American Association of Psychiatric Pharmacists (aapp.org)

Psychedelic Therapies: Safety and Legality of Psychedelic Compounds

Meagan Dean, PharmD, November 2023

Overall Key Safety Features of Psychedelics[33, 34,35]

- Low risk of misuse (no dependence or compulsive use)
- No symptoms of withdrawal seen
- No worsened suicidality
- Low biological toxicity

Psychedelic Psychotherapy – What is it?

Psychedelic = "mind manifesting." When proper doses of psychedelics are taken, most describe their experiences as "out of body" with a new stream of consciousness. This may be key in the treatment of various psychiatric conditions. Psychedelics are used with psychotherapy for patients to open up about their experiences, especially in cases of post-traumatic stress disorder (PTSD). Most classic psychedelics (such as psilocybin and LSD) work to increase serotonin receptor activity in the brain. This may enhance the action of first-line antidepressants, such as selective serotonin receptor inhibitors (SSRI) and serotonin norepinephrine receptor inhibitors (SNRIs).[1]

Legal Status

All listed agents are currently Schedule I controlled substances by the DEA (CS-I). This category includes substances with high potential for abuse, no currently accepted medical use in treatment in the US, and a lack of accepted safety for use under medical supervision. This limits the feasibility for large clinical trials of psychedelics due to restrictions on access and quantity available for research. Most recently the FDA published draft guidance on psychedelic drug development for industry on June 26, 2023 (currently in open-comment period, not yet for full implementation). This FDA guidance provides considerations for industry sponsors (drug companies) looking to develop psychedelics for the use and treatment in medical conditions such as psychiatric and substance use disorder. This is a step in the right direction by providing federal support for the investigation of therapeutic benefit versus abuse potential of psychedelics (including psilocybin, LSD, and MDMA).[11]

Risks

There are three main risks involved with psychedelics: "bad trip," worsening of psychotic conditions, and physical effects. A "bad trip" is described as anxiety, negative mood, confusion, and/or acute delusional reactions. These "bad trips" typically occur at high doses. They may lead to dangerous behaviors if these reactions occur in unsupervised settings.[1] Some users of psychedelics may have increased risk of psychosis. Users with personal or family history of psychosis are at higher risk and may experience a prolonged psychotic reaction (lasting more than 48 hours). Additionally, there are physical effects involved with using psychedelics. These include an increase in blood pressure and heart rate while the substance is in the system. Other risks include dose-related headaches, nausea, and vomiting. These adverse effects are often short-lived, but patients with heart conditions must be closely monitored during use of psychedelics due to these risks.[1] Furthermore, due to the current illegality of psychedelics, people are likely to obtain them from unsafe sources (e.g., the street), where the product they are receiving may be tainted with other harmful substances (such as fentanyl). When psychedelics are obtained from unreliable sources, the risk of other harmful substances being mixed in increases which may lead to an overdose and, ultimately, death of the person taking it. Lastly, if psychedelics are combined with other medications or substances (e.g., alcohol or cannabis products) there is a risk of severe physical harm and death in some cases.

Table 1. Origin of Psychedelics

Product	Origin/Previous Uses	Possible Effects	Comments
Ayahuasca[2,3]	Brewed tea from plants Ceremonial use in Central/South America	Altered consciousness Enhanced emotions, memory, and visions	Contains dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOi)
Mescaline[4,5]	Flowering head of peyote cactus Religious ceremonies in northern Mexico and Southwestern US	Altered consciousness Visions of: colors, mosaics, animals/humans, pleasant feelings, transcendence	Used therapeutically in the 1950s
Psilocybin[6]	Variety of mushrooms Religious ceremonies in Mexico, Central and South America since 1500s	Altered consciousness Visual alterations, enhanced emotion, spiritual awakening	Transforms to active component in body: psilocin
LSD[7,8]	Synthetic – developed from fungus in 1938 Psychedelic effects discovered in 1943 Military use as a "truth drug" starting in the 1940s[9]	Altered consciousness Enhanced emotion, new interpretation of self and surroundings	Popular in 1960s-1970s prior to becoming classified as CS-I
MDMA[8, 10]	Synthetic – developed in 1912	Altered consciousness Increased communication, empathy, and ability to process painful or negative emotions	Used to enhance psychotherapy in 1970s prior to becoming classified as CS-I

