of the Multidisciplinary Association for Psychedelics Studies in 1986 and the first prospective study in human subjects examining the pharmacokinetics of DMT in 1994[31] that began a shift, or looking back on it now, a ''renaissance'' of psychedelic research began.[8,32] In 2006, human studies of psilocybin in both healthy subjects and clinical subjects were published.[33,34]

Breakthrough status for psychedelics

This resurgence of interest in psychedelics as a potential therapeutic tool for mental health has now led to FDA-registered trials of MDMA-assisted therapy for PTSD and psilocybin facilitated therapy for depression, both of which have shown promising results.[35,36] It is often assumed that if a drug being tested in Phase 2 and Phase 3 trials is more efficacious than placebo or the current standard of care, or more tolerable than extant treatments, then the findings from these studies will provide a sufficient basis for replacing the current standard of care.

One reason for this assumption is that the FDA will sometimes designate a potential drug or treatment as a ''breakthrough,'' as was the case with MDMA-assisted therapy for PTSD and psilocybin-facilitated therapy for depression.[37,38] The term ''breakthrough'' implies that the efficacy of the drug is a *fait accompli*, but breakthrough status as the FDA uses the term simply means that the new approach is promising enough for the FDA to work with the sponsor of the drug to design studies and then to approve the drug if the mutually agreed upon studies yield data that demonstrate statistical significance of the drug over the comparison condition.[39]

The term ''breakthrough'' creates the impression that the new treatment renders prior approaches to be less meritorious. This is sometimes the case. But often there can be practical and logistical barriers to adopting a superior treatment that might be cause for concern when a health care system is considering adopting a superior-performing treatment or a third-party payor is considering reimbursing it.

Once the FDA approves a drug for clinical use, particularly in mental health, it becomes easier to conduct widespread research in populations that reflect those seen in clinical settings. The kind of research performed, following approval, generally answers many relevant clinical questions that were not addressed in safety and efficacy studies designed to create a treatment for a given disorder. Adverse events that emerge following approval may cast a pall on those treatments leading to restrictions in use, or sometimes, a change in status, as was the case when an increased risk of suicidal ideation in young people treated with antidepressants was noted, leading to a black box warning.[40]

Why Clinical Research on a Drug Continues Beyond the FDA Approval Process

The short answer to this question is that very often, decisions made regarding the design of a clinical trial or occurrences during the course of the trial result in data that may not be representative of the population suffering from the clinical condition, challenging the generalizability of the treatment. Further, as in all scientific research, results of a particular trial may raise many questions that need to be answered through more investigation to increase the viability of the treatment.[41]

Indeed, in almost all cases involving new therapies in mental health, there is a wide abyss between how a clinical trial has been conducted under the very stringent protocol requirements and inclusion/exclusion criteria of the participants versus how the same treatment will be applied in clinical practice. Failure to conduct the effectiveness studies demonstrating what happens when a

promising treatment is moved from the more rarefied world of the clinical trial into clinical practice may result in a backlash among clinicians and their patients.

This is true even for psychological treatments that do not involve medications or FDA approval. A cogent example of this occurred more than a decade ago when the field of PTSD began embracing cognitive behavioral therapies such as prolonged exposure. Prolonged exposure therapy showed extraordinary benefit for PTSD (compared with a condition in which participants were placed on a waitlist) in early clinical trials and was quickly ratified into treatment algorithms by receiving the highest recommendations for gold-standard status.[41]

However, as dissemination efforts were initiated and clinicians began trying these treatments on their own patients, the effects observed were more modest and the treatment was not well tolerated, leading to diminished enthusiasm for these approaches among many providers. In a recent effectiveness trial at the VA comparing the two leading cognitive behavioral therapies, prolonged exposure, and cognitive processing therapy, there were statistically significant reductions in symptom severity for patients completing the trial, but about half of the patients dropped out.[42]

Whether or how any treatment becomes or is sustained as a ''gold-standard'' for therapy of a particular condition depends on a myriad of factors, but almost always also reflects the enthusiasm of the academic and medical community, which is communicated through clinical trials and published guidelines from professional organizations such as the American Psychiatric Association. As research in an area continues, observations are made that confirm, contextualize, or maybe diminish initial enthusiasm.

Typically, the FDA approves a drug once clinical efficacy, compared with a placebo, is repeatedly demonstrated. Psychotherapy is usually not regulated by the FDA (unless attached to an FDA-regulated medical device). The case of FDA approval for psychedelic-assisted therapies is unique in that many proponents of psychedelic use for mental health emphasize that ingesting the drug alone will not yield therapeutic benefits or if benefits do occur that they would not endure beyond the duration of drug effects.[43]

The term ''set and setting'' denotes that a person's intention when using the drug (e.g., recreation, seeking spirituality, or obtaining an insight that will place them on the path of reducing mental health symptoms), as well as the environment in which the psychedelic is used, is critical.[44] For mental health treatment, the intentions for use are generally clear, but what is important is the therapeutic container and the clinicians who can provide psychotherapy before, during, and after psychedelic use.

It can be anticipated that when PAT's do become FDA approved, questions will arise about the extent to which clinical practice with the psychedelic compound will need to conform to the protocols used in clinical trials or whether other types of psychotherapy or support can equally assist the patient. Issues such as dose, number of sessions, number of therapists, and use of psychedelics with other compounds are likely to emerge, not to mention, one of the most contentious questions of all—what credentials or training are necessary to safely facilitate a PAT for a mental health patient.

These questions—which currently constitute fundamental gaps in knowledge—will need to be answered in future studies. Indeed, the answers to these questions will greatly impact the practice and perhaps scalability of these approaches and will influence how education and training for future psychedelic therapists will occur. At this time, there are no reliable data from controlled or even naturalistic studies to understand the level of flexibility that can be exercised in the ''extra-pharmacologic'' components of psychedelic therapy. However, recently, several concerns have been noted regarding the lack of standardization of psychotherapy with suggestions for future research in this area.[45] There is no question that the psychotherapy portion of psychedelic-assisted psychotherapy has received less attention that it will likely need to receive in future studies.

Potential influence of post-approval observations

The FDA continues to scrutinize the safety of a drug following its approval and has the power to modify or withdraw it from use. Following approval, phase 4 or post-marketing surveillance begins. Post-marketing surveillance refers to the process of monitoring the safety of drugs once they reach the market, after the successful completion of initial clinical trials. This is standard practice for all drugs and is separate from the preliminary research that led to drug approval.

The purpose of this surveillance is to identify previously unrecognized adverse effects and to see whether the drug shows benefit for other conditions (i.e., off-label use). The burden of monitoring these effects falls on the sponsor of the drug that has received the approval and is part of the conditional approval granted by the FDA. If an adverse event is repeatedly reported to the FDA, a drug can be restricted from use, or even pulled from the market.

This occurred with Chantix (varenicline), a novel smoking cessation drug approved by the FDA in 2006.[46] Shortly after FDA approval, repeated reports of the drug causing exacerbation of existing severe mental illness, such as schizophrenia or bipolar disorder, led to the FDA placing a ''black box warning'' on the drug in 2009 (the strongest action they could take short of removing it from the market), severely curtailing its prescription among people with serious mental illnesses.

Since people with these conditions use tobacco at a much higher rate than their non-mentally ill peers, this

black box warning significantly reduced the use of varenicline with these patients. Seven years later, faced with new evidence that did not confirm the link between varenicline and exacerbation of mental illness, the FDA retracted the black box warning.

Despite this exoneration, the number of patients treated with this drug did not significantly increase.[47] A sullied reputation, once established, is difficult to rehabilitate. Negative outcomes can happen with all drugs. To prevent a similar reflexive regulatory response with PAT, it will be critical to amass safety data with more trials that can identify emergent patterns of harm and for clinicians to begin to take steps toward mitigating these potential risks.

Current gaps in knowledge

The types of questions that will need to be addressed in order for clinicians to have greater confidence in adopting psychedelic therapies in mental health are delineated in Table 1.

What conditions can benefit from the therapy? There are many Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM5-TR) diagnoses, such as generalized anxiety disorder, acute stress disorder, obsessive-compulsive disorder, and non-DSM5-TR diagnoses, such as complex PTSD and the effects of intergenerational trauma that have generated interest as potential targets for PAT but have not yet been thoroughly studied. Off-label use of a drug refers to a common practice in medicine and mental health in which a provider will prescribe a treatment approved for one condition to a person who is presenting with a different disorder.

For example, an FDA-approved treatment for major depressive disorder might be prescribed for someone with PTSD or prescribed for someone with depressive symptoms who does not meet full diagnostic criteria for major depression. This clinical practice generally helps identify other conditions that may benefit from a given treatment.

On the other hand, prescribing off label is risky because a clinician may not know for sure whether the drug will be safe and effective in a different condition (or in a population that was not represented in clinical trials to date). To manage this clear risk/reward ratio, REMS programs are imposed by the FDA, adding additional restrictions on how the drug is used and who is permitted to administer it, including monitoring off-label use.

Table 1. Gaps in Current Psychedelic Research

Gap	*Remediation*
What other conditions can benefit from the therapy?	This is best answered with clinical trials seeking to study the utility of psychedelic-therapy in other mental-health conditions and evaluating the extent to which the presence of comorbid conditions affects clinical outcomes.
Are the findings generalizable to clinical populations with the indication?	Future trials should have participants who reflect a broader racial, ethnic, and socioeconomic range representative of clinical populations. Presence or factors previously excluded in trials should be evaluated (e.g., presence or Traumatic Brain injury and other physical, medical, or psychiatric conditions). Finally, investigations on the use of psychedelic therapies in tandem with psychiatric medicines such as SSRIs should be examined.
What risks are not yet known?	Postmarketing surveillance should be conducted to monitor for uncommon side effects of PAT. The research questions cited earlier may very well identify risks in more diagnostically complex patients.
Is the psychotherapy component optimized? What kinds of therapies can be delivered? How should therapists be trained?	Different modalities and durations of psychotherapy (including little or no therapy) should be tested in PAT models.
Is it possible to increase the benefits of fewer psychedelic doses by adding more opportunities for integration?	Integration should be seen as an ongoing process that will include community institutions. These institutions should be identified and developed as resources to those who have undergone PAT.
How do PAT outcomes compare with those of gold-standard treatment for the disorder? What are the minimum effective doses of psychedelics? How long do the benefits persist? Can PAT be safely and effectively provided in group settings? Can different psychedelics be provided in combination?	PAT should be compared with a known treatment modality in head-to-head studies to establish comparative superiority and relative value to better inform placement of PAT in treatment algorithms. Group therapies and combinations of psychedelic treatments should be studied, and long-term treatment durability should be tracked.

PAT, psychedelic assisted therapy; SSRI's, Selective Serotonin Reuptake Inhibitors.

The absence of an REMS program with racemic ketamine led to widespread off-label use of the drug in a way not seen with its enantiomer, esketamine, which is only indicated for treatment-resistant depression or major depression with suicidal ideation or behavior and governed by a REMS.[48] In addition, the absence of an REMS for ketamine has led to widespread prescription of unsupervised, at-home ketamine treatments, with a low bar to access, raising concerns of risk to patients.[48,49]

The presence of an REMS may frustrate sectors of the psychiatric profession who are eager to offer PAT to patients without indicated diagnoses, especially to those who have not benefited from previous treatments. However, evidence should be gathered to understand the risks and benefits of PAT for patients who have diagnoses outside of the labeled indications and future research should examine these populations and conditions that may fall outside the initial FDA-approved indications.

Are the findings generalizable to people with the indication groups that were excluded in trials? The relative racial and socioeconomic homogeneity of PAT clinical trial populations to date leads to challenges in extrapolating whether those same outcomes will be replicable in patients who do not mirror the characteristics of clinical trial subjects and has been discussed.[50]

Media portrayals of successful treatments with PAT often focus on atypical patients in a given population, for example, Navy SEALS treated with PAT in overseas clinics, implying that these findings are generalizable to a more typical VA population with PTSD when this generalizability is not yet known.[51]

How generalizable are findings to clinical populations seeking help for their symptoms? What risks are not yet known? Clinical trials attempt to estimate the effects of a given treatment in a sample that represents the clinical population on whom a treatment will eventually be deployed. The more a study population mirrors the clinical population, the more the results of the trial become generalizable. Studies that exclude subjects with many common clinical presentations will lead to datasets that cannot predict real-world outcomes and may lead to REMS that restrict the use of PAT in many patients.

In the interest of safety, study sponsors and institutional research boards often require stringent exclusions of patients that represent the people who are seen in clinical practice: subjects with diagnostic complexity and those who are more medically vulnerable. This tension between generalizability to a population and maintaining safety for study subjects leads to gaps in knowledge.

Study sponsors, in the interest of generating clear and unambiguous outcome data, require study subjects to clearly meet the diagnostic criteria for a clinical diagnosis and to be free of other specific psychiatric diagnoses. This diagnostic certainty is not often seen in clinical practice. Translational gaps occur when a clinician cannot anticipate potential adverse events in a real-world clinical patient, because the subjects in a clinical trial are diagnostically dissimilar from actual patients. For example, patients with PTSD are 2–2.9 times more likely to have a substance abuse disorder (SUD), yet most trials of PAT exclude patients with SUD's.[52]

In addition, many patients may have a history of psychological trauma, but do not meet full criteria for PTSD. Further, people with borderline personality disorder (BPD) may seek treatment with PAT, especially since BPD is a condition that is highly comorbid with trauma.[53] However, people with BPD have been excluded from extant trials of psychedelics, which means we do not know whether PAT will be effective, or even possibly harmful in people with BPD.

Attachment issues common to patients with BPD in therapy may necessitate the duration of PAT to be extended beyond the two to three sessions of preparation and integration typically done in existing studies to build trust and facilitate appropriate termination of PAT therapeutic relationships. Future studies should consider including subjects with BPD to see whether PAT is effective and safe in this population.

Many future PAT patients will likely be taking psychiatric medications, however many PAT studies to date have required subjects to stop conventional psychiatric medications during the study. In clinical practice, this may not be practical or safe. As such, studies that permit patients to continue taking their existing medications, whenever possible, should be completed to guide future clinical practice.

Is the psychotherapy optimized? What kind of therapy should it be? How should therapists be trained? Extant studies of PAT have paired psychedelic drugs with psychotherapy, however the optimum type of psychotherapy and number of sessions has yet to be determined. Most of these therapeutic models, carried forward from early PAT work in the 1950s, encourage inward focus with the use of eyeshades and pre-selected music played during the session. Preparatory sessions may include aspects of mindfulness and somatic therapy, teaching subjects to utilize deep breathing and grounding techniques if they experience distress during the drug session.

Unlike conventional therapy where the patient and clinician are in active dialogue during the treatment, conversation between the patient and therapist often largely occurs before and after the drug sessions. In MDMA PAT studies, participants are asked to address the trauma at some point during the drug session but are permitted to visit this material at their own pace, dissimilar from extant models, such as prolonged exposure, that focus

extensively on repeatedly revisiting the traumatic event to facilitate extinction of PTSD symptoms.

Groff encouraged psychedelic therapists to facilitate an ''inner healing intelligence'' in sessions, an oft quoted but vaguely defined concept that has been difficult to test in empiric studies.[54] Some authors have argued that third-wave cognitive behavioral therapy modalities such as Acceptance and Commitment Therapy and Dialectical Behavioral Therapy should be the default treatment in PAT, but this declaration has not been adequately proven, as there have not yet been direct comparative studies against other modalities.[55]

PAT studies comprise one to three psychedelic sessions, bookended by non-drug therapy, delivered by a team of clinicians who are separate from the patient's ongoing therapist, similar to how procedures such as electroconvulsive therapy (ECT) are not usually provided by the primary psychiatric clinician. It is unknown whether this outsourcing of PAT could negatively affect existing therapeutic relationships.

In addition, current studies usually use larger doses of these drugs. Pre-prohibition use of LSD sometimes used a model employing more frequent, but lower doses of drugs as a psycholytic adjunct to therapy, reducing defensive structures but maintain verbal abilities and concentration so that psychotherapy could be provided through the drug session. This psycholytic approach is largely unstudied in the current research.[56]

Like the psycholytic approach, the current popular phenomenon of ''microdosing'' or using sub-perceptual doses of psychedelics on a semi-regular basis raises a key question about the minimum effective therapeutic dose of these drugs.[57] Further, clinical trials should include a long-term follow-up arm to examine the durability of benefits and to monitor for any emergent adverse events.

Finally, in anticipation of the FDA approval of these drugs, many entities have begun to offer therapist training in PAT,[58] speculating as to what kind of skills and knowledge regulators may be required of future psychedelic therapists. The curricula of these programs are anticipating what the FDA/REMS or psychedelic drug manufacturers will require of psychedelic therapists, and as such, remain somewhat speculative in their content. As regulators begin to clarify these requirements, future educational outcome research should examine the best practices for training psychedelic therapists.

Many will be interested in reducing the cost and time required to deliver PAT.[59] At this juncture, we do not know whether these compressed or truncated models will be as safe or provide the same outcomes as studies to date. For example, most studies have used two therapists for all sessions, for practical reasons (allowing for breaks during a long day), and ethics/accountability (protecting patients while in a nonordinary state of consciousness), which adds considerable cost to the model.

It would be useful for a randomized study to know whether the same outcomes can be delivered with one therapist. In addition, the optimum ''dose'' of preparatory and integration therapy has yet to be studied or whether different clinical populations will need more or less therapy than what has been utilized in studies to date. Other ongoing studies are examining whether a two-dose MDMA-PAT protocol is as effective as a three-dose treatment.[60]

As such, it would be of interest to study whether the same efficacy and safety seen in PAT studies to date are retained when the psychotherapy aspect is removed or significantly reduced. Finally, the use of group therapy as a means of reducing cost of PAT has been demonstrated in pilot studies but needs additional study.[61]

Is it possible to increase the benefits of fewer psychedelic doses by adding more opportunities for integration? Therapeutic integration of psychedelic experiences appears to be critical to generating a positive outcome.[62] As psychedelic experiences become more commonplace (both inside and outside of medical contexts), it is important to study and understand which cultural institutions are best equipped to receive these people, helping to integrate and make meaning of the psychedelic experience.

Although some may continue this integration process with an existing psychotherapist, it is worth considering how larger, nonclinical, community institutions might accommodate this need to make sense of a psychedelic experience and to implement any personal learnings or changes from the session into their life. Studying psychedelic community groups modeled after existing institutions such as 12-step meetings, psychedelic societies, or spiritual groups could provide useful guidance as to how to help those who have recently had a significant psychedelic treatment to integrate the experience.

How do PAT outcomes compare with those of gold-standard treatment for the disorder? Clinical trials are designed to answer the question of whether a treatment works, compared with placebo, in a given population. Clinical treatment is intended to provide clinical care and does not involve a placebo. As such, translation is needed and head-to-head studies need to be conducted that compare PAT with existing treatments, such as Selective Serotonin Reuptake Inhibitors (SSRI) or Cognitive Behavioral Therapy (CBT), to establish the place of PAT in treatment algorithms and guidelines.

In the one study of escitalopram to psilocybin PAT for MDD (both groups received equivalent psychological support), psilocybin was not found to be superior to escitalopram on the primary outcome of changes in depression as measured by the Quick Inventory of Depression Symptomatology—Self report ($QIDS\text{-}SR_{16}$). On the

secondary measures of depression and well-being, psilocybin did show greater improvements.[63]

Subsequently, the research team published a critique of the QIDS as a measure of depression despite having selected it as their primary outcome.[64] If the QIDS does, indeed, have psychometric shortcomings, the study should be repeated with an alternate metric of the primary antidepressant outcome.

Patients want to receive the most effective treatments with the fewest side effects. Payors of health care and health care systems want to offer the most cost-effective treatments to patients. However, with the current relative absence of head-to-head studies and cost-benefit analyses, it will be difficult to know where PAT will reside in treatment algorithms. PAT often has significant upfront labor costs with many hours of therapy concentrated in a short period of time.

However, if the gains occasioned by PAT prove to be enduring, these initial costs may be offset by long-term savings in the form of reduced treatment utilization, but more long-term treatment durability studies need to be undertaken. Further, if PAT could cure conditions that currently remain chronic, this modality could significantly reduce long-term health care costs.[65] Studies directly comparing the cost, safety, and efficacy of PAT against existing treatments need to be completed.

Implications of Nonclinical Stakeholders

Adding to the complexity of the adaptation of psychedelics is that clinicians, patients, payors, and mental health care systems are not the only stakeholders in this repositioning of psychedelics in the larger culture. Cognitive libertarians wish to engage in the use of psychedelics for recreational personal exploration, a practice that is currently illegal under current laws.[66] This group is often supportive of drug policy reformers who have been successful in decriminalizing certain psychedelics (usually from plant and fungal sources) in cities such as Denver and Oakland for personal use.[67] Advocates of drug policy reform have long stated that prohibition is a failed policy and that incarceration for individual drug use is unjust, and ineffective, particularly toward the goal of harm reduction.

This message is clearly coming across in regional and national policies with respect to cannabis and will likely generalize to psychedelics over time. However, although legalization and decriminalization efforts may seek to correct an over-inclusive drug policy that has denied many the opportunity for spiritual or recreational use and resulted in disproportionate rates of incarceration among certain groups, it will certainly allow unfettered access to psychedelics for people who are more vulnerable and whom would need a more therapeutic container for safer use.

If the efforts of those who wish to see psychedelics more widely available lead to negative outcomes in these unsupervised settings, the potential backlash could threaten the availability of PAT as medical treatments. It is clear that harm reduction resources will be needed in the future, but a few studies on the effects of harm reduction are available.[68]

Recent efforts by advocates have led to successful initiatives for legal access to psilocybin in 2 states, including Oregon, who will roll out a framework for psilocybin retreat centers in 2023, and at the writing of this article, 17 states are drafting legislation to change the legal status of psychedelics.[69,70] The pharmaceutical industry and investors of venture capital also have significant interests in the outcome of PAT research, with the psychedelic pharmaceutical industry estimated to be worth over $8 billion US Dollars by 2027.[71]

This excitement has been further amplified by the popular press, in which journalists highlight dramatic PAT experiences that resulted in positive outcomes, often high-profile ex-military or celebrities, sometimes overlooking those who did not have such a significant response.[72] Many advocacy groups are seeking to accelerate the process of legalization of psychedelics and may have agendas that are significantly different than those of clinicians.

These nonclinical stakeholders have a vested interest in accelerating access to psychedelics (it should be noted that Indigenous groups, such as the Native American Church, that use peyote as a constitutionally protected sacrament, are intentionally left from this list of stakeholders as their agenda is not to expand access to psychedelics in the larger population, but rather to allow for the sacramental use of peyote among indigenous communities).

It is tempting to confuse medical approval of psychedelics with widespread legalization, when, in fact, these are two significantly different policies. It is unknown what risks that increased non-medical use of psychedelics may occasion if medicalization appears to provide endorsement for recreational use, and whether these unknown risks may threaten the future medical uses of PAT.

Next Steps

The psychedelic renaissance is at a place where the call to have these treatments broadly available in and out of mental health settings is currently outpacing the science. The risk of this exuberance is that unforeseen perils lead to negative outcomes that could contribute to another call for banning these substances. Although PAT research has contributed much to our understanding of these treatments, the bulk of the work lies ahead of us, not behind us.

Temperance in the psychedelic space is required to allow time for dispassionate science to try to answer the questions posed in this article. Temperance, or self-restraint—referred to as *sophrosyne* in ancient Greek philosophy—is a means to counterbalancing the risks of hubris.[73]

The French philosopher, Michel de Montaigne, remarked in 1588 on temperance, ''Greatness of soul consists not so much in mounting and in pressing forward, as in knowing how to govern and circumscribe itself.''[74] There are many stakeholders—society at large, cognitive libertarians/ ''psychonauts,'' patients, clinicians, payers, drug policy reformers, and the pharmaceutical industry—who may attempt to drive this process faster than the scientific evidence.

However, conflating the interests of clinical research with the interests of cognitive libertarians, drug policy reformers, or the stock market will not narrow gaps in knowledge. These stakeholders may pose a distraction from the slow, deliberate research needed to determine whether these treatments are safe and effective in clinical populations and may jeopardize the use of these compounds as mental health treatments.

Asking and answering the important scientific questions will take longer, but eventually will yield useful tools for mental health along with appropriate attendant regulation. Failure to first advance scientific and medical interests may yield a backlash due to adverse events, even if the negative outcomes are uncommon, especially if these adverse events are highlighted by the same popular press that is currently championing these drugs.

Advocates of psychedelic therapies should welcome the opportunity to work together as a united group rather than to reflexively extinguish calls for caution as advocacy for continued prohibition of psychedelics. Continuing a federally prohibitionist policy in response to unanticipated adverse events would be a facile response from government regulators who may be apprehensive about the changing status of psychedelics, so it is incumbent upon the field to anticipate and avoid these pitfalls by continuing to undertake studies that yield critical information needed to make the prudent policy decisions that will best serve our patients.

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