Psychedelic medicine: a re-emerging therapeutic paradigm

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In clinical research settings around the world, renewed investigations are taking place on the use of psychedelic substances for treating illnesses such as addiction, depression, anxiety and posttraumatic stress disorder (PTSD). Since the termination of a period of research from the 1950s to the early 1970s, most psychedelic substances have been classified as "drugs of abuse" with no recognized medical value. However, controlled clinical studies have recently been conducted to assess the basic psychopharmacological properties and therapeutic efficacy of these drugs as adjuncts to existing psychotherapeutic approaches. Central to this revival is the re-emergence of a paradigm that acknowledges the importance of set (i.e., psychological expectations), setting (i.e., physical environment) and the therapeutic clinician–patient relationship as critical elements for facilitating healing experiences and realizing positive outcomes.[1,2]

The public is often well-versed in the potential harms of psychedelic drugs, but much of this knowledge is from cases involving patients who used illicit substances in unsupervised nonmedical contexts. We discuss the emerging research for therapeutic purposes involving human subjects, considering both the possible benefits and the potential harms of using psychedelic agents as adjuncts to psychotherapy or counselling for mental illness.

Types of psychedelic drugs

"Psychedelic" drugs include a range of substances with varying pharmacological profiles that all have strong effects on conscious experience (Table 1).[3–18] We will focus on two classes of psychedelics: classic psychedelics and "entactogens."

The classic psychedelics exert primary activity as agonists at the 5-HT$_{2A}$ receptor (e.g., lysergic acid diethylamide [LSD], psilocybin, dimethyltryptamine [DMT] and mescaline).[19] Many of these substances are found — or are close analogues of chemicals found — in plants or fungi used traditionally for millennia in spiritual or folk healing rituals, such as the ergot fungus (*Claviceps purpurea*) from Eurasia, morning glory (*Turbina corymbosa*) and peyote cactus (*Lophophora williamsii*) from Central and North America, and the ayahuasca brew (*Banisteriopsis caapi* and *Psychotria viridis*) from the Amazon.[20]

The second class of psychedelic substances, the entactogens, includes methylenedioxymethamphetamine (MDMA), which acts primarily as a serotonin-releasing agent and has effects that somewhat overlap but are substantially distinct from classic psychedelics.[21]

Other substances that are sometimes classified as "psychedelic" — such as ketamine (a dissociative anesthetic), scopolamine (an anticholinergic) or ibogaine (a substance with a complex neuropharmacology) — are beyond the scope of this review. This article will focus on clinically relevant studies with patient populations in which psychedelic drugs are used as adjuncts to psychotherapy. Besides a few brief mentions, we do not cover findings from research on healthy participants, although such studies have been the basis of renewed neuropharmacologic science in this field.

Contexts and indications

Some of the mental disorders for which psychedelic-assisted treatments are currently being researched include anxiety, addiction and PTSD. The findings presented in this analysis are preliminary, and most are results from small-scale pilot studies with relatively few participants. Further study is warranted before any unambiguous clinical utility may be confirmed, but the new generation of investigators is attempting to over-

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KEY POINTS

- Medical interest in psychedelic drugs as treatments for illnesses such as anxiety, addiction and post-traumatic stress disorder has been renewed.

- Small-scale studies involving human participants in the United States, Europe and Canada are showing that such research can be conducted in a safe and scientifically rigorous manner.

- Preliminary findings show some successful results for these treatments, with significant clinical improvements and few — if any — serious adverse effects.

- The emerging results may have implications for future medical and neuroscientific research, medical education and training, and public policy.

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come some of the methodological weaknesses of earlier research on these substances.

Anxiety

In 2014, a small randomized controlled trial in Switzerland suggested LSD-assisted psychotherapy had the potential to reduce the anxiety associated with terminal illness.[4] Twelve participants with life-threatening illness were enrolled in the study to receive treatment that involved drug-free psychotherapy sessions supplemented with two LSD-assisted sessions two to three weeks apart. The participants were randomly assigned to either the treatment group (receiving 200 μg LSD [$n = 8$]) or the active control group (20 μg LSD [$n = 4$], with an open-label crossover to 200 μg LSD after the initial blinding was unmasked). At two months' follow-up, the State–Trait Anxiety Inventory (STAI) showed nonsignificant reductions in

Table 1: Psychedelic agents currently under investigation for their potential benefits as adjuncts to psychotherapy

Substance	Derivation or chemical analogues	General effects and properties	Potential harms*	Potential therapeutic uses†
LSD	Ergot fungus (*Claviceps purpurea*); morning glory (*Turbina corymbosa*); Hawaiian baby woodrose (*Argyreia nervosa*) — sources of ergine or lysergic acid amide	• 5-HT$_{2A}$ (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (e.g., alcohol)[3] • Anxiety associated with terminal illness[4,5]
Psilocybin	Psilocybe and other genera of mushrooms (various species)	• 5-HT$_{2A}$ (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (tobacco, alcohol)[6,7] • Anxiety associated with terminal illness[8]
Ayahuasca brew (admixtures contain DMT)	Chacruna leaf (*Psychotria viridis*); Chagropanga vine (*Diplopterys cabrerana*); ayahuasca vine (*Banisteriopsis caapi*); assorted other admixture plants	• 5-HT$_{2A}$ (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Nausea, emesis • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Serotonin syndrome and other dangers from medication interactions due to monoamine oxidase inhibitory activity	• Addiction (alcohol, cocaine, tobacco)[9,10] • Depression, anxiety[11–14]
Mescaline	Peyote cactus (*Lophophora williamsii*); San Pedro cactus (*Echinopsis pachanoi*)	• 5-HT$_{2A}$ (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis	• Addiction (alcohol)[15]
MDMA	Sassafras tree (*Sassafras albidum*) — source of safrole, precursor chemical	• Serotonin, dopamine and noradrenaline agonist • Euphoria • Arousal • Perceptual alteration • Enhanced empathy and sociability	• Potential neurocognitive deficits (e.g., memory impairment) • Sleep disruption • Short-term depression	• PTSD[16–18]

Note: DMT = dimethyltryptamine, LSD = lysergic acid diethylamide, MDMA = methylenedioxymethamphetamine, PTSD = posttraumatic stress disorder.
*Potential harms identified here are associated with illicit and unsupervised non-medical uses of psychedelic substances (often in the context of polysubstance use); current clinical studies on psychedelic agents have not reported such chronic adverse sequelae.
†Potential therapeutic uses are identified based on evidence from past (i.e., 1950s–1960s) and current research on psychedelic drugs.

trait anxiety, but significant reductions in state anxiety.

Follow-up with nine participants one year after treatment showed a sustained therapeutic benefit with no acute or chronic drug-related severe adverse events, and there were no adverse effects lasting more than one day after an LSD-assisted session.[4]

Psilocybin has likewise shown promise as a treatment for anxiety in patients with terminal illness.[8] A 2008 study on ameliorating end-of-life anxiety focused on 12 participants with end-stage cancer.[8] After several non–drug-assisted therapy sessions, participants underwent a within-subject crossover study in which they received the experimental medication (0.2 mg/kg psilocybin) and the active placebo (250 mg of niacin) across two sessions a few weeks apart. Findings showed that psilocybin-assisted psychotherapy lowered anxiety and improved mood, without clinically significant adverse effects.[8]

MDMA-assisted therapy is also being studied as a treatment for social anxiety in adults with autism, although findings have yet to be published.[22]