Psychedelic Therapies

Product *Other names*	Clinically Studied Uses	Mechanism of Action	Duration of Effect	Physical Effects	Risk when misused
Ayahuasca *DMT*: CS-I [12]	Anxiety, depression[3, 13] SUD [12]	Psychoactive drink containing DMT and MAOis. MAOis prevent oral inactivation of DMT. DMT: agonist at 5-HT_{2A} receptors [12]	Initial: 45 – 60 min[2] Peak: 1.5 – 2 h[2] Duration: 4 – 6 h[2]	Elevated blood pressure, nausea, vomiting [4] Skin sensitivity, heat/cold waves, and yawning[2]	Anxiety reactions, dissociative episodes, psychotic symptoms lasting longer than 6 h[2]
Mescaline *Peyote, Buttons, Mesc* [14] CS-I [4]	Anxiety, depression, AUD, SUD[5]	Acts at serotonin and dopamine receptors (Most activity at 5-HT_2) Partial agonist: 5-HT_{2A}, [2B] Full agonist: 5-HT_{2C} [15,16]	Initial: 1 – 2 h[16] Duration: >10 – 12 h[16]	Nausea, vomiting, pupil dilation, increased heart rate, increased blood pressure, sweating, headache, muscle weakness, impaired coordination [4]	Death (although rare) [16]
Psilocybin *Magic mushrooms, Shrooms* [14] CS-I [4]	TRD (w/risperidone) [17] TRD [18,19] OCD [20] Smoking cessation [21, 22] AUD [23]	Activates serotonin receptors (5HT_{2A}) in the neocortex [15]	Initial: 20 – 30 min [16] Duration: 3 – 6 h[16, 24]	Nausea, vomiting, muscle weakness, lack of coordination[4]	Poisoning, death[4]

Psychedelic Therapies (Cont.)

LSD *Acid*[14] CS-I [4]	Alcoholism[25] PTSD[8]	Activates most types of serotonin (5-HT_{2A}), dopamine, and adrenergic receptors.[15]	Initial: 30 – 40 min[16] Duration: 8 – 12 h[16]	Dilated pupils, higher body temps, increased HR & BP, sweating, loss of appetite, sleeplessness, dry mouth, tremors [4]	"Bad Trip" HPPD
MDMA *Molly, Uppers, Ecstasy* [14] CS-I [4]	AUD[26] Borderline[27] Depression[28], Social Anxiety[29] PTSD [27-31]	Induces serotonin release by binding to pre-synaptic serotonin transporters (some dopamine and norepinephrine)[31]	Initial: 20 – 60 min[10] Peak: 2 h[10] Half-life: 8 h[10]	Short-term high BP, increased HR,[4] increased sweating and body temperature, feeling cold[28]	Coma, seizures, hyperthermia, death[32]

DMT = dimethyltryptamine; SUD = substance use disorder; MAOi = monoamine oxidase inhibitor; TRD = treatment-resistant depression = lack of response to > 2 antidepressant trials of at an adequate dose for an appropriate trial (> 6 weeks); OCD = obsessive compulsive disorder; SI = suicidal ideation; PTSD = post-traumatic stress disorder; AUD = alcohol use disorder; Borderline = borderline personality disorder; HPPD = hallucinogen persisting perception disorder = flashbacks; HR = heart rate; BP = blood pressure; h = hours; min = minutes; NMDA = N-methyl-D-aspartate; BDNF = brain-derived neurotrophic factor; AD = antidepressant

Summary

Clinical trials using psychedelics are becoming more common as these substances used in combination with psychotherapy have shown efficacy in treatment of numerous hard-to-treat mental health conditions such as: substance use disorder and treatment-resistant depression. Overall, psychedelics are safe when used at appropriate doses and monitored in a controlled setting. It is not currently recommended to utilize psychedelics at home, without the supervision of a medical practitioner, as some patients are more vulnerable to certain side effects with taking them.

Additional Resources

- How To Join a Psychedelic Clinical Trial · Psychedelic Support: https://psychedelic.support/resources/how-to-join-psychedelic-clinical-trial/
- Psychedelic therapy: a roadmap for wider acceptance and utilization | Nature Medicine: https://www.nature.com/articles/s41591-021-01530-3
- Center for Psychedelic & Consciousness Research (hopkinspsychedelic.org): https://hopkinspsychedelic.org/
- Home - UC Berkeley Center for the Science of Psychedelics: https://psychedelics.berkeley.edu/

Go online to find more information and to view the references for this toolkit.

aapp.org/591375