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Psychedelics

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VIEWPOINT

Psychedelics in the context of stress and psychiatric disorders: A new horizon in mental health treatment

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Psychiatric illness, particularly stress-related disorders including depression, anxiety and posttraumatic stress disorder, presents a considerable health burden worldwide with high prevalence, disabling symptoms, and scant efficacy of available treatments. Chronic stress is a major contributor to the origin and development of these conditions, to the detriment of both individual and, by extension, public health. More recently, psychedelics such as psilocybin, lysergic acid diethylamide, and 3,4-methylenedioxymethamphetamine (MDMA) have gained attention as potential therapeutic tools, mainly because of their ability to elicit altered states of consciousness and their impact on neuroplasticity, emotional processing, and serotonin pathways. This perspective paper discusses the mechanisms underlying the therapeutic effects of these substances, their potential utility for treating stress-related psychiatric disorders, and the need for a paradigm shift in the prevailing view of the intricate relationship between psychedelics, stress, and mental well-being.

Introduction

Stress is a natural component of human life with adaptive and dysfunctional health aspects. Whereas acute stress can improve cognitive function and initiate a cascade of physiological changes conducive for survival (1), chronic or excessive types of stress degrade the way that the brain works and disrupt mental health. It has a known risk factor for multiple mental health conditions—depression, anxiety, and posttraumatic stress disorder (PTSD), among them. Persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis with chronic stress results in extended increase in cortisol exposure which damage brain areas involved in mood regulation and memory like the hippocampus and amygdala (2). Such neurobiological disturbances contribute to the development and maintenance of psychiatric disorders and emphasize the development of creative pharmacological strategies to limit the consequences of stress.

While existing treatments such as selective serotonin reuptake inhibitors and cognitive behavioral therapy work for some, they are not universally successful. Residual symptoms or side effects affect many patients. These limitations have reignited interest in nonconventional treatments including psychedelics, in stress-related disorders.

Psychedelics, which were used in traditional religious and healing practices, captured Western medical interest in the mid-20th century as a possible treatment for alcoholism, anxiety, and depression. However, most studies were suspended after these substances were outlawed in the 1970s. Scientific developments in the field of neuroscience have contributed to renewed interest in psychedelics in recent years, particularly for their potential to support neuroplasticity and enable emotional and cognitive change. If this is the case, psychedelics may represent a new class of therapeutics, uniquely positioned to address the biological underpinnings of psychiatric disorders such as depression, PTSD, and anxiety (3). There is now a growing contingent of individuals calling for the consideration of psychedelics as medication-assisted therapies for stress-related psychiatric disorders, the subject of the present perspective paper, which will discuss where we stand based on modern psychedelic-related research, and outline what next steps may be for the field of psychedelic research in clinical psychiatry.

Neurobiological mechanisms of psychedelics in stress and psychiatric disorders

Stress-related psychiatric diseases, including depression, anxiety, and PTSD are often associated with aberrant emotional processing, including an enhanced reaction to negative stimuli, a defect in emotion regulation, and the impairment of traumatic memory processing. Long-term stress leads to a reduction in neuroplasticity, which decreases synaptic connectivity as well as cognitive and emotional flexibility. It also evokes elevated inflammation, which is implicated in the etiopathogenesis of these psychiatric disorders (4). Addressing these neurobiological changes is essential for effective treatment.

Psychedelics offer a potential in counteracting the damaging effects from prolonged exposure to stress. One of their key modes of action is to foster neuroplasticity, perhaps allowing a recovery of function of brain regions, such as the hippocampus and amygdala, that have been impacted by excessive exposure to cortisol. Through an easing of the grip of unmet emotional needs and trauma, psychedelics enable individuals to confront and integrate unsolved stressors, contributing to a more rounded form of treating mental health. While conventional treatments generally treat symptoms, psychedelic therapy treats the roots of stress-based disorders, bringing about the prospect of sustained relief. Consistent with the HPA axis signals noted above, some human trials and laboratory sessions have paired psychological change with endocrine modulation—for example, acute cortisol elevations during dosing (interpreted as state arousal/engagement) followed by normalization or improved diurnal regulation at follow-up—suggesting that stress-system recalibration may accompany therapeutic gains.

