Psychedelics as Reemerging Treatments for Anxiety Disorders: Possibilities and Challenges in a Nascent Field

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Although psychedelics initially showed promise in treating anxiety disorders, psychedelics were criminalized and research halted in the early 1970s. A subsequent resurgence of research into psychiatric benefits of psychedelic-assisted psychotherapy in the last 20 years has led to a potential paradigm shift in the treatment of numerous psychiatric disorders, including anxiety disorders. Despite accumulating evidence and likely U.S. Food and Drug Administration approval in the next 2–3 years, the emerging field of psychedelic medicine faces several challenges. Obstacles include ongoing barriers on the regulatory level, lack of education, stigma among mental health clinicians, cost and scalability, and a dearth of specialized personnel prepared to provide these treatments. Deeper issues of ethical responsibility and inclusivity also exist given the historical discovery and use of psychedelics by indigenous peoples throughout the world as well the ongoing disparities in mental health delivery and access within psychiatry and psychedelic research.

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Despite decades of research, first-line pharmacotherapy for anxiety disorders and stress-related disorders still relies on modulation of monoaminergic systems, which on a conceptual level has advanced very little since the first development of monoamine oxidase inhibitors in the 1950s (1). Although the subsequent development of serotonin and serotonin-norepinephrine reuptake inhibitors has led to greater safety and tolerability, substantial numbers of patients will not recover (2). Moreover, these treatments are not "cures" and do not permanently shift underlying neurobiology, thus likely requiring continuous treatment to exert an effect (3). Although the development of cognitive-behavioral therapies for specific anxiety and stress-related disorders has also led to some success, these treatments are only moderately effective, leaving a substantial proportion of patients remaining symptomatic (4).

In recent years, research and media attention have dramatically increased as to the potential for psychedelics and psychedelic-assisted psychotherapy to treat mood and anxiety disorders, trauma and stress-related disorders, and substance use disorders. Several factors suggest that psychedelic-assisted psychotherapy may be useful for treating anxiety disorders. First, a handful of studies have specifically examined psychedelic-assisted psychotherapy for specific anxiety disorders. Second, studies examining other psychiatric disorders, such as mood disorders and trauma and stress-related disorders, have demonstrated reductions in psychological factors that as a whole may also be present in anxiety disorders, thus pointing the way for utilization of psychedelic-assisted psychotherapy. Third, neuroscientific evidence is accumulating that psychedelics and psychedelic-assisted psychotherapy modulate neural circuitry and neuropsychological constructs associated with pathology across a broad array of psychiatric disorders, including anxiety disorders.

Despite significant clinical and scientific advances in psychedelic medicine, and designation of MDMA- and psilocybin-assisted psychotherapy protocols as "breakthrough therapies" meriting priority review by the U.S. Food and Drug Administration (FDA) (5, 6), knowledge and potential clinical applications of psychedelics remain largely unknown to most psychiatrists. In addition to a lack of education about psychedelic medicine, significant issues face this nascent field, including goals of use; accessibility of these treatments once available; as well as broader ethical, anthropological, and social justice issues within the fields of psychedelics, medicine, and psychiatry. The purpose of this synthesis is therefore to review the clinical evidence to date, with a focus on why psychedelic-assisted psychotherapy may ultimately be found to be beneficial in treating anxiety disorders, followed by a discussion of the barriers and issues requiring attention in the coming years.

PSYCHEDELIC-ASSISTED PSYCHOTHERAPY

Early uses of psychedelics were modeled on contemporary, psychoanalytically based understanding of psychiatric illness and focused on the perceived ability of psychedelic compounds to reduce ego defenses during psychotherapy (7). This model, known as psycholytic therapy, used repeated, low to moderate doses of psychedelics, usually lysergic acid diethylamide (LSD), during therapy sessions and sought to use the drug experience to enhance a psychodynamic understanding of patients' symptoms (8). By the early 1960s, a radically different model began to be increasingly used, with a vastly different structure, approach, and conceptualization. Dubbed psychedelic therapy, or psychedelic-assisted psychotherapy, it drew heavily from the school of transpersonal psychology and was often deepened by drawing on quasi-religious or spiritual traditions (9, 10).

