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Psychedelics: Overlooked Clinical Tools with Unexplored Ergogenic Potential

Short Review

Steven B. Machek[1]

[1] Department of Health, Human Performance, and Recreation; Exercise and Biochemical Nutrition Laboratory; Baylor University, Waco, TX, USA

Abstract

Psychedelics are a stigmatized, under-researched class of hallucinogenic drugs with unprecedented boundless potential. Despite a historically widespread cultural use, these drugs were denigrated and prematurely banned before clinical trials could demonstrate their value. It is now known that through full or partial serotonergic receptor agonist activity, psychedelics impart positive effects on a broad spectrum of psychiatric disorders including depression, anxiety, post-traumatic stress disorder, and obsessive-compulsive behaviors. Furthermore, extremely small, non-intoxifying microdosed psychedelics ($1/10^{th}$-$1/16^{th}$ typical dose) may potentiate similar effects to full doses without undesirable side effects. These compounds are also unexplored for their potential role in physically active populations. A preponderance of subjective claims and fervent anecdote indicate psychedelics may enhance mental acuity and subsequent exercise performance. Through the same serotonergic-mediated mechanisms that invoke neuroplasticity, psychedelics possibly augment exercise adaptation and offer safer alternatives to current pain management strategies. Despite a wealth of promising clinical data and high drug safety, federal restriction remains a psychological barrier to research and general public acceptance. Therefore, the purpose of this short review is to 1) briefly demonstrate the clinical value of psychedelics, and 2) highlight the potential of microdosing as an effective alternative to full-dose psychedelics whilst emphasizing their latent ergogenic ability.

Keywords: Hallucinogen; microdosing; nootropic; depression; athletic performance; pain management

Corresponding author: Steven B. Machek, Steven_Machek2@baylor.edu

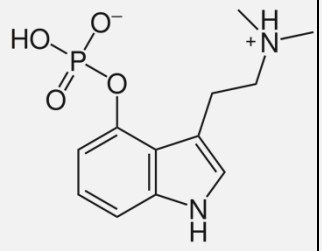
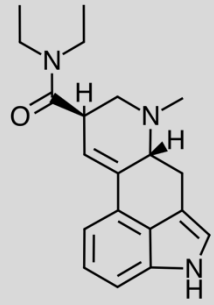
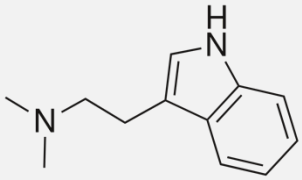
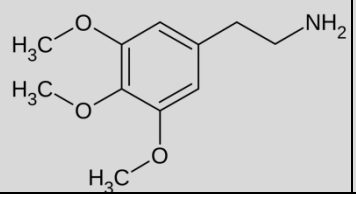
Background

Originally coined by Humphrey Osmond in 1957, the term "psychedelic" denotes mind-manifesting capabilities and hidden properties of the brain.[1] As a class of hallucinogenic drugs, psychedelics encompass a bevy of compounds, including – but not limited to – lysergic acid diethylamide (LSD), psilocybin, mescaline, and N, N-dimethyltryptamine (DMT) (Table 1). Historically, several cultures have utilized psychedelics in sociocultural and ritualistic contexts.[1] Psilocybin-containing mushrooms were used by the Aztecs in healing and religious rituals.[1] The peyote cactus (Lophophora williamsii) and its active psychedelic component, mescaline, were used as religious sacrament in the Native American Church.[2] DMT has an extensive history in the Amazon valley of South America; natives brewed DMT-containing ayahuasca from the crushed bark of Banisteriopsis caapi and the leaves of Psychotria virdis[3]. Regardless, these compounds were subject to scrutiny during periods of political unrest in the United States.[1] Similar to cannabis at that time, psychedelics became a scapegoat for antiwar sentiments and rebellious attitudes, resulting in the Controlled substance act of 1970.[1] This policy severely restricted psychedelics before sufficient research could surface to display their latent therapeutic potential.

While sparse, the existing and growing psychedelic literature is optimistic. A dwindling stigma and concomitant improvements in public perception has motivated research to demonstrate the clinical value of psychedelics in populations from the depressed to the terminally ill.[4,5] Several of these compounds are characterized for their ability to invoke neuroplasticity, resulting in profound effects on mood and

anxiety.[6] Beyond the clinical realm, otherwise healthy demographics are beginning to experiment with extremely small "microdoses" of psychedelics to improve their cognitive performance.[7] Microdoses commonly entail subthreshold doses of psilocybin (0.1-0.5 mg) or LSD (6-25 μg) in lieu of full-fledged administration (6-20 mg and 75-150 μg for psilocybin and LSD, respectively).[8] Despite their immense potential, psychedelics are heavily under-researched in human populations, require extensive subject screening, and are not without risk.[9] Therefore, the purpose of this short review is to 1) briefly demonstrate the clinical value of psychedelics, and 2) highlight the potential of microdosing as an effective alternative to full-dose psychedelics whilst emphasizing their latent ergogenic ability.

Table 1. List of Common Psychedelic Substances [1,10]

Compound Name	Common Name/Source	Typical Dosages (Microdose if applicable)	Pharmacokinetic Notes
Psilocybin/ Psilocin 	"Magic Mushrooms" Commonly Psilocybe Cubensis	6-20 mg MD 0.1-0.5 mg	Onset 20-30 min 4-8 hr duration
Lysergic Acid Diethylamide (LSD) 	"Acid"	~75-150 μg MD 6-25 μg	Onset 20-60 min 6-12 hr duration
N-N-Dimethyltryptamine (DMT) 	Ayahuasca (mixture of Banisteriopsis caapi crushed bark & Psychotria viridis leaves)	~60,000 mg MD ~1mg/kg bw	Onset ~60 sec ~10-60 min duration
Mescaline 	Peyote Cactus (Lophophora williamsii)	200-400 mg	10-12 hr duration Peak levels at ~60 min in rodents

Bw = bodyweight; Hr = hour; MD = microdose; Min = minute; Sec = second
Note: The above table is not an exhaustive list of compounds labeled as psychedelics and their pharmacokinetics.

Purported Benefits of Psychedelic Use

While not fully elucidated, it appears that psychedelics function as serotonergic agonists or partial agonists.[1,5,11] Several psychedelics, including psilocybin, LSD, DMT, and mescaline are structurally similar to 5-hydroxytryptamine (serotonin) and have high affinity for the serotonin 2A (5-HT_{2A}) receptor.[1,11] Primarily through 5-HT_{2A} activation-mediated mood regulation, psychedelics impart effects on cognitive flexibility and associative learning, as well as exerting anti-depressive and anxiolytic properties.[1,5] Additionally, there is evidence that psychedelics can attenuate obsessive-compulsive and post-traumatic stress disorder (PTSD) tendencies. Generally, psychedelic compounds like psilocybin have displayed an intriguing ability to reduce cerebral blood flow to areas of the brain tasked with social attributions, waking consciousness, and self-reflection.[8] This reduction is hypothesized to accompany increased connectivity between brain regions (that normally function independently) to reduce depressive symptoms.[5,8] Given these mechanisms, psychedelics may fit a unique role in treating psychiatric disorders. An investigation by Carhart-Harris et al.[5] utilized an acute 25mg psilocybin dose in patients with treatment-resistant depression, where ultimately all 19 patients showed a reduction in symptom severity. Surprisingly, this attenuation persisted at 3-months post-intervention. The long-term psychological benefits are corroborated by Griffiths et al.[4], who investigated the impact of psilocybin on patients concurrently suffering from life-threatening cancer and clinical depression. Treated subjects saw acute improvements in subjective well-being and life satisfaction that persisted six months following a single high-dose.

Mood and anxiety disorders are a United States epidemic and economic burden.[6] Shockingly, depression annually costs the nation $200 billion on clinical treatment.[12] Patients suffering from depression are commonly prescribed selective serotonin reuptake inhibitors and benzodiazepines, which are subject to diminished returns and withdrawal, respectively.[4] Conversely, psychedelics display no tendency for dependence *or* addiction.[1,5,8,13] Psychedelics have even been touted for their ability to ameliorate addiction of drugs such as tobacco and alcohol.[1] Daily use of hallucinogenic substances is not habit forming due to rapid 5-HT_{2A} receptor downregulation, a phenomenon deemed tachyphylaxis.[1] Persistent alcoholism and nicotine addiction are linked to altered serotonergic activity in the brain and an increased 5-HT_{2A} receptor density.[14,15] Ostensibly, psychedelic-mediated 5-HT_{2A} receptor activation facilitates drug rehabilitation by exerting "mystical" subjective effects that promote acute enhancement in therapeutic suggestibility. Subsequent rapid downregulations in 5-HT_{2A} receptor density further operate to prevent drug relapse.[16] Unlike standard allopathic approaches, psychedelics are devoid of insidious, chronically damaging side effects. They have an extremely low risk of overdose, and a lethal administration is between 100-to-1000 times an effective quantity.[13] Most undesired effects following acute administration are transient, including increases in (systolic and diastolic) blood pressure, as well as altered spatial working memory, delayed temporal perception, and slowed reaction time.[11,17] Opponents of psychedelics are often concerned with hallucinogenic effects and subsequent alterations in behavior.[18] Colloquially known as a "bad trip", an improper dose of psilocybin, LSD, and other psychedelic compounds may result in extremely traumatizing experiences.[9] Users have reported acute fleeting symptoms (i.e. dizziness, weakness, drowsiness, and dysphoria), but also more prominent feelings of fear, anxiety, and paranoia. Frightening illusions, distressing self-thoughts and even an awareness of a perceived "greater evil" may also manifest.[9] These episodes are uncommon and typically occur from ingesting high relative doses and/or unfavorable associations with the user's environment.[18] Nevertheless, psychedelic use should be heavily cautioned in those with previous psychiatric disorder and/or with concurrent serotonergic-mediated medications.[9]

Microdosing Practice

First introduced in James Fadiman's "The Psychedelic Explorer's Guide", microdosing is the practice of ingesting a very low dose of hallucinogen.[8] Typically, a small dose (around one-tenth to one-sixteenth) of psilocybin or LSD is used, resulting in little-to-no identifiable acute drug effects.[7] Microdosing may represent a method to actualize many of the benefits of psychedelic compounds without potentially deleterious intoxication. The practice has become extremely popular in mainstream media, with proponents claiming enhanced vitality, creativity, productivity, social ability, focus, analytic thinking, positive mood, memory, and general wellbeing.[8,19] Many self-reports also claim that microdosed psychedelics are capable of clinical benefits similar to a full-fledged dose, attenuating symptoms of depression, anxiety, pain, as well as reducing PTSD-related and obsessive-compulsive behaviors.[20] Catlow et al.[21] previously demonstrated that low dose psilocybin administration (0.1 mg/kg for 1 month) in mice

led to 5-HT_{2A}-mediated increases in hippocampal neurogenesis and trace fear extinction, ultimately suggesting a reversal in PTSD-associated fear conditioning.[1] Cameron et al.[6] similarly found enhanced fear extinction in rodents administered low-dose DMT (0.1 mg/kg every third day for two weeks). Purported improvements in fear extinction may have future implications in clinical PTSD treatment, or perhaps in rehabilitation settings to restore normal movement after debilitating injury.[6,22] While not fully elucidated, psychedelics may attenuate obsessive compulsive behaviors by rapidly inducing 5-HT_{2A} receptor downregulation.[1] Clinical manifestations of obsessive compulsive disorder are characterized by an upregulation in 5-HT_{2A} receptors due to serotonin insufficiency and subsequent negative feedback between the thalamus, orbitofrontal cortex, the caudate nuclei, and the globus pallidus.[1] Although microdosing mirrors many of the purported benefits of full-dose psychedelics, there is a stark paucity of literature investigating its efficacy (see table 2). Regardless, psychedelic microdoses have gained traction in the general population as a means of augmenting work performance. Unlikely users, including students and Silicon Valley workers have adopted microdosing to gain a competitive advantage through enhanced work efficiency[7].

Table 2. Current literature investigating the effect of microdosed psychedelics [6-8,17,19,20,23]

Author	Subject Demographics	Substance &Dose	Significant Findings
Johnstad[20]	21 internet respondents	10-25 μg LSD & 0.1-0.3 *Psilocybe Cubensis* (psilocybin)	Common effects include depression & anxiety relief, pain management, reduction of obsessive-compulsive & PTSD symptoms Done to improve concentration & problem solving
Prochazkova et al.[7]	38 subjects at "microdosing event"	0.22g psilocybin (low bw) 0.33g psilocybin (average bw) 0.44g psilocybin (high bw)	↑ divergent & convergent thinking ↔ fluid intelligence
Anderson et al.[23]	909 snowball sampled self-described microdosers	Dose N/A LSD and/or psilocybin	↓ dysfunctional attitudes & negative emotionality ↑ wisdom, open-mindedness, & creativity
Cameron et al.[6]	Young M & F postnatal (day 56) rats	DMT every 3rd day for 2 weeks 1 mg/kg (1/10 typical hallucinogenic dose)	↑ fear extinction & swimming + climbing behavior (antidepressant response) in DMT vs CON ↓ immobility in DMT vs CON ↔ impairments in working/short-term memory in DMT vs CON ↑ non-adipose (white or brown) weight gain rate in M DMT vs F DMT & CON

Polito & Stevenson[8]	1181 microdosers completing an online questionnaire (22.2%M/77.8%F; 71% completed post-graduate education)	~6-25 μg LSD & 0.5 psilocybin	↑ subjective focus & productivity ↓ stress, mind wandering 8.06% subjects report microdosing experience among 5 most meaningful life experiences
Hutten et al.[19]	1116 microdosers completing an online questionnaire	Most used substances were LSD, psilocybin, & MDMA	Microdosed for performance, empathy/spirituality & mood enhancement, symptom relief, & curiosity
Yanakieva et al.[17]	48 adults aged 55-75	5, 10, or 20 μg LSD every 3 days	↑ over-reproduction of suprasecond intervals on temporal reproduction task (altered time perception)

CON = control; DMT = N, N-dimethyltryptamine; F= female; LSD = lysergic acid diethylamide; M = male; PTSD = post-traumatic stress disorder; MDMA = 3,4-methylenedioxy-methamphetamine

Ergogenic Potential of Full-Dose & Microdosed Psychedelics

It may be pragmatic to view microdosed psychedelics as nootropics, or compounds used to enhance cognitive function.[24] Nootropics are becoming an increasingly popular method to gain a cognitive edge in competitive environments.[25] Adderall (amphetamine) and Ritalin (methylphenidate) are illicitly used to improve work efficiency and focus, disregarding addictive potential or risk of psychological dependence.[25] The impetus to augment performance with precarious stimulant use is further present in the sports realm, where athletes are willing to risk their careers and health to gain an edge.[26] Apart from inherent clinical value, psychedelic compounds might serve as a novel ergogenic aid in lieu of precarious stimulant use. To the author's knowledge, no literature has investigated the effects of psychedelics on mental acuity in athletic settings. Curiously, historical reports give credence to this notion, whereby ancient Greek Olympic athletes consumed psilocybin mushrooms as a means to enhance performance.[26] For nearly five decades, clandestine extreme sportsmen have used psychedelics in microdoses for their so called "psycholytic" effects.[27] They attest to improvements in stamina, reflex time, and balance. Athletes participating in extreme snowboarding, mountain-biking, surfing, and various other sports describe how psycholytic doses of LSD and psilocybin can facilitate an unparalleled focus, whereby time slows to their advantage and coordination becomes effortless[27]. Notably, professional baseball player, Dock Ellis, pitched a no-hitter under the influence of LSD; a task deemed nearly insurmountable considering the extensive history of baseball.[27] Notwithstanding these astonishing anecdotes, researchers have neglected the ergogenic potential of psychedelics in athletes. While there is no clinical literature investigating the effects of psychedelics on enhanced cognitive function, there is a mechanistic basis to suggest 5-HT_{2A} receptor agonist (or partial agonist) activity plays a beneficial role in working memory.[1] Furthermore, rodents administered mescaline demonstrated robust increases in the neurotransmitter, acetylcholine.[1] It is important to emphasize that these drugs not only lack addictive potential, but also impart several qualitative effects valued amongst athletes.[8,13,27] A wealth of survey-based subjective descriptions claim enhanced focus, vitality, and productivity, lending the potential to facilitate greater training quality across all exercise modalities. [8,19,20] Lastly, psychedelics may find a supplementary role to caffeine. As a ubiquitous stimulant, caffeine has extensive evidence as an ergogenic aid to enhance athletic and cognitive performance. However, chronic use results in addiction, tolerance, and diminished effects.[28] Psychedelics may improve athletic performance without risk of tolerance whilst simultaneously acting to attenuate caffeine addiction.[1,5,8,13,29] Given the propensity of subjective psychedelic benefit, microdosing practice warrants further investigation on its ability to augment athletic endeavors.

Psychedelics also have a largely unexplored impact beyond neural physiology. Administration of microdosed DMT has shown increased rates of non-adipose weight gain in male rodents, which may

indicate accretion of skeletal muscle or connective tissue.[6] Activation of the 5-HT_{2A} receptor stimulates the mammalian target of rapamycin (mTOR), promoting rapid growth of dendritic branches, spines, and synapses. The mTOR pathway is heavily studied in exercise science as a master regulator of muscle growth.[30] Nevertheless, it is unknown whether psychedelic-mediated stimulation of this pathway may facilitate the accretion of contractile proteins. The extracellular regulated kinase 1/2 (ERK1/2) and p38 pathway are also activated in response to 5-HT_{2A} agonist action; these cassettes of the mitogen-activated protein kinase family play significant roles in cell proliferation and survival.[1,31] Commonly discussed in exercise adaptation, ERK1/2 crosstalks with the mTOR pathway, facilitating muscle growth independent of ERK1/2-specific effects.[30] On the other hand, the p38 pathway may exert hypertrophic-associated effects by increasing phosphorylation and subsequently inactivating the MRF4 myogenic regulatory factor, which is involved in the late stages of myogenesis and adult skeletal muscle maintenance. Inactivation of MRF4 promotes proper cellular differentiation via cell cycle withdrawal.[31] Further research is required to uncover the utility of full-dose and microdosed psychedelics in serotonergic agonist-mediated lean mass modification. Perhaps these compounds play a dualistic role in potentiating the molecular responses to both neurogenesis and molecular exercise adaptation.

Finally, psychedelic compounds may facilitate pain management in both athletes and the general population. Subjective survey data indicates users commonly employ psychedelics for pain reduction.[20] Furthermore, anecdotal reports from extreme sport athletes claim psycholytic doses of LSD make them impervious to pain and fatigue.[27] These analgesic properties may be due to psychedelic-induced reductions in tumor necrosis factor alpha (TNF-α)-mediated inflammation across various tissues.[1] TNF-α and several other pro-inflammatory cytokines are implicated in the initiation and persistence of chronic pain via activation of nociceptive neurons.[1] Additionally, serotonin is thought to play a role in pain perception and 5-HT_{2A} receptor agonist activity has demonstrated anti-nociceptive effects in non-human primates.[16] Incessant pain is common in the general population and extremely prevalent in athletes, frequently leading to drug abuse.[22] Athletes obtain over-the-counter and prescription non-steroidal anti-inflammatory drugs (NSAIDs) to manage minor aches and injuries, however there is evidence that NSAIDs delay the tissue healing process by inhibiting pro-inflammatory prostaglandin synthesis.[22,32] For chronic and serious injuries, opiates may be prescribed to provide greater pain relief.[22] These powerful drugs warrant extreme regulation, however, due to their highly addictive nature and causal relationship to drug-related mortality.[33] Therein lies a novel position for psychedelics to augment existing pain management strategies: psychedelics have a propensity to attenuate pain symptoms without risk of inhibiting recovery or developing addiction. Furthermore, comparable to effects in alcohol and tobacco, psychedelics may assist in addiction recovery following opiate prescription.[5] Opiate addiction is characterized by increased serotonergic activity in various areas of the brain, whereby psychedelic-mediated rapid 5-HT_{2A} receptor downregulation may attenuate dependence.[16] The overall utility of full-dose and microdosed psychedelics as analgesics are in desperate need of further investigation. Similar to their potential efficacy in psychiatric illness, these compounds may represent a safer alternative and/or preemptive treatment to standard, allopathic approaches.

Final Remarks

Considering their potential to facilitate treatment in a variety of extremely prevalent national health issues, it seems rational to reconsider the role of psychedelics in society. A small number of cities in the United States have started a paradigm shift by decriminalizing psilocybin mushrooms and loosening regulation on distribution, consumption, and possession. Nevertheless, likely due to their legal status, data on the human physiologic response to psychedelics remains scarce. Statutory restrictions foster risk of illicit acquisition and the potential purchase of contaminated products.[1,34] Additionally, the mercurial "bad trip" is largely uninvestigated and behavioral impacts of unregulated psychedelic use remain a concern amongst the general population. Microdosing small, non-intoxifying doses of these drugs may be the answer to reconcile the issue, but time alone will tell.[23] Therefore, future research is tasked with elucidating the impacts of acute and long-term psychedelic administration in varying doses, as well as establishing appropriate subject psychiatric screening methods.[9] With sufficient evidence, the decriminalization of psilocybin mushrooms may catalyze a paradigm shift where the full clinical potential of psychedelics may be realized.

Media-Friendly Summary

The preponderance of data on psychedelic compounds warrants reevaluation of their societal value. Aside from extensive evidence supporting psychedelics in the treatment of clinical depression and anxiety, these drugs have applications in reducing addictive, obsessive-compulsive, and PTSD-related behaviors. Nevertheless, the acute and long-term side effects of hallucinogenic administration and intoxication remain under-researched. Microdosing, a growing practice amongst students and office employees to enhance work efficiency, may reconcile this issue. Utilizing sub-threshold doses, microdosing claims to impart many of psychological benefits of full-dose psychedelics without intoxication risks. While specific mechanisms remain uninvestigated, many subjective reports claim microdosing can enhance cognitive function and exercise performance. Furthermore, there is credence to suggest various psychedelic doses may enhance athletic performance via augmenting exercise adaptation and facilitating existing pain management strategies. As time progresses, sufficient research may uncover the full potential of psychedelics as both an invaluable clinical tool and novel ergogenic aid.

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