Addiction

Researchers in the 1950s and 1960s studied the use of psychedelic-assisted therapy for the treatment of addictions such as alcohol dependence,[23] some key findings of which were recently reviewed in a meta-analysis that suggested a significant beneficial effect.[3] In renewed clinical research on treating alcohol dependence with psilocybin-assisted therapy, a New Mexico team recruited 10 participants with a diagnosis of active alcohol dependence (and no concurrent mental illness or other substance use disorder).[6] Participants received pre- and post-psychosocial support (motivational enhancement therapy) over 12 weeks, with one or two intervening open-label sessions at weeks four (0.3 mg/kg psilocybin, $n = 10$) and eight (0.4 mg/kg psilocybin, $n = 6$, or 0.3 mg/kg psilocybin, $n = 1$). Among the participants who completed the study, the self-reported mean percent drinking days and percent heavy drinking days were reduced by more than half of what had been reported at baseline.[6] Acute adverse effects such as nausea and mild headaches were reported by some participants, but no clinically significant or lasting harms resulted from the administration of psilocybin.

Other recent research on psilocybin-assisted psychotherapy for addiction includes a pilot study of treatment for tobacco dependence. This investigation was an open-label design involving 15 participants who smoked at least 10 cigarettes per day and had multiple previous unsuccessful cessation attempts.[7] Participants received cognitive behavioural therapy before and after treatment with psilocybin. Treatment included two or three psilocybin-assisted psychotherapy sessions (doses of either 20 mg/70 kg or 30 mg/70 kg), with the first session occurring on the target quit date. At six months' follow-up, 12 of the 15 participants were abstinent (biologically verified by exhaled carbon monoxide and urinary cotinine levels).[7] Smoking cessation outcomes were significantly correlated with a measure of mystical experience on session days, as well as retrospective ratings of personal meaning and spiritual significance of psilocybin sessions.[24] The same research team is currently designing a follow-up randomized controlled study to compare a similar psilocybin intervention with nicotine-replacement therapy.

The Amazonian folk medicine ayahuasca is a plant-based preparation with the psychoactive constituents DMT, which is chemically related to psilocybin, and harmala alkaloids, which are reversible monoamine oxidase inhibitors. An observational study of an ayahuasca-assisted intervention in a Coast Salish First Nations community in British Columbia for people ($n = 12$) seeking treatment for addictions to substances such as alcohol and cocaine showed statistically significant improvements in measures of mental health and reductions in self-reported use of these substances after six months, with no lasting adverse physical or psychological effects.[9]

Observational research involving members of Brazilian religious groups who regularly drink ayahuasca sacramentally has shown that, compared with a matched control group, long-term regular drinkers of ayahuasca tend to have a lower prevalence of substance use,[10] structural brain changes that do not suggest evident pathology[11] and better neuropsychological performance and psychosocial adaptation.[12] Other studies involving similar populations of long-term drinkers of ayahuasca have shown lower rates of psychoactive substance use and psychopathology.[13,14]

Canadian researchers are currently coordinating an international research study to investigate ayahuasca's potential as a treatment for addiction, with clinical sites in Brazil, Peru and Mexico.[25]

Ayahuasca differs from the other substances covered in this review, inasmuch as it is a plant-based preparation of variable composition and strength, and typically used in ceremonial contexts, which makes it more difficult for researchers to isolate the factors that may contribute to therapeutic efficacy.[26,27]

Posttraumatic stress disorder

In a pilot randomized controlled trial investigating MDMA-assisted psychotherapy to treat chronic treatment-resistant PTSD in the United States, outcomes from 20 participants with a mean illness

duration of 19 years showed that the experimental treatment may improve upon the best currently available pharmacotherapies and psychotherapies.[16] The clinical protocol involved several weeks of preparatory and follow-up non–drug-assisted psychotherapy, during which the members of the experimental group received two MDMA-assisted sessions. No serious adverse effects were reported. Outcomes included a significant and sustained reduction in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS), with 83% of participants in the experimental group (v. 25% in the placebo group) showing a reduction in symptom severity of more than 30%. Furthermore, some members of the experimental group no longer met criteria for PTSD as stated in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV).[16] A long-term follow-up study involving the same participants showed that, although two patients relapsed, 74% (14/19) of patients still showed meaningful, sustained reductions in their CAPS scores three and a half years later.[17]

An additional small (*n* = 12) randomized controlled trial investigating MDMA-assisted psychotherapy for PTSD was recently completed in Switzerland.[18] This study compared three full-dose MDMA-assisted sessions per patient (with non–drug-assisted therapy before and after) with low-dose active placebo in a crossover design. Participants had no serious drug-related adverse events, and although reductions in CAPS scores were not statistically significant, self-assessment of PTSD symptoms as measured by the Posttraumatic Diagnostic Scale questionnaire was significantly reduced.

In 2015, researchers in Vancouver began a similar pilot study of MDMA-assisted psychotherapy for patients with PTSD, the first clinical study involving psychedelic drugs in Canada in more than 40 years.

Historical lessons

Experience from previous research — both positive and negative — has provided important lessons for current methodological designs, ethical strictures and clinical protocols and for renewed research on psychedelics involving human participants. In the 1950s and 1960s, methodological challenges confounded the advancement of psychedelic medicine, with researchers disagreeing about the suitability of randomized controlled trials and the possibility of double-blinding.[28] More infamously, egregious violations of ethical protocols, such as lack of informed consent (in some cases through military or intelligence agency–

supported research) resulted in substantial and long-lasting harms to some patients.[23] Furthermore, unsupported claims about purported benefits of psychedelics, and sometimes explicit encouragement for non-clinical use, by some members of the research community, may have contributed to unsupervised and uncontrolled recreational use of psychedelic substances. Consequently, by the mid-1970s, clinical access to and professional interest in psychedelic drugs waned, leading to a quiescence in research for several decades.

Although methodological and political challenges remain to some degree,[27] recent clinical studies have shown that studies on psychedelics as therapeutic agents can conform to the rigorous scientific, ethical and safety standards expected of contemporary medical research.[29] For example, patients undergo careful screening, fully informed consent is obtained and protocols are approved by ethics review boards. In addition, contemporary investigators are mindful of the checkered history of psychedelic research, and are thus cautiously reserved in reporting their findings, doing so with appropriate caveats and limitations.

Potential risks and their mitigation

Most psychedelic drugs are classified and legally scheduled as having no or very limited medical purpose, a high potential for abuse and a lack of accepted safety for use under medical supervision.[30] Potential health risks of these substances include the precipitation of psychotic breaks in patients with psychotic disorders or a predisposition to these disorders.[31] Thus, participation in contemporary psychedelic research typically excludes people with a personal or family history of psychosis or bipolar disorder.[29]

A further risk associated with psychedelic drugs is Hallucinogen Persisting Perception Disorder (HPPD), sometimes known as "flashbacks," although HPPD is more uncommon and more clinically severe than the flashbacks or visual distortions sometimes described in the days following illicit use of psychedelics.[32,33] However, the incidence of adverse effects such as psychosis or HPPD in the general population is believed to be relatively low, and these effects are generally associated with the use of illicitly procured psychedelic substances, which often involves polysubstance use in uncontrolled settings without supervision.[34] In light of these concerns, it is worth noting that lifetime use of classic psychedelics at the population level is associated with decreased psychological distress;[35] thus, potential individual instances of harm may be overshadowed by instances in which people experience benefit or no harm.

The most common adverse effects from the administration of psychedelics under clinical supervision are limited to the time of drug action, such as acute increases in anxiety, fear, heart rate and blood pressure.[29] Without careful supervision, fearful responses could lead to dangerous behaviour (e.g., fleeing the study site). In addition, delayed-onset headache is sometimes caused by psilocybin use and possibly by other classic psychedelics.[36] Although adverse effects of MDMA overlap somewhat with those of classic psychedelics, cardiovascular effects (e.g., tachycardia) are generally greater with MDMA, whereas adverse psychological reactions are more likely with classic psychedelics. It is important to note that acute adverse effects are readily managed,[37] and that, as described previously, none of the new clinical research studies have reported long-term harms.

