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Guest Editorial

Transdiagnostic use of 3,4-methylenedioxymethamphetamine-assisted therapy to treat obsessive–compulsive disorder

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Summary

This article explores the potential of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy to enhance exposure and response prevention in obsessive–compulsive disorder treatment. We discuss the mechanisms of MDMA, including fear extinction, psychological flexibