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THE EFFECTS OF MDMA AND OTHER PSYCHEDELIC SUBSTANCES - A POSSIBLE THERAPEUTIC APPROACH?

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Abstract

Recent research papers have shed light on the potential benefits of psychedelics when administered in regulated environments under the guidance of qualified professionals, such as medical practitioners, despite widespread opinion on the harmful nature of these drugs and their addictive properties. These substances, including psilocybin, LSD, and MDMA, are classified as illegal drugs in many countries. However, researchers are increasingly investigating the potential positive applications of psychedelics for the treatment of various diseases, as well as for the enhancement of individuals' quality of life, particularly of patients with specific diagnoses. This article will provide an overview of recent research in this field, highlighting the effects of psychedelics on mental disorders, including drug-resistant depression, eating disorders, post-traumatic stress disorder (PTSD), and social impairment.

KEYWORDS: LSD, MDMA, psilocybin, serotonin, social impairment

INTRODUCTION

Psychedelics are categorized into three groups based on their chemical composition: tryptamines, ergolines, and phenethylamines. Tryptamines are distinguished by an indole structure, consisting of a 6-member benzene ring fused to a 5-member pyrrole ring with an ethylamine chain at the C3 position.[1] By adding methyl groups to the ethylamine chain and various functional groups at other positions like C4 and C5, compounds such as psilocybin, psilocin, DMT, and 5-MeO-DMT are formed.[1] These substances share similarities with the neurotransmitter serotonin, which is a tryptamine with a hydroxyl group at the C5 position. Ergolines, derived from the ergot fungus and further processed through chemical reactions, include lysergic acid diethylamide (LSD).[1] The phenethylamine class, characterized by a benzene ring with an amino group attached through two-carbon, encompasses substances like 2C-B, mescaline, DOI, DOM, and derivatives like 25I-NBOMe.[1] Apart from the classical psychedelics, there are also some atypical compounds that can produce similar psychological effects. However, these compounds have a different way of working compared to the classical ones.[1] Some examples of these atypical compounds are 3,4-Methylenedioxy-methamphetamine (MDMA), muscimol, scopolamine, salvinorin A, ibogaine, nitrous oxide, PCP, and ketamine.[1] Interestingly, these atypical compounds are sometimes considered psychedelics, but under a broader definition. For full names of psychedelics see Table 1. The impact of psychedelics on the brain can be examined at various levels: molecular, cellular, circuit, and network.[1] Molecularly, psychedelics activate serotonin receptors at nanomolar concentrations, influencing specific cell types and brain regions based on the intricate expression patterns of serotonin receptors.[1] When considering the entire brain, the effects of psychedelics on different regions can be observed through techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).[1]

THE PHARMACOLOGY OF MDMA AND CLASSIC PSYCHODELICS

MDMA, commonly known as ecstasy, is a synthetic drug that acts both as a stimulant and hallucinogen.[2] Its effects include increased energy, alterations in time perception, and increased enjoyment of sensory experiences. It has been also classified as an entactogen, a drug that can enhance self-awareness and empathy.[3] MDMA affects the brain by boosting the activity of three neurotransmitters: serotonin, dopamine, and norepinephrine. Similar to other amphetamines, MDMA enhances the release of these neurotransmitters and/or inhibits their reuptake, resulting in their elevated levels in the synaptic cleft. Specifically, MDMA primarily induces a greater release of serotonin and norepinephrine compared to dopamine.[4] Serotonin plays a crucial role in regulating mood, sleep, appetite, and various behaviors. Therefore, the excessive release of serotonin caused by MDMA is likely responsible for its mood-elevating effects.[2] The chemical structure of MDMA, as well as the chemical structures of other hallucinogens, are shown in Figure 1.

Table 1. Full names of psychedelics based on source 1.

DMT	N,N-dimethyltryptamine
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
LSD	lysergic acid diethylamide
LSA	d-lysergic acid amide
DOI	2,5-dimethoxy-4-iodoamphetamine
DOM	2,5-dimethoxy-4-methylamphetamine
2C-B	4-bromo-2,5-dimethoxyphenethylamine
MDMA	3,4-methylenedioxymethamphetamine
25I-NBOMe	2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine.