The clinical protocols for contemporary psychedelic studies draw on lessons learned from the earlier era of psychedelic research, and incorporate some common elements to minimize risks and maximize potential therapeutic benefit. After obtaining fully informed consent from the patient, clinical sessions take place in health care facilities, in quiet treatment rooms with pleasant and comfortable decor. Headphones deliver music, hospital and laboratory equipment are minimal and discreetly placed, and a two-person cotherapist team is in attendance throughout the drug's action. During a session, interaction between patient and therapists is kept to a minimum, with the patient encouraged to spend much of the time engaging in self-reflection while listening to carefully selected music. Follow-up sessions that are non-drug assisted provide opportunities to integrate the insights gleaned from the experimental sessions. As research on psychedelic medicine advances, further refinements in screening, safety and therapeutic protocols will be possible.

Questions for future research

Numerous scientific and empirical questions remain in the field of psychedelic medicine. With respect to basic neuroscience research, progress in understanding the human brain and its functional relationship to mind and consciousness would be substantially advanced by further determining how psychedelic drugs work neuropharmacologically.[30] This kind of knowledge would in turn be useful in applied fields such as psychology, psychiatry and addiction medicine, both to help explain mechanisms for the therapeutic results that renewed psychedelic studies are yielding and to advance understanding about optimal therapeutic protocols for these forms of treatment. With respect to clinical applications, different psychedelic medications may be indicated for different specific illnesses. Further research should elucidate not only respective efficacy, but also optimal pharmacotherapeutic and ancillary psychotherapeutic choices.

Beyond basic research on neuropharmacological mechanisms and clinical outcomes are potential economic arguments for psychedelic therapies. Substance dependence and mental disorders, such as depression and anxiety, are substantial and growing sources of illness and health system costs worldwide.[38,39] Given these trends, investment of resources into researching novel treatments for mental and substance use disorders is warranted. Because preliminary evidence suggests psychedelic therapies require relatively time-limited interventions (i.e., they do not involve long-term ongoing courses of pharmacotherapeutic intervention), they may prove to be economically viable in comparison with currently available treatments.

Conclusion

Renewed scientific interest in psychedelic medicine is generating new knowledge about a class of pharmacologic substances that humans have long used for ceremonial, therapeutic and cultural purposes. As this field of research evolves, medical school curricula may need to be updated to include the latest knowledge about psychedelic drugs. This would encompass scientific evidence about relative risks and harms of psychedelic drugs — which is largely absent in current drug control scheduling classifications[40] and reflects adverse outcomes from uncontrolled recreational use rather than supervised clinical settings. In addition, it would encompass knowledge about the potential therapeutic uses of these agents, particularly because patients may query their physicians about research findings reported in the media. If further scientific evidence accumulates on the therapeutic value of psychedelic medicines, specialized clinical training for physicians, nurses, psychologists and other health professionals will be required to meet an increased demand for such treatments.

It behooves policy-makers to be aware of and open to new approaches to treatments emerging in the field of psychedelic medicine. This is particularly important for those concerned about the growing prevalence of mental illness, including addiction, as well as its associated human, social and economic costs. This applies not only to elected officials, but also to civil servants in health ministries and research granting agencies, where advances and innovations are translated from the clinical research laboratory into options for health care improvements that are in the public interest. Currently, international drug control scheduling classifications and popular miscon-

ceptions about the relative risks and harms of psychedelic drugs make research involving humans difficult. However, continued medical research and scientific inquiry into psychedelic drugs may offer new ways to treat mental illness and addiction in patients who do not benefit from currently available treatments. The re-emerging paradigm of psychedelic medicine may open clinical and therapeutic doors long closed.

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