Psychedelic-assisted psychotherapy relied on a high degree of preparation with extensive therapy sessions leading up to a single, high-dose drug session, which was then followed by a series of integration therapy sessions in which the patient was encouraged to interpret what transpired during the psychedelic experience. The psychedelic session, presided over by a therapist at all times but with emphasis on the patient's internal experience (nondirective), was augmented by the use of ensuring a calm environment and décor, often with the accompaniment of music and eyeshades to accentuate an internally focused experience (11). Special attention was paid to set (the mindset or expectations brought by the patient to the session) and setting (a comfortable, nonclinical environment) (11). This model has been largely retained today, and it has been utilized in some degree by nearly all clinical studies in the contemporary era. Although some protocols may embed psychedelic-assisted therapy sessions into preexisting structured psychological programs, such as programs based on cognitive-behavioral therapy or motivational therapy (12, 13), the drug-administering sessions usually retain this nondirective, psychedelic psychotherapy model.

PROPOSED MECHANISMS

The primary pharmacologic mechanism of all psychedelics is by way of agonist activity at the serotonin (5-HT) 2A receptor, and significant advancements have been made in the past decade in uncovering potential effects of this action. One of the most well-established and increasingly researched effects of psychedelics on the brain is in modulation of the default mode network (14), a network of the brain that normally becomes activated during mental time travel (15), self-reflection (16), and theory of mind (17). The default mode network is implicated in the pathogenesis of rumination in depression (18), and abnormal default mode network activity has been described in numerous psychiatric conditions, including substance use disorders (19), posttraumatic stress disorder (PTSD) (20), and various anxiety disorders; for a review, see Sylvester et al. (21). The acute effects of a psychedelic experience, particularly when conducted in a therapeutic setting, have also been shown in a variety of studies with 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, and ayahuasca. These effects appear to be associated with durable alterations in personality characteristics, with decreases in neuroticism (22, 23), increases in openness to experience (22–25), and increases in extraversion (22). These findings, in addition to shining light on psychological mechanisms of change following psychedelic-assisted psychotherapy, are provocative because they suggest that contemporary conceptions of the stability of adult personality characteristics may be less durable than currently thought (26).

Among the psychedelics, MDMA is somewhat unique and deserves specific mention. MDMA acts primarily via release of the monoamines serotonin, norepinephrine, and dopamine; it also stimulates release of central neurohormones, including oxytocin and prolactin (27). MDMA produces positive affective and prosocial states (28) and has been found to modulate neural circuitry involved in emotion regulation and memory, including the amygdala and hippocampus (29). These findings have led to the suggestion that MDMA may exert its effects via altered trauma-related memory reconsolidation and fear extinction (30), thus making it perhaps uniquely suited for treatment of anxiety and stress-related disorders.

CLINICAL STUDIES OF PSYCHEDELIC COMPOUNDS

Although numerous psychedelic compounds are known to exert similar effects on the human brain, only a few have been researched in human studies in any significant fashion. Moreover, even fewer agents have been tested for potential clinical application, including MDMA, psilocybin, LSD, and dimethyltryptamine (DMT).

MDMA

MDMA, perhaps better known by the recreational name "Ecstasy," first found its way to human use in the 1970s. Within the first few years of its discovery, MDMA was used as an adjunctive agent in psychotherapy (31). However, by the early 1980s, it became increasingly associated with illicit use as a club drug. In 1985, it was designated a schedule I drug (i.e., no potential medical use) by the U.S. Drug Enforcement Administration (DEA). Unlike the so-called classical or tryptamine psychedelics, MDMA is a substituted phenethylamine that is structurally similar to mescaline and amphetamine (32). Its mechanism of action is less clear, but it appears to be due to both partial agonist activity at serotonin type 2A, 2C, and 1A receptors, directly inducing the release of serotonin and norepinephrine as well as inhibiting their reuptake; increases in oxytocin have also been implicated (33). The effects of MDMA include increases in prosocial behavior as well as thinking and bonding (34). Other effects include decreases in social anxiety, increased trust,

and facilitation of emotional disclosure (35). For these reasons, MDMA has been proposed to be particularly well suited to trauma-related disorders such as PTSD, characterized as they are by pathological fear responses, social disconnection, and emotional numbing (36).

Several studies have highlighted the promise of one to three sessions of MDMA-assisted psychotherapy in producing durable recovery among patients with treatment-resistant PTSD. These studies include a phase II clinical trial among patients with treatment-resistant PTSD (23); in addition, two phase III clinical trials are nearing completion (37). Long-term follow-up from several earlier studies by the same group found that recovery from PTSD persisted for up to 6 years following treatment with MDMA-assisted psychotherapy (38). Similarly, MDMA-assisted psychotherapy has also shown promise when integrated into previously established treatment programs for PTSD. A pilot study successfully integrated an MDMA therapy session into a program of cognitive-behavioral conjoint therapy in which both the patient and the patient's partner received MDMA-assisted psychotherapy (39); moreover, additional studies seeking to integrate MDMA-assisted psychotherapy into courses of prolonged exposure and cognitive processing therapy for PTSD are currently being developed (40). Finally, MDMA has shown promise in treating social anxiety disorder among adults with autism. A randomized, double-blind, placebo-controlled pilot study examining the effects of two 8-hour sessions of MDMA-assisted psychotherapy found a rapid and durable improvement in social anxiety scores among patients who received MDMA (41).

Psychedelic Tryptamines: LSD, Psilocybin, and DMT

The so-called classical or serotonergic psychedelics all exert their primary effect via agonist activity at the 5-HT 2A receptor (42, 43), although the 5-HT 1A receptor has also been implicated (44). LSD was studied extensively in the 1950s and 1960s for applications across a wide range of mental disorders (8); however, it ultimately gained notoriety because of a rapid increase in recreational use and, along with psilocybin, was placed under DEA schedule I status in 1970. Within this first phase of research, composed mostly of smaller case reports, LSD was applied successfully in the treatment of anxiety state (45), obsessional neuroses (46, 47), and anxiety associated with terminal cancer (48, 49); in addition, LSD was widely studied for treatment of alcohol use disorder (50). More recent clinical work using LSD-assisted psychotherapy to treat any psychiatric disorder is limited to a single randomized, double-blind pilot trial, with an open-label crossover design, for the treatment of anxiety associated with serious medical illness (51). Treatment resulted in insightful, cathartic, and interpersonal experiences as well as significant reductions in state anxiety that persisted at 12-month follow-up.

Psilocybin, which occurs naturally in mushrooms of the genus *Psilocybe*, is a prodrug of the active compound psilocin (42). It is the most widely studied psychedelic compound in the modern phase of psychedelic research; it has shown benefit in numerous, mostly small, studies and pilots for conditions as diverse as alcohol use, smoking cessation, treatment-resistant depression, and anxiety disorders (52). Psilocybin, relative to some longer-acting psychedelic agents such as LSD, has a duration of effect of 4–6 hours and a large therapeutic index; these properties make it more practical than longer-acting agents, such as LSD, to work with in a therapeutic setting (43).

Building on work from a previous successful pilot study (53), two recent randomized, double-blind, placebo-controlled trials utilizing a crossover design reported substantial reductions in both depression and anxiety among patients with anxiety and depressive disorders associated with life-threatening or advanced cancer (54, 55). Both studies utilized a single session of psilocybin-assisted psychotherapy, with 60%–80% of participants in each trial reporting sustained reductions in depression and anxiety at 6 months. Improvements in existential distress, well-being, and attitudes toward death were also found. Interestingly, in both trials, the degree to which the psilocybin session induced a mystical experience was found to correlate positively with the effects on anxiety and mood. The effects appear to have been durable, with one study site finding, at 4.5-year follow-up, sustainment of clinically significant reductions in anxiety and depression (56).

Psilocybin has also been proposed as a potential treatment of obsessive-compulsive disorder (OCD). One modified double-blind trial of nine patients found reductions in OCD symptoms following four sessions of psilocybin-assisted psychotherapy in which varying doses of psilocybin were given across a 4-week period (57). Two additional clinical trials are currently under way to study use of psilocybin for OCD (58, 59). Finally, an open-label study using psilocybin-assisted psychotherapy for treatment-resistant depression also found significant reductions in scores on the State-Trait Anxiety Inventory; these results were sustained at 6-month follow-up (60, 61).

Ayahuasca is an herbal decoction composed of an admixture of two Amazonian plant species: *Psychotria viridis* and *Banisteriopsis caapi*. *P. viridis* is a shrub containing DMT, which is not normally orally bioavailable because of degradation by monoamine oxidase; however, the other component of ayahuasca, *B. caapi*, contains harmaline alkaloids that produce monoamine oxidase inhibition, thus allowing DMT to exert its effect (62). Like psilocybin-containing mushrooms, ayahuasca has long been used by indigenous peoples for healing purposes for a wide array of physical and mental conditions; recently, ayahuasca has begun to expand into the Western world where it is increasingly being used, underground, for similar purposes (63). Although ayahuasca has not yet been studied for any specific anxiety disorder, observational studies and clinical trials have found reductions in anxiety and in psychological traits associated with anxiety. Observational studies of ayahuasca used in a ritual setting have found lasting effects of

relaxation and inner peace following a single session in an ayahuasca-naïve, nonclinical sample (64); moreover, reductions were found in psychopathological symptoms, including anxiety and trait harm avoidance, in one subgroup at 6 months (65). Another observational sample showed improvements in both mindfulness and cognitive flexibility (66).

Ayahuasca, administered in a controlled clinical setting, has led to increases in the ability to take a nonevaluative stance toward thoughts and emotions in two studies of community samples (67, 68), which may indicate reduced levels of anxiety (69). Trials using ayahuasca for treatment of depression have also found reductions in anxiety as secondary outcomes. An open-label trial found decreases in the anxious-depression subscale of the Brief Psychiatric Rating Scale following one ayahuasca session that were sustained at 21 days postintervention (70). In addition, a recent randomized, double-blind, placebo-controlled trial reported significant decreases in panic-like symptoms during the ayahuasca session itself (71). Decreases in anxiety (measured by the Symptom Checklist 90–Revised) persisting up to 1 month following treatment have also been observed following ritual use of ayahuasca (72). A pilot study integrating traditional Amazonian medicine and ayahuasca into an addictions residential treatment program also found significant reductions in anxiety scores as measured by the Beck Anxiety Inventory (73).

ISSUES FACING THE NASCENT FIELD OF PSYCHEDELIC MEDICINE

Taken together, evidence is accumulating to suggest that psychedelics, when provided in a structured setting, either as psychedelic-assisted psychotherapy or in a more traditional setting, such as an ayahuasca ceremony, hold vast potential for fundamentally shifting symptoms in a variety of anxiety disorders. Despite the current promising findings, nearly all studies conducted to date have focused largely on either PTSD or depression. Further research is clearly needed.

However, psychedelic research and medicine currently faces several issues concerning barriers to research, education of clinicians and other stakeholders, scalability, and cultural equity and social justice. First, psychedelics have a unique history that affects contemporary research efforts directly, via an anachronistic legal legacy, and indirectly, via associated attitudes and biases toward the substances among those in the medical community. Despite a thriving research scene and growing evidence to suggest the efficacy of psychedelics in the treatment of a variety of mental conditions, progress in psychedelic research was abruptly curtailed in the early 1970s when the federal government, due not to science but to a cultural backlash and moral panic, criminalized the agents as having no medical potential. This move plunged psychedelic research into 3 decades of quiescence and prohibition out of which the field is only beginning to recover.

The current wave of research on psychedelics, dubbed by some a "psychedelic renaissance" (74), may face similar issues of conscious and unconscious bias and stigma because of the past notoriety of these drugs, which is reinforced by their categorization by the DEA as schedule I compounds (i.e., having no possibility of therapeutic potential). In addition to perpetuating stigma against psychedelics, this designation also results in practical barriers to conducting clinical research with these agents that may be prohibitive (75, 76); these barriers stifle research endeavors at a time when novel therapeutics for anxiety disorders are critically needed. Although rigorously designed studies must be conducted before these treatments can judiciously be approved for widespread use, the medical and psychiatric community can and should do more to advocate for more sensible drug policy because it shapes and hamstrings efforts at carrying out this research in the first place.

Evidence suggests that this stigma may also perpetuate negative bias against psychedelics by psychiatrists and related clinicians themselves. Despite the increasing likelihood of approval of both psilocybin- and MDMA-assisted psychotherapy in the next 2–3 years by the FDA (5, 6), psychiatrists have reported a lack of education and knowledge about psychedelics' potential clinical applications; moreover, surveys have revealed a dearth of didactic time in psychiatric training programs focused on this growing area (77). Similarly, psychiatrists and other medical specialists have reported concerns about potential hazards of psychedelics but overall have reported optimism in their potential uses for the future (77, 78).

Psychiatry training programs and psychiatry departments should implement curricula and programs to educate trainees and faculty alike on the current evidence base for psychedelics so that misinformation and stigma do not dominate perceptions of a treatment that will likely be legal and widely available in the coming years. Given the significant media attention, it is also likely that patients will be seeking these treatments before approval; thus, they will be using psychedelics in nonmedical settings with the goal of relieving psychiatric symptoms, including anxiety disorders. Psychiatrists should be prepared to answer questions from patients planning such quests; if not able to support the plan itself, they should nonetheless be willing and able to provide accurate information and harm reduction whenever possible.

Second, current models of psychedelic-assisted psychotherapy require extensive training of therapists (e.g., the only current certification for psychedelic therapy training in the United States, offered by the California Institute of Integral Studies [CIIS], requires 150 hours of training) (79); in addition, the therapeutic process itself includes multiple hours of therapy sessions, including preparatory and integration sessions before and after therapy, as well as long (≥8 hours) psychedelic therapy sessions themselves. Evidence certainly supports the need for adequate training of therapists who will work with these substances: psychedelics produce a complex, and often unpredictable, experience that can raise unique challenges for both the patient and the therapist (80). Because of putative concerns over

adverse events occurring in the drug treatment sessions, many studies utilize protocols that allow only practitioners with advanced degrees (i.e., M.D. or Ph.D.) to act as psychedelic therapists. Thus, the current model requires substantial resources, many training hours, as well as specialized and costly personnel; these requirements may limit the scalability of such treatments after FDA approval occurs.

A similar issue is the lack of current training programs for psychedelic therapists; currently, only one fully operational training program (CIIS) exists in the United States outside of training for clinical trials (79). This lack of programs indicates that if and when FDA approval occurs, the field may be facing an inadequate supply of trained therapists available to meet the demand of these novel treatments, despite the increasing interest expressed by psychiatrists for specialized training in this area (B. Barnett et al., submitted manuscript, 2020). Furthermore, although the current model of psychedelic-assisted psychotherapy has been shown to be effective, it should not prevent future investigations into alternative therapeutic models. Further explorations have begun to assess whether psychedelic-assisted psychotherapy may enhance preexisting therapy programs, such as programs based on cognitive-behavioral therapy (39); however, more work is needed. For example, consideration of group therapy models, as practiced in both traditional settings and in some semistructured Western models (51), could lead to a significant reduction in cost and wider accessibility. Indeed, some steps have already been taken toward successful integration of group therapy with integrated psychedelic sessions (81) and even group psychedelic therapy (51).

Third, psychedelics have been utilized by indigenous peoples for thousands of years across every continent; in nearly all cases, the prohibition of these natural medicines was originally a central component of the cultural suppression imposed by European-Western colonialist conquests (82). Current drug approval is proceeding under a Western medical model that emphasizes these treatments as nothing more than medical interventions operating under a doctor-patient contract, devoid of further spiritual or community implications. Although this model is certainly in line with the mechanism for which drugs must be approved as medicines to treat specific illnesses, well-established, traditional uses of these compounds have strongly emphasized the importance of community, culture, and spirituality as critical pieces of the partaker's recovery. As paradigm shifting as psychedelic-assisted psychotherapy may be, future work can and should consider the broader cultural and anthropological history of these agents; indeed, evidence from both waves of psychedelic research has strongly supported the fact that context is critical for maximal optimization of the impact of these compounds (11).

In similar fashion, numerous indigenous groups continue to practice healing using psychedelics (such as Santo Daime in Brazil and the Native American Church in the United States). As psychedelic compounds make their way through the U.S. medical regulatory system, the field must also consider the rights of other indigenous healers whose work with psychedelics may currently be jeopardized by persecution and criminalization. It can well be argued that the continued criminalization of these treatments by people who have thousands of years of experience using them as medicines is only the continued legacy of colonial and Western-centric suppression (82). Respecting the role of traditional healers and the history of cultural appropriation may also reduce the ongoing racial disparity in the field of psychedelic studies, in which the vast majority of participants and therapists have not been from racial-ethnic minority groups (83). As part of a broader cultural and political focus on inclusivity in medicine, psychedelic research, as a nascent arena, has an opportunity to establish itself as an inclusive and forward-thinking field from its (re)inception in the current wave of research. This foundation might have broader implications in addressing the disparities that continue to exist in clinical psychiatry and research (84, 85).

CONCLUSIONS

Pschedelics thus present unique opportunities in the study and treatment of anxiety disorders, and mental illness more broadly, at a time when existing treatment options are failing many patients and psychopharmacological research has otherwise slowed. As a time-limited treatment that produces significant and durable results, psychedelic-assisted psychotherapy would represent a paradigm shift in conventional treatment models within psychiatry. This fact alone inherently suggests that the field of psychiatry has a great deal of work ahead. Efforts to reform psychedelic drug policy at the federal level must be supported insofar as current policy acts as a major barrier to much-needed research. Educational programs to prepare psychiatrists and psychiatric trainees about these uniquely acting compounds must also be developed, including guidelines for treatment and therapist training.

Finally, as agents that have been used in traditional healing practices across the world for thousands of years, psychedelics have a unique history that sets them apart from any currently existing psychiatric treatment; this narrative shines more light on implications for Western-dominated conceptions of treatment versus healing, illness and disease, and inclusion versus exclusion. For the field to realize its maximum potential, psychiatrists and other medical specialists would do well to consider these possibilities now.

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