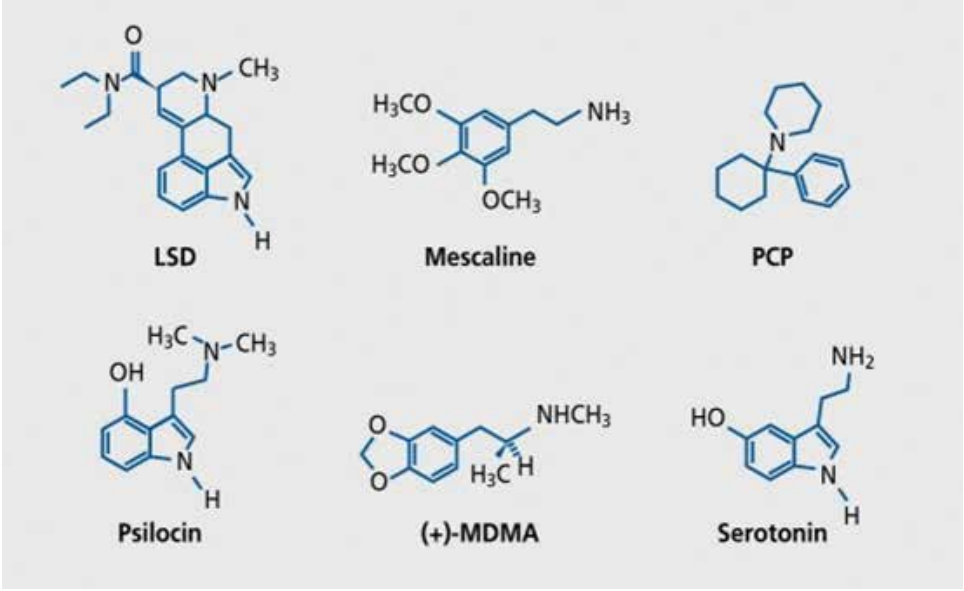


Figure 1. Chemical structures of some important representatives of hallucinogens.
Classic serotonergic hallucinogens encompass indolamines, like the semisynthetic lysergic acid diethylamide (LSD), and psilocybin/psilocin, as well as phenylethylamines, such as mescaline. Both indolamines and phenylethylamines exhibit striking structural similarities to the neurotransmitter serotonin (5-HT). Dissociative or psychedelic anesthetics, on the other hand, include phencyclidine (PCP) and its related substances, like ketamine. Entactogens, such as 3,4-methylenedioxymethamphetamine (MDMA), induce psychedelic-like symptoms but lack significant hallucinatory effects. These entactogens are structurally alike to both serotonergic hallucinogens (mescaline) and classic stimulants (amphetamines).

Source: Vollenweider FX. Brain mechanisms of hallucinogens and entactogens. Dialogues Clin Neurosci. 2001 Dec;3(4):265-79. doi: 10.31887/DCNS.2001.3.4/fxvollenweider. PMID: 22033605; PMCID: PMC3181663.
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Classic psychedelics (e.g. psilocybin, DMT, mescaline, LSD) refer to a collection of serotonergic compounds that can cause profound shifts in perception and have the ability to induce long-lasting personal and spiritual experiences of great mystical significance.[3]

LSD is a well-known psychedelic substance that acts on the serotonergic system and is commonly used for recreational purposes.[5] It is a classical hallucinogen that was accidentally synthesized by Albert Hoffman while experimenting with substances.[5] The primary mode of action of LSD involves the activation of 5-HT2A receptors and modulation of 5-HT2C and 5-HT1A receptors[6] (Figure 2). However, the precise relationship between 5-HT receptor activation or modulation and the resulting cognitive impairment and hallucinations remains poorly understood.[6]

Psilocybin, a naturally occurring chemical found in over 100 species of mushrooms worldwide, is a pro-drug that undergoes dephosphorylation into its active metabolite

psilocin, which is responsible for the psychoactive effects.[6] As shown in Figure 3, the chemical structure of psilocin is similar to serotonin.[6] The psychoactive effects of psilocin are believed to be mainly mediated by its activity as a relatively non-selective 5-HT2A receptor partial agonist[6] (Figure 3). The activation of 5-HT2A receptors in the thalamus, which is responsible for sensory input, decreases thalamic activity, leading to sensory alterations and hallucinations.[6]

