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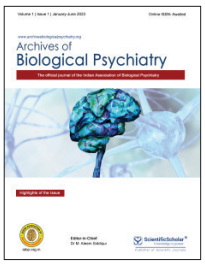

Editorial Psychiatry

Psychedelic therapy: Can't stop the wave, let's learn to surf!

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Medicinal uses of addictive substances have been well known since ancient days. Ever since the United States (US) declared the "War on Drugs" in the 1970s and subsequent sanctions imposed on the production and use of these substances worldwide, the focus on their medicinal uses was lost. This focus, however, has been revived in the past few years. Regulatory approvals in the US for several cannabinoid formulations, such as dronabinol, nabilone, nabiximols, and epidiolex, for various indications have stirred a wave. In the pursuit of not missing out on the medicinal benefits of cannabinoids, India too approved the use and marketing of cannabidiol oil (for refractory epilepsy in children) about a year ago, on April 6, 2023. This marked the beginning of off-label use of cannabidiol for psychiatric disorders. About a year ago was also when Australia approved two psychedelics – 3,4-methylene-dioxy-meth-amphetamine (MDMA) and psilocybin for prescription by psychiatrists in post-traumatic stress disorder (PTSD) and depression. The US Food and Drug Administration has set August 11, 2024, as the target action date for possible approval for MDMA-assisted therapy. Sooner than later, India is also set to approve psychedelic-assisted therapies for psychiatric disorders. We deem that it is essential for us psychiatrists in India to get ourselves conditioned to this construct. Fittingly, a recent editorial in the Journal of the American Medical Association has heralded psychedelic therapy as "a new paradigm for care in mental health."[1]

Psychedelics, also called as hallucinogens or psychotomimetics, exert their effects by means of inducing mystical experiences. They are broadly classified as entheogens (also called classical hallucinogens) and empathogens (also called as entactogens). The former class of psychedelics stimulates intense primary religious or "peak experiences", and the latter induces emotional communion or oneness. While plant-based psychedelics – lysergic acid diethylamide (LSD, an example of ergolines derived from ergot); N, N-Dimethyltryptamine (DMT, an example of tryptamine derived from ayahuasca); psilocybin (an example of tryptamine derived from psilocybe mushrooms or magic mushrooms); and mescaline (an example of phenylethylamine derived from peyote cactus) are classified as entheogens, MDMA is an entactogen.[2] Cannabinoids and dissociative agents like ketamine, despite their hallucinogen properties, are not classified as psychedelics.

Conventionally, psychedelics were understood to facilitate serotonergic (5-hydroxytryptamine [5-HT]) neurotransmission. While entheogens are 5-HT receptor agonists, entactogens are 5-HT-releasing agents. At present, they are proposed to exert their brain effects at various different levels, too:[3,4]

1. Gross brain level
    a. Reduced thalamocortical gating
    b. The relaxed beliefs under the psychedelics model – according to which psychedelics control and reduce the precision of high-level priors from the cortex, cause more entropy, and lead to more relaxed and flexible cognitive processes.
    c. Disruption of the claustrocortical circuit, which exerts strong cognitive control.
2. Neuronal/synaptic level
    a. Psychoplastogenic effects
    b. Increased production of synapses and enhanced synaptic growth
    c. Increased complexity of dendrites.
3. Molecular/cellular level
    a. Enhanced serotonergic neurotransmission
    b. Stimulate dopaminergic and trace amine-associated receptors
    c. Increase the levels of oxytocin, glutamate, and Brain derived neurotrophic factor (BDNF)
    d. Anti-inflammatory mechanisms.

Apart from these brain mechanisms, the psychological effects of the "set" (mystical/religious mindset and beliefs) and the "setting" (mystical/religious environment and socio-historical context) also seem to have a major influence on the way psychedelics act.

The most recent meta-analysis on the efficacy and safety of psychedelics suggests strong therapeutic effects of Psilocybin, DMT, MDMA, and LSD on psychiatric disorders.[5] While more evidence is available for psilocybin for depression and MDMA for PTSD, psilocybin and DMT for depression show the strongest effects. The indications, respective effect sizes, and drug doses are shown in Table 1. This meta-analysis reports that no serious adverse events are reported in about 40% of cases, that headache is the most common adverse event and that transient anxiety, delusions, elevated blood pressure, dizziness, nausea/vomiting, and fatigue may be seen.

Table 1: Indications, effect sizes, and doses of psychedelics.

S. No.	Psychedelic	Indications	Effect sizes	Doses
Entheogens				
1.	Psilocybin	Depression (major depressive disorder – single as well as recurrent; treatment-resistant depression)	Large	10–50 mg (most studies have used 25 mg); 0.2–0.3 mg/kg. Available in capsule preparation.
		Alcohol use disorder	Moderate	
		Tobacco cessation Obsessive-compulsive disorder Cluster headache Migraine Body dysmorphic	Low/less evidence	
2.	DMT	Depression (major depressive disorder – single as well as recurrent; treatment-resistant depression)	Large	0.1–2.2 mg/kg. Prepared as DMT hemifumarate vials (5 mg/mL or 18 mg/mL infusion)
		Substance use disorder Social anxiety disorder Borderline personality disorder	Low/less evidence	
3.	LSD	Depression (major depressive disorder – single as well as recurrent; treatment-resistant depression)	Large	100–200 mcg (3 mcg/kg). Available in oral solution
		Alcohol use disorder	Moderate	500–800 mcg
Entactogens				
1.	MDMA	PTSD	Large	40–125 mg. Available in capsule preparation.
		Depression Anxiety	Moderate	75–125 mg
		Insomnia Eating disorders Alcohol use disorder	Low/less evidence	

DMT: N, N-Dimethyltryptamine, LSD: Lysergic acid diethylamide, MDMA: 3,4-methylene-dioxy-meth-amphetamine, PTSD: Post-traumatic stress disorder

Typically, the schedule of the psychedelic-assisted therapy involves 1–2 dosing sessions (more, i.e., 3 dosing sessions are required for MDMA in PTSD) that involve administration and experiencing the effects of the psychedelic agent used, preceded by three sessions of therapy (preparation phase) and then succeeded by three sessions of therapy (integration phase). This entire schedule begins with a preliminary evaluation that includes consent and willingness of the client, followed by tapering of existing medications.[6] The most important phase in the schedule is considered to be the integration phase, which, in general, is also called "psychedelic integration," in which the mental health professional needs to be trained specifically.[7] In "psychedelic integration," "the goal is to consolidate the insights gleaned during dosing and help the patient apply these changes to their daily life."[6]

Supported by advances in neuroscience research and results of clinical trials, the wave of psychedelic therapy is inevitable, let us learn to surf and embrace it!

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