The renaissance of psychedelic-assisted psychotherapy

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Abstract

Globally, the revival of psychedelic substances for the treatment of mental health conditions has evolved. Conditions such as depression, anxiety, addiction and post-traumatic stress disorder (PTSD) have been investigated. During the 1950s to 1970s psychedelics were regarded as drugs of abuse. Recent clinical trials have shown the efficacy of these substances. The probable harms of psychedelics are from cases where illicit substances were used in non-medical settings. The different types of psychedelics in the treatment of mental health conditions are discussed.

Keywords: psychedelics, psychotherapy, mental health

S Afr Pharm J 2024;91(1):62-65

Introduction

The word "psychedelic" is made up of two words: "psyche" (soul) and "deloun" (to reveal).[1] Psychedelics have been used in indigenous cultures for many years and have now entered the mainstream arena.[1] The potential of psychedelics to treat mental health conditions is on the rise.[2] They are still illegal in some countries and underground use has been noted.[2] Those who can afford it may travel to countries where some psychedelics are legal (e.g. Jamaica).[3] In 1943 lysergic acid diethylamide (LSD) was discovered by the scientist Albert Hofman and during the 1950s and 1960s research on psychedelics increased.[3] Tens of thousands of patients are thought to have received "psychedelic psychotherapy" over the course of roughly 15 years, thanks to early reports on the distinct potency and remarkable subjective effects of LSD in the early 1950s.[3] This led to the widespread use of psychedelics, and particularly LSD, in research and clinical practice by psychologists and psychiatrists.[3] The ability of psychedelic research to influence and possibly advance psychology and psychiatry thought and practice was increasingly restricted starting in the mid-1960s; however, as popular and countercultural movements embraced the drugs more and more, their societal impact multiplied.[3] The medical community received its first warning about the risks associated with LSD in 1962 from Sidney Cohen. When LSD first arrived in the US in 1949, it was thought to be a psychotomimetic that could induce a model of psychosis.[4] However, intellectuals in Southern California redefined LSD as a psychedelic that could lead to mystical enlightenment in the middle of the 1950s.[4] Even though LSD was only approved for experimental use and was still under investigation, by the late 1950s, psychologists and psychiatrists were using it to treat alcoholism, neuroses, and to boost creativity.[5,6] In 1962, Cohen issued a warning about the dangers of LSD spreading due to his concerns about its popularisation, non-medical use, black market sales, and patients who were harmed by the drug.[4,5] Cohen's 1960 study on the effects of LSD had concluded that the drug was safe if administered in a supervised medical setting. Medical, not social, concerns led to the subsequent government crackdown and regulation of LSD, which came before the drug movement of the 1960s.[4,5] In 1970, the USA classified psychedelics as Schedule I of the Controlled Substances Act, considering them to have no medical value.[3] This ban spread globally which quickly halted psychedelic research.

After years of inactivity, a new cohort of psychedelic science is resurging.[3] Hopeful early work at Johns Hopkins University and Imperial College, London was seen.[4] Positive preliminary reports have now been published on the safety and tolerability of psilocybin for the treatment of obsessive compulsive disorder, alcohol and tobacco addiction as well as major depressive disorder.[3] Both psilocybin and LSD have shown efficacy for the treatment of psychological distress associated with end-of-life situations.[3] The fact that many of these trials report on small sample sizes and are best classified by conventional standards as "safety and tolerability" studies is an important caveat.[3] Psychedelics are a special class of drugs that frequently result in deep psychological and mystical experiences along with vivid hallucinations.[4] The Default Mode Network (DMN) is a collection of linked brain regions that exhibit enhanced temporal coherence while at rest.[5] Numerous studies evaluating the DMN's function in self-referencing, mind-wandering, and autobiographical memories have focused on it.[5] Many neuropsychiatric disorders, including depression, anxiety, obsessive-compulsive disorder, attention deficit hyperactivity disorder, schizophrenia, and PTSD have been linked to altered connectivity in the DMN.[4,5,6] This review aims to cover the different types of psychedelics and their benefits for the treatment of mental health conditions.