The significant impact of psychedelics with addictive properties cannot be emphasized enough. Addiction, a chronic recurrent condition that has afflicted many individuals, poses a big challenge to "cure" and imposes a long-term burden on the healthcare system. Acute use of MDMA causes euphoria, arousal and increased heart rate, but also hyperthermia, cortisol and prolactin release, nausea, agitation, headache, and dry mouth.[8] Chronic use causes psychomotor, psychobiological and cognitive changes like retrospective, prospective and working memory impairment.[8] Deficits in complex cognition in ecstasy users may be related to serotonergic dysfunction which makes treatment difficult for both the patient and medical professionals.[8] To emphasize the prevalence of this addiction, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) states that in Croatia in 2015, a total of 7,537 individuals sought treatment within the healthcare system.[7] The majority of those who sought treatment in 2015 received care in outpatient facilities.[7]

THE EFFECTS OF PSYCHODELICS ON SOCIAL IMPAIRMENT

Social impairment is a defining characteristic of various mental health conditions, including anxiety, depression, and schizophrenia, that have a significant societal cost, as they place a burden on patients, caregivers, and treatment institutions.[4] Current investigations seek to examine potential protective effects of MDMA and classical psychedelics on social functioning within a real-life setting.[4] New research indicates a link between MDMA and a boost in cognitive empathy, suggesting that individuals who take MDMA are more likely to empathize with the emotions of others, as well as to understand their perspective.[4] Additionally, it seems that MDMA can temporarily enhance emotional empathy, allowing people to truly feel someone else's experiences.[4] Furthermore, MDMA use might lead to a greater willingness to engage in social interactions, decreased aggression, and a reduced emotional response when faced with social rejection.[4] Therefore, scientists believe that MDMA has the ability to alleviate social impairment.[4] However, the amount of evidence remains low, due to limited number of clinical investigations in this research field and the small sample sizes of previous studies.[4] Jones et al. (2023) demonstrated that individuals who had utilized MDMA/ecstasy at any point in their lives had a diminished chance of facing impairments in their social functioning. Correlation between MDMA use and reduced likelihood of social impairment could be due to changes in serotonin transmission, oxytocin release, and decreasing amygdala activity.[4] Lower levels of serotonin in the prefrontal cortex could lead to higher aggressive behavior, but on the other hand, serotonin supplementation can promote agreeable, cooperative, and friendly behaviors in both humans and animals.[4] The positive impact of MDMA on social impairment could be also result of its ability to inhibit transporter proteins that remove serotonin from the synaptic cleft, leading to increased serotonin levels.[4] In addition, MDMA may enhance sociability through increase of oxytocin release, which is influenced by changes in serotonergic neurotransmission and is known to foster trust and emotional bonding.[4] MDMA might also enhance sociability by decreasing the amygdala's response to social situations, which happens as a result of alterations in serotonergic neurotransmission and oxytocin release.[4] According to a study conducted in 2009 using fMRI, Bedi et al. discovered that MDMA reduced the amygdala's reactivity to angry facial expressions, in line with observed positive social effects of MDMA.[9] There is a connection between the mystical experiences produced by classic psychedelics and increased prosocial attitudes and behaviors, while some researchers also linked classic psychedelics with improved emotional empathy and sociality.[4] Therefore, these substances could potentially be used to address social impairments associated with mental health disorders.[4] On the other hand, Jones et al. (2023) demonstrated no connection of classical psychedelics with impairments in social functioning or higher chances of social impairment.

POTENTIAL THERAPEUTIC EFFECTS OF PSYCHODELICS

Recently, LSD has been investigated for its potential therapeutic effects in patients with psychiatric conditions, such as anxiety and depression.[10] While LSD can produce positive experiences of altered consciousness, it can also lead to negative subjective effects, including acute anxiety.[10] These negative psychological effects are considered the main risk associated with the use of psychedelic substances in humans.[10] However, clinical trials have shown an association between positive psychedelic-induced experiences and long-term therapeutic improvements in patients undergoing psychedelic-assisted therapy.[10] The recreational use of MDMA and LSD, commonly referred to as "candyflipping", produces enhanced positive mood effects when taken together.[10] In a pioneer double-blinded placebo study conducted by Straumann et al. (2023), the acute effects of co-administration of MDMA and LSD were examined using a single medium-high dose of MDMA,[3] in a controlled laboratory setting, where they observed subjective, autonomic, and endocrine effects,[10] though certain positive experiences were not measured.[3] In a subsequent observational study by Zeifman et al. (2023), the association of co-administration of psilocybin/LSD and MDMA with lower acute challenging experiences and increased acute positive experiences was investigated.[3] The primary discovery from the pioneering research by Straumann et al. (2023) indicated that the addition of MDMA did not significantly modify the immediate psychedelic effects of LSD, but resulted in more pronounced autonomic effects, such as heightened blood pressure, heart rate, and pupil dilation, when compared to LSD alone.[10] Nevertheless, the combination of LSD and MDMA extended the duration of the subjective effects experienced during the acute phase and the peak plasma concentration of LSD was higher, in contrast to LSD monotherapy.[10] Additionally, the administration of MDMA by itself, as well as in the combination with LSD, significantly elevated oxytocin