Psychedelics predominantly affect the serotonergic system in the brain, and they do so by primarily acting through serotonin 2A (5-HT_{2A}) receptors, which are highly expressed in brain areas involved in mood, emotion, and cognition, such as the prefrontal cortex (Figure 1). This receptor activation promotes neuroplasticity, functional connectivity within the brain and emotional processing that could, in turn, counteract the structural and functional damage induced by chronic stress. Preclinical studies indicate that psilocybin microdosing can upregulate brain-derived neurotrophic factor and enhance dendritic arborization in the prefrontal cortex of animal models, processes implicated in mood regulation (5). While these findings offer mechanistic insights, direct evidence in humans with alcohol use disorder remains scarce. It has been hypothesized, however, that such neuroplastic effects could contribute to

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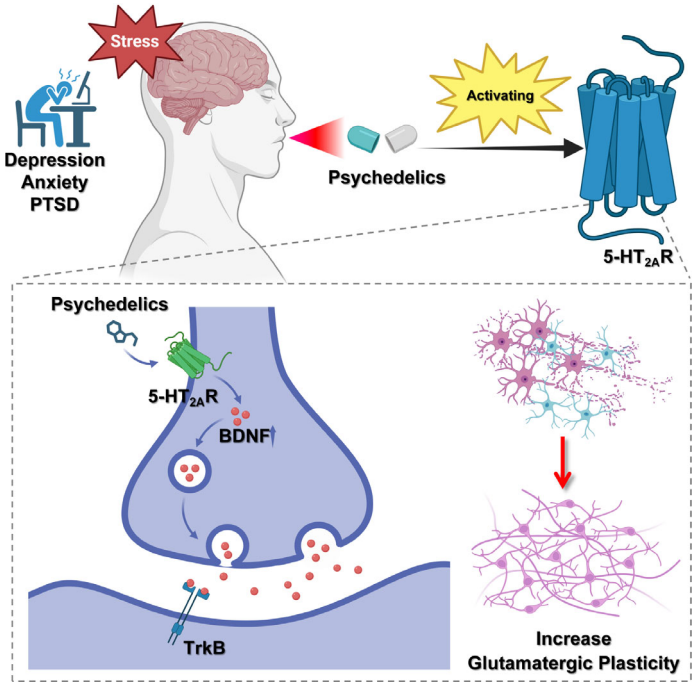

Figure 1. Psychedelics activate the 5-HT_{2A} receptor, upregulate brain-derived neurotrophic factor, and enhance synaptic plasticity, leading to therapeutic potential for stress and psychiatric disorders.

resetting maladaptive neural circuits and thereby support the sustained symptom improvements observed in some clinical trials.

Classic psychedelics, including psilocybin and lysergic acid diethylamide (LSD), also dismantle fixed, maladaptive thought patterns characteristic of disorders such as depression, anxiety, and PTSD. They accomplish this by activating 5-HT_{2A} receptors and their effects produce precisely described states of consciousness involving changes in perception, affect, and cognition. This activation of the receptor leads to decreased neuronal rigidity, enabling people to reframe experiences and learn more appropriate coping mechanisms. For example, psilocybin has been shown to decrease activity in the amygdala—a structure involved in the processing of anxiety and fear—resulting in decreased emotional reactivity to stressors and enhanced emotional regulation.

3,4-Methylenedioxymethamphetamine (MDMA) is a nonclassical (entactogenic) agent. In PTSD, its primary therapeutic signal appears to derive from acute prosociality, reduced fear reactivity, and enhanced memory reconsolidation during psychotherapy rather than from 5-HT_{2A}–driven phenomenology. Pharmacologically, it acts as a monoamine-releasing agent (serotonin $>$ dopamine $\approx$ norepinephrine) and promotes emotional openness, empathy, and decreased fear. Pharmacologically, it functions as a monoamine-releasing agent, inducing session-specific state changes that in a therapeutic context make it easier for patients to access traumatic memories without being overwhelmed, facilitating adaptive reconsolidation and reintegration. Framing MDMA-assisted therapy as a synergy between these pharmacological state effects and structured psychotherapy is critical to disrupt the vicious cycle of stress and psychiatric symptomatology and to support durable symptom improvement.

Recent evidence indicates that psychedelics may also have anti-inflammatory effects that likely contribute to the success of their therapeutic trials. For example, psilocybin has been shown to decrease proinflammatory cytokines both in preclinical and preliminary clinical studies (6). Given that psychedelics reduced inflammation, they may have additional protective benefits for the brain and body from the harmful effects of stress as they pertain to mental health. Because inflammatory tone and HPA axis function are tightly coupled, concurrent monitoring of cytokines and diurnal cortisol in future trials could clarify whether immune changes mediate, moderate, or merely accompany endocrine normalization.

In closing, the exceptional capacity of psychedelics to support neuroplasticity, improve emotion processing and decrease inflammation indicates that they might provide a new and perhaps valuable treatment for stress-related psychiatric disorders. These processes are not only critical to the symptomatic improvement of the person, but also allow the person to modify their maladaptive thought patterns and put into place new and improved mood and resilience responses to future stress exposure.

Clinical applications of psychedelics in psychiatric disorders

The therapeutic potential of psychedelics is perhaps best illustrated in the treatment of depression. Psilocybin has been studied extensively for its antidepressant effects, particularly in individuals with treatment-resistant depression. Psilocybin was administered to patients with depression who had not responded to traditional therapies (7). The results were striking: a single dose of psilocybin produced significant reductions in depressive symptoms over a period of 3 weeks, with some patients maintaining these improvements for 6 months after the treatment. Similar results have been observed in patients with anxiety associated with life-threatening illnesses, where psilocybin significantly reduced anxiety and improved quality of life. Psilocybin appears to work by reducing activity in the default mode network (DMN), a collection of brain regions that are typically overactive in individuals with depression. By quieting the DMN, psilocybin enables patients to break free from the repetitive negative thought patterns that characterize depression.

MDMA has shown remarkable promise in treating PTSD, a disorder characterized by intrusive memories, hyperarousal, and emotional numbing following trauma. In a landmark study by Mithoefer et al (8), MDMA-assisted psychotherapy significantly reduced PTSD symptoms in patients with chronic, treatment-resistant PTSD, with many experiencing long-term remission. MDMA's ability to dampen the amygdala's fear response enables patients to safely reprocess traumatic memories during therapy. A recent phase 3 clinical trial further demonstrated significant reductions in PTSD symptoms, with 67% of participants no longer meeting diagnostic criteria for PTSD after treatment (9). However, on June 4, 2024, a U.S. Food and Drug Administration (FDA) advisory committee voted overwhelmingly against approval, citing concerns over methodological limitations (e.g., challenges with blinding), variability in psychotherapy delivery, and insufficient long-term safety reporting. While this regulatory decision represents a significant hurdle, it underscores the need for more rigorous trial designs, standardized therapeutic protocols, and enhanced monitoring frameworks. Despite these challenges, MDMA remains one of the most promising novel interventions for PTSD and continues to warrant careful investigation and development.

LSD, while studied less extensively than psilocybin and MDMA, has also demonstrated potential in the treatment of anxiety and mood disorders. In a randomized, double-blind, placebo-controlled study by Gasser et al (10), patients with anxiety related to life-threatening illness received LSD-assisted psychotherapy. The study reported significant reductions in anxiety, with effects persisting for up to 12 months posttreatment. LSD's capacity to enhance emotional openness and diminish fear-based responses suggests it may be especially effective in addressing existential anxiety, a frequent challenge for patients facing terminal illness. Furthermore, the FDA has recently granted LSD a breakthrough therapy designation for the treatment of anxiety, highlighting its therapeutic promise in this area.

In addition to depression and anxiety, psychedelics have shown potential in treating other psychiatric conditions, including obsessive-compulsive disorder (OCD) and addiction. Early-phase studies involving small human samples suggest that psilocybin may alleviate OCD symptoms by disrupting the repetitive thought patterns that characterize the disorder. Similarly, psychedelics have been explored as potential treatments for substance use disorders, with promising results for reducing alcohol and nicotine dependence. These findings suggest that psychedelics may have broad applicability across a range of psychiatric disorders, particularly those involving rigid or maladaptive patterns of thought and behavior.

The therapeutic effects of psychedelics have frequently been linked to a "mystical-type experience," characterized by feelings of unity, transcendence, and a sense of interconnectedness (11). Such experiences may contribute to the therapeutic process by allowing individuals to access new insights, reframe negative thought patterns, and develop a sense of acceptance and meaning. Studies have shown that the intensity of these mystical experiences is positively correlated with the degree of symptom improvement in patients with depression and anxiety (12). Importantly, these experiences are neither necessary nor sufficient to account for clinical benefit; independent lines of evidence associate symptom improvement with enhanced cognitive and emotional flexibility and with measurable network-level neuroplastic changes (e.g., altered DMN dynamics and large-scale connectivity). Additionally, preliminary anti-inflammatory and immunomodulatory signals have been reported, and contextual factors—such as the therapeutic alliance, expectancy, and set/setting—may further shape outcomes, warranting systematic study.

Psychedelic-assisted treatments, including serotonergic agents and ketamine, can produce predictable, generally transient adverse effects such as nausea, headache, dizziness, and dissociation. Safety considerations also include cardiovascular and autonomic changes (elevations in blood pressure and heart rate), anxiety or panic in vulnerable settings, and variability in adverse event reporting across studies. Accordingly, best practice includes careful medical screening, real-time physiological monitoring, and standardized "set and setting" procedures, alongside transparent, harmonized safety reporting (13). Finally, trials in this space face well-recognized blinding and expectancy challenges due to noticeable drug effects; interpretations of efficacy should therefore incorporate strategies to mitigate and quantify expectancy (e.g., active controls and credibility checks) and report blinding integrity.

Challenges and future directions

There remain significant hurdles before psychedelics can be integrated into mainstream psychiatric practice. Chief among these is the current legal framework, which classifies most psychedelics as Schedule I controlled substances, severely restricting clinical research and therapeutic implementation. While some U.S. municipalities have moved to deprioritize enforcement of possession laws, and a few states have enacted forms of decriminalization, these measures do not equate to regulated medical access. More structured models are emerging in Oregon and Colorado, where statewide initiatives have established licensed service programs that allow supervised psilocybin use within defined therapeutic settings. As the clinical evidence base grows (14), these evolving policy experiments highlight both opportunities and challenges in making psychedelic-assisted therapies safely and responsibly accessible.

Further effort may be invested to optimize such treatments, by evaluating the most effective doses, treatment length, and patient genomes. Longitudinal studies comparing the effects of psychedelic-assisted therapy and conventional therapies for stress-related disorders are also required. Finally, larger clinical trials are necessary to validate the safety and efficacy of psychedelics over a range of psychiatric diagnoses. The development of novel psychedelic compounds that have improved safety and tolerability could overcome at least some of these limitations and improve the therapeutic efficacy of psychedelic-assisted therapy.

In addition, attempts are needed to discover and validate reliable biomarkers that can be used to enhance diagnostic accuracy and personalize treatments for stress-related psychiatric disorders (e.g., neuroimaging markers, cytokine levels, and microRNAs). The application of big data and artificial intelligence approaches could additionally lead to enhanced individualized therapeutic strategies, prediction of treatment responses, and minimization of adverse effects. To move forward in understanding stress mechanisms, promoting innovation, and translating discoveries to new therapeutic tools, interdisciplinary interaction at the levels of neuroscience, psychology, engineering, and pharmacology is required. Insights into stress-activated neural circuits and the molecular mechanisms of plasticity and receptor function may offer new targets for intervention to prevent or treat psychiatric disorders.

In order to bring these substances into the fold of mainstream psychiatry, specialized training programs for therapists will be necessary. Psychedelic therapy is qualitatively different from traditional forms of psychotherapy which rely on solely verbal interactions between the patient and doctor, in much the way that taking penicillin for a sore throat is very different from getting a throat massage. These therapists should not only have a solid understanding of psychedelic pharmacology, but also experience in working with patients through the psychedelic process, handling difficult emotions, and help in integrating these sessions into life (15).

While obstacles are significant, the promise of psychedelics to change the face of stress and psychiatric treatment is great. The profound, rapid, and sustained impact that these agents have demonstrated in numerous patients highlights their therapeutic promise for treatment-refractory or recalcitrant patients. Overcoming barriers to optimizing treatment interventions, patient screening, and safety will be critical for the clinical use of psychedelics. Their distinct modes of action as mediators of neuroplasticity, modulators of emotional plasticity, and as immune regulators unveil a fresh lens on the treatment of stress related psychiatric disorders based on the pathogenesis of these diseases.

Conclusion

Psychedelics are a potential new frontier for stress-related psychiatric disorders as they point us in a direction for treating the root cause of conditions such as depression, PTSD, and anxiety. By engaging critical neurobiological systems implicated in stress and emotion regulation, such as 5-HT_{2A} receptor activation, neuroplasticity, modulation of the DMN, and anti-inflammatory properties, psychedelics enable significant positive changes in how we process emotions, help us integrate traumas we haven't resolved, give patients different perspectives on underlying stressors, and enable the development of more adaptive coping strategies—especially when used in the context of psychotherapy. Even with obstacles, including safety, regulatory hurdles and the requirement for more, bigger clinical trials and specialized training programs for therapists, the evidence is accumulating that psychedelics could one day be a mainstay of psychiatric treatment that could change mental health care—and offer hope for patients who have not benefited from conventional therapies. There is, however, a need for continued research, and it is important to acknowledge the possible positive (and negative) side effects of these compounds, as their promise lies not only in their ability to help alleviate symptoms, but also in enabling us to gain greater insight into the human mind and to facilitate personality transformation.

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Author contributions

SJ, HW, and XW wrote the manuscript. XW oversaw the entire work, and supervised SJ and HW. The manuscript has been read and approved by all authors. All authors take full responsibility for all text and figure, and approve the content and submission of this work. No related work is under consideration elsewhere.

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Author disclosures

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