Background

Hallucinogens extracted from plants have been used in religious ceremonies for many years.[3] In 1938 Albert Hofmann synthesised

LSD and in 1943 he came into contact with it and described "fantastic pictures, shapes and a kaleidoscope of colours".[7] In 1947, the company Sandoz began to market LSD under the trade name Delysid as a psychotherapy medication and for experimental study for psychoses.[6] In 1960, Harvard psychologist Timothy Leary began experiments under the Harvard Psilocybin Project to determine whether psilocybin was an effective substance in psychotherapy.[7] In the 1964 book, *The Psychedelic Experience*, psychologists Timothy Leary, Ralph Metzner and Richard Alpert stated that a psychedelic drug is like "a chemical key" that "opens the mind, frees the nervous system of its ordinary patterns and structures".[6,7] Since LSD was being used extensively in medically unsupervised settings, the last of Sandoz's patents for its production expired in 1963, leading to an increase in illicit production of the drug.[7] Governments in the US and Europe expressed alarm in 1965 over the use of LSD and psilocybin by the general public.[7] The Drug Abuse Control Amendments were passed by the US Congress, making it illegal to manufacture or sell LSD without a license and compelling researchers who had not received Food and Drug Administration (FDA) exemptions for experimental new drugs to give up their LSD supplies.[7] Experiments with psychedelics decreased and were stopped by the Controlled Substances Act of the Comprehensive Drug Abuse Prevention and Control Act of 1970.[7]

The idea that psychedelic-induced "mystical" or "spiritual" experiences are correlated with participant responses is central to psychedelic-assisted therapy.[7] Based on the 30-item Mystical Experience Questionnaire (MEQ-30) scores of participants, the researchers in studies observed correlations between symptom reduction and the participants' assessments of their psychedelic experiences as personally meaningful.[7] A validated instrument for measuring mystical experiences, the MEQ-30 evaluates seven distinct domains: internal and external unity; noetic quality which is the feeling of perception or revelation experienced during the experience; sacredness; positive mood; transcendence of time/space; and ineffability which is the difficulty of explaining the experience to others.[7] The instrument's validity and reliability have been confirmed by confirmatory factor analyses, and its external and convergent validity have been shown by latent variable scores that positively predict psychedelic-related changes in behaviour, attitudes, and well-being.[7]

Types of psychedelics

Psychedelics can be separated into four classes based on their pharmacological profiles and chemical structures:[7,8]

- classic psychedelics (serotonin 2A [5-HT_{2A}] receptor agonists)
- empathogens or entactogens (mixed serotonin and dopamine reuptake inhibitors and releasers)
- dissociative anaesthetic agents (*N*-methyl-D-aspartate [NMDA] antagonists)
- atypical hallucinogens, which affect multiple neurotransmitter systems.

Forms of administration:[6,8]

- LSD is available in tablet or capsule form, as well as tiny squares of blotting paper or gelatine that have been soaked in the drug before being ingested.
- Psilocybin (magic mushrooms) is eaten raw or cooked, or boiled into a drink. Psilocybin is also used in dried capsule form.
- Dried and ground peyote buttons are found as capsules, while mescaline from the peyote cactus is found as a white powder. Although it can be chewed or smoked, it is typically swallowed.
- Plant-based ayahuasca is a type of hallucinogenic tea. Used historically in some regions of South America.
- Dimethyltryptamine (DMT) is the psychoactive component of ayahuasca and can be found in many different plants. Typically, it is a white synthetic powder.
- Although 0.5 mg/kg of ketamine is the most often used dosage, some patients may respond to as little as 0.1 mg/kg, and others may need as much as 0.75 mg/kg. Traditionally, the ketamine dosage is spread out over 40 minutes.

The type of psychedelic, the dosage, the user's tolerance, whether or not they have taken other drugs, and the user's functioning and mental state will all affect the effects that they experience.

Generally speaking, psychedelics can have the following common effects:[6,8]

- visual, auditory, tactile, and taste hallucinations
- a loss of clarity in perception, such as the ability to "feel" sounds or "hear" colours
- feeling cut off from the physical form
- time, direction, and distance distortions
- relaxation
- elevated heart rate
- dilated eyes
- nausea as well as appetite loss.

Psychedelics do not always produce the same effects.[6] Even if the user has a great "trip" their first time, it doesn't mean they will always be pleasant.[6,8] Everyone is susceptible to experiencing a "bad trip." Fearful hallucinations, acute panic, paranoia, and nausea are some of the symptoms.[6,8] It is also feasible to experience both positive and negative things during the same trip.[8]

The classic psychedelics are separated into phenethylamines and tryptamines. The tryptamines comprise the synthetic LSD as well as the plant-derived indoleamines psilocybin and DMT.[7] The effects of the classical psychedelics vary slightly from one another, but generally speaking, they cause strong emotions, enhanced cognitive flexibility, and changes in perception (such as hallucinations, illusions, distortions, or amplifications in various sensory modalities).[8] Classical psychedelics can cause mystical experiences, ego dissolution, and a sense of interconnectedness among all beings in certain patients who take high enough doses.[8] Additionally, they have the power to cause severe anxiety

and dysphoria.[8] Psilocybin is one of the traditional psychedelics that is thought to be relatively safe and well-tolerated in terms of safety.[8] Serious side-effects were not observed in any of the larger clinical trials examining the use of psilocybin in major depressive disorder.[8] Thirty-three percent of patients had self-limited headaches, and only one patient had a brief increase in blood pressure.[8] No significant cardiac or neurological events occurred.[8] Other dangers include experiencing nausea or vomiting soon after taking psilocybin.[8] Despite the fact that professionals view a personal or first-degree family history of psychosis as a disqualifier for psilocybin-assisted psychotherapy, research participants in clinical trials have not experienced psychotic episodes thus far.[8]

The phenethylamines include methylenedioxymethamphetamine (MDMA) and mescaline.[7,8] The tryptamines share their core structure with the neurotransmitter serotonin (5-HT) and modulate multiple targets, including 5-HT receptors, monoamine transporters, and trace-amine-associated receptors.[8] The entactogen/empathogen MDMA (a phenethylamine) is pharmacologically related to mescaline, amphetamine, and methamphetamine and acts as a serotonin agonist and releases both dopamine and norepinephrine.[8] MDMA is known for fostering interpersonal connectedness, attachment, trust, and empathy.[8,9] MDMA can also result in feelings of euphoria and a sense of purpose.[8,9] In general, MDMA's effects on perception are less dramatic than those of traditional psychedelics, but they can still be noticeable.[8,9] Additionally, it modifies the way users perceive emotions, causing them to react more strongly to positive emotions and to perceive anger in others more slowly.[8,9] There are numerous physiological effects of MDMA such as negative effects on the heart which can result from stimulant-induced tachycardia and hypertension.[8,9] Heat-related injuries can result from hyperthermia, whereas seizures can be brought on by hyponatraemia.[8] There is also a chance of hepatotoxicity and neurotoxicity.[8,9] Thankfully, there hasn't been any evidence of severe toxicity or drug-seeking behaviour in research participants following MDMA administration.[8,9] Even though MDMA is usually regarded as safe in comparison to other recreational drugs, serious side-effects are possible.[8] The dissociative anaesthetic ketamine, which has psychedelic properties, is an NMDA receptor antagonist that has shown antidepressant efficacy across multiple clinical trials and efficacy in decreasing suicidal ideation.[8] While not a classic psychedelic, ketamine can cause dose-dependent dissociation, alterations in the perception of sight and sound, derealisation, "mystical-type" effects, paranoia, and transient confusion.[8] Table I depicts the different types of psychedelics and Figure 1 illustrates the chemical structures.

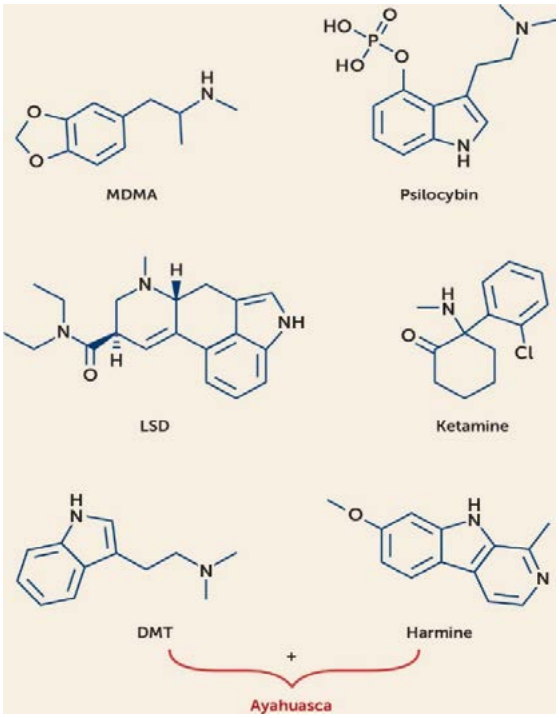

Figure 1: Chemical structures of psychedelics[7]

Microdosing has become more popular recently.[10,11] It is the practice of ingesting sub-hallucinogenic amounts of a psychedelic

Table I: The different types of psychedelics[1,7,9,10,11]

Substance	Derivation	Mechanism of action	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	Addiction (alcohol), anxiety and associated with mental illness
Psilocybin	Psilocybe and other genera of mushrooms (various species)	5-HT_{2A} (serotonin) agonist of pyramidal neurons	
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	Addiction (alcohol, cocaine, tobacco), depression and anxiety
Mescaline	Peyote cactus (*Lophophora williamsii*); San Pedro cactus (*Echinopsis pachanoi*)	5-HT_{2A} (serotonin) agonist of pyramidal neurons	Addiction (alcohol)
MDMA	Sassafras tree (*Sassafras albidum*) — source of safrole, precursor chemical	Serotonin, dopamine and noradrenaline agonist	PTSD
Ibogaine	Derived from Root bark of West African shrub *Tabernantheiboga*	Blocks the uptake of dopamine and serotonin	Stimulant and opiate addiction
Ketamine	Cyclohexane derivative classified as a dissociative anaesthetic	NMDA receptor antagonist	Pain, depression and anxiety

DMT = dimethyltryptamine, LSD = lysergic acid diethylamide, MDMA = methylenedioxymethamphetamine, PTSD = post-traumatic stress disorder

substance.[11] Experts typically define microdosing as taking 5–10% of a full dose of a psychedelic (usually psilocybin or LSD) in order to obtain the drug's purported benefits for mental health without experiencing the hallucinogenic high.

Difficult experiences might be less common with microdosing because it does not require the same level of experience as full-dose research.[11] However, even at the extremely low doses used in microdosing, one may expect less frequent, less intense versions of full-dose challenges to occur (e.g. restlessness, mild anxiety, mild headaches).[11] Microdosing may be studied as a possible adjunct, substitute, or improvement over full-dose interventions for drug use disorders or smoking cessation.[11]

Many reasons are given for microdosing; among the main ones mentioned by survey participants are lowering anxiety and depression, increasing wellbeing, and improving cognitive function.[12] Given how important it is to address mental health issues and improve psychological health and cognition, it is possible that a sizable percentage of microdosers are trying to treat mental illness symptoms or stave off cognitive decline.[12] In fact, microdosers report lower levels of stress, mood enhancements and as well as a reduction in symptoms of PTSD, obsessive-compulsive disorder, depression, and anxiety.[12] Additionally, studies have shown that people may believe microdosing to be more successful than traditional therapies for mental health issues.[12]

In addition to highlighting the importance of therapeutic and wellness reasons for microdosing psychedelic drugs, this analysis of a sizable international sample of adults also found that microdosers had lower levels of anxiety and depression than controls.[12] Additionally, a wide range of microdosing techniques with notable variances in dosage, frequency, and usage of mixtures of psychedelic and non-psychedelic drugs (also known as stacking) were discovered.[12] To learn more about how these specific practices – and microdosing in general – affect the aspects of mood, cognition, and wellbeing that microdosing is meant to improve, further research is necessary.

Conclusion

Psychedelics have revealed great potential in treating mental-health conditions, but their use is restricted by legal hindrances. The debate over psychedelic access and use is progressing, sometimes going beyond the parameters of their therapeutic application and the findings of clinical studies. Best practices, clinical guidelines, and protocols for the medically supervised administration of psychedelics have not yet been developed, despite the fact that research on the supervised clinical use of psychedelic substances has advanced over the past 20 years. The risk is that the market will open up to unsupervised self-medication and recreational use before supervised therapeutic use is established because the perception of psychedelics as effective treatments for mental health disorders – a view that is strongly supported by an increasing number of advocacy groups and commercial interests– will spread more quickly than scientific evidence. This might even jeopardise the advancement of psychotherapy using psychedelics. There is also a chance that not everyone will be able to receive the supervised medical treatment and psychotherapy as this will probably need significant resources such as infrastructure and qualified personnel. This could lead to the emergence of a dangerous black market for these therapies with all the dangers that come with mishandling and abusing an unlicensed profession. Retreats that cater to psychedelic tourism and other commercial interests are outpacing clinical evidence of psychedelics' therapeutic benefits. This is evident in some US jurisdictions where policy developments are occurring. The aforementioned factors have the potential to foster the growth and establishment of markets that lack regulation or oversight regarding the quality of substances and "therapies". This, in turn, may make it easier for people to use psychedelic substances for recreational, non-medical, and unsupervised purposes.

Continued research on the usefulness of psychedelics for the treatment of psychiatric disorders is necessary. The future of psychedelic psychotherapies involves alliances between patients, psychiatrists and other healthcare workers. Risk-benefit assessments for individuals will be required.

Conflict of interest

The author has no conflict of interest.

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