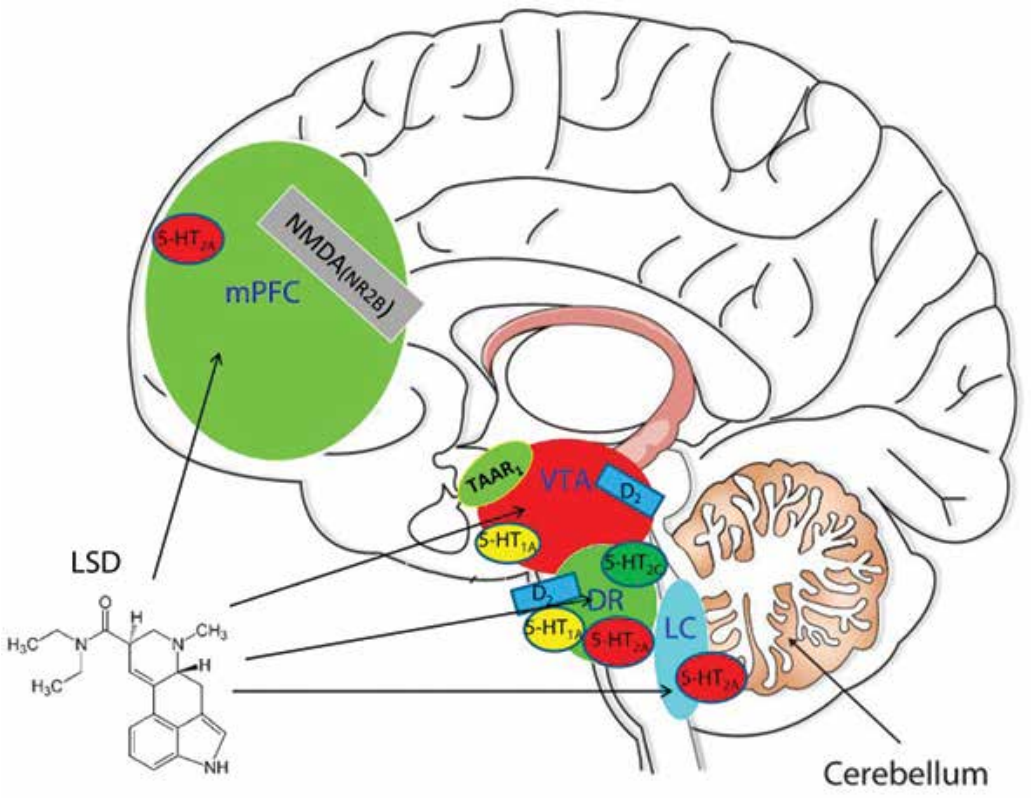


Figure 2. The mechanism of action of LSD and its interaction with various brain regions.
LSD acts on serotonin 5-HT1A, 5-HT2A, 5-HT2C receptors, as well as dopamine D2 receptors in the Dorsal Raphe (DR). In the Ventral Tegmental Area (VTA), it affects dopamine D2 receptors and Trace Amine Associate Receptor 1 (TAAR1), while in the Locus Coeruleus (LC), it primarily targets 5-HT2A receptors. These three nuclei project to the prefrontal cortex (PFC), where they modulate the release of neurotransmitters, thereby influencing the occurrence of psychotic-like effects and cognitive changes. The medial prefrontal cortex (mPFC) and N-methyl-d-aspartate (NMDA) receptor subunit NR2B also contribute to these processes.

Source: De Gregorio D, Comai S, Posa L, Gobbi G. d-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology. International Journal of Molecular Sciences. 2016; 17(11):1953. https://doi.org/10.3390/ijms17111953
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levels which may mediate some of the subjective effects of MDMA.[10] On the other hand, LSD administered alone only resulted in minimal increases in oxytocin levels.[10]

There are several factors that can contribute to the intensity of challenging psychedelic experiences.[3] These factors include trait level neuroticism, preparedness for the psychedelic experience, and the setting in which the psychedelic is used.[3] Additionally, the co-use of other pharmacological agents can either intensify or buffer against these experiences.[3] For example, when classic psychedelics are used in combination with lithium and other mood stabilizers, the intensity of challenging experiences tends to be higher, and can lead to medical complications, such as seizures.[3] Another study found a quadratic relationship between the co-use of cannabis and classic psychedelics, suggesting a positive association between increasing doses of cannabis co-use and the intensity of challenging experiences.[3] In a recent double-blind placebo-controlled study, no significant differences were observed in acute experiences between LSD (100 µg) plus placebo and LSD (100 µg) plus MDMA (100 mg).[3] However, this study was conducted in a controlled setting and excluded individuals with a personal or family history of psychiatric disorders, which could have minimized the occurrence of LSD-related challenging experiences and resulted in floor effects.[3] The results of the study by Zeifman (2023) et al. showed that, compared to the use of psilocybin or LSD alone, the combination of psilocybin or LSD with a low dose, but not a medium-high dose, of MDMA resulted in noticeably reduced levels of total challenging experiences.[3] When examining the different groups based on the Challenging Experience Questionnaire (CEQ) subscales, it was found that the co-use of MDMA with psilocybin or LSD led to significant differences in experiences of grief and fear, but not in physical distress, insanity, isolation, death, or paranoia.[3] Moreover, the combination of psilocybin or LSD with a low dose, but not a medium-high dose, of MDMA led to even greater feelings of self-compassion, love, and

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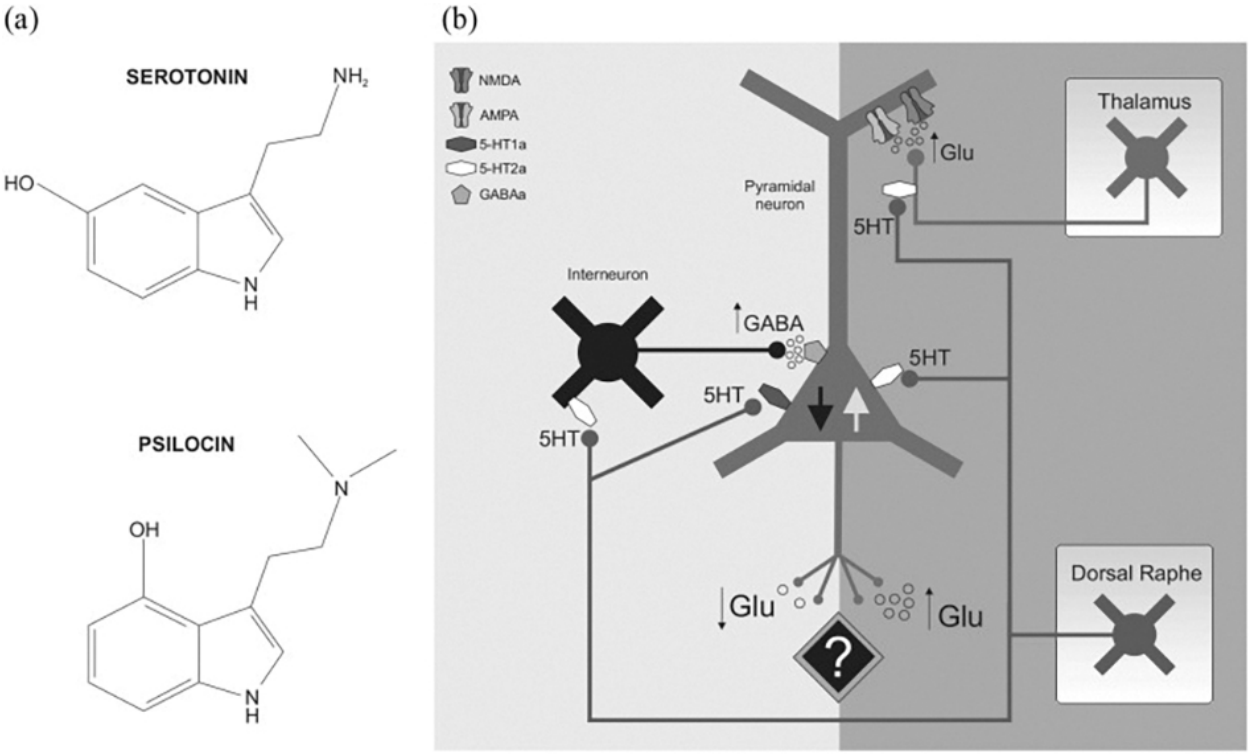


Figure 3. Psilocin's impact on receptors, pyramidal neurons, and PFC activity.
It can be attributed to two main factors. (a) Firstly, due to its chemical structure closely resembling serotonin (5-HT), psilocin has the ability to activate various subtypes of 5-HT receptors. (b) Secondly, psilocin has the potential to decrease the excitability of pyramidal neurons (PYR) by promoting the release of GABA from interneurons through the activation of 5-HT2A-R receptors and by activating 5-HT1A-R receptors on PYR neurons. Conversely, psilocin can also enhance PYR activity by directly activating 5-HT2A-R receptors on PYR neurons (as shown by the projections originating from the dorsal raphe (DR) nucleus) and thalamo-cortical afferent terminals. This activation leads to the release of glutamate (Glu), which further depolarizes PYR neurons by opening their glutamatergic cation channels (AMPA and NMDA receptors).

Source: Smausz R, Neill J, Gigg J. Neural mechanisms underlying psilocybin's therapeutic potential – the need for preclinical in vivo electrophysiology. Journal of Psychopharmacology. 2022;36(7):781-793. doi:10.1177/02698811221092508
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gratitude.[3] The co-use of MDMA with psilocybin or LSD did not show any significant differences in compassion or mystical-type experiences.[3]

Recent studies have revealed that psychedelic-assisted therapy can be an effective treatment option for a range of psychiatric disorders, including eating disorders, mood disorders and post-traumatic stress disorder (PTSD).[11] Results from several studies indicated that the use of MDMA-assisted psychotherapy in the treatment of PTSD has shown promising outcomes.[12] Specifically, approximately 70% of participants no longer met the diagnostic criteria for PTSD after undergoing this treatment, whereas around 85% of individuals experienced significant benefits from the therapy.[12] In the case of major depressive disorder, the positive effects of psilocybin usage have been observed to persist for a considerable duration, exceeding one year.[13] A study conducted by Gukasyan et al. (2022) revealed that 75% of participants experienced a reduction of over 50% on the symptom scale after consuming psilocybin, whereas 58% of the participants achieved remission from their depressive symptoms after undergoing a 12-month treatment period.[13] In patients with drug-resistant depression, a noteworthy decrease in symptoms lasted for 3-6 months.[13] The potential benefits of psychedelic-assisted therapy has been indicated in treating eating disorders, due to its ability to enhance perceptions of body image, restore normal reward processing, foster cognitive adaptability, and aid in the processing of traumatic experiences.[11]

CONCLUSION

In summary, the use of psychedelics and amphetamines to enhance the mental state of individuals who are struggling with their daily lives is yielding positive results. These promising outcomes hold the potential to revolutionize the use of psychedelics worldwide for treating mental disorders. However, the exact underlying mechanisms of the beneficial effects of psychedelics and amphetamines remain unknown, especially when considering the limited number of clinical investigations and the small sample sizes of previous studies in this research field. Nevertheless, it is crucial to acknowledge the prevailing resistance towards these substances due to the widespread biases, which act as a barrier, impeding society from embracing the verified positive effects suggested from recent scientific research.

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UTJECAJ KORIŠTENJA MDMA I KLASIČNIH PSIHODELIKA – MOGUĆI TERAPEUTSKI PRISTUP?

Sažetak

Nedavni istraživački radovi naglasili su potencijalne dobrobiti psihodelika kada se primjenjuju u reguliranim uvjetima pod vodstvom kvalificiranih stručnjaka, kao što su liječnici, unatoč stavovima o štetnoj prirodi ovih lijekova i njihovim ovisnim svojstvima.. Ove tvari, uključujući psilocibin, LSD i MDMA, klasificirane su kao ilegalne droge u mnogim zemljama. Međutim, znanstvenici sve više istražuju moguće pozitivne učinke psihodelika za liječenje raznih bolesti i poboljšanje kvalitete života pojedinaca, posebice onih s određenim dijagnozama. Ovaj će članak dati pregled nedavnih istraživanja, ističući učinke amfetamina i psihodelika na stanja i poremećaje mentalnog zdravlja, uključujući depresiju otpornu na lijekove, poremećaje prehrane, PTSP i socijalne poteškoće.

KLJUČNE RIJEČI: LSD, MDMA, psilocibin, serotonin, socijalne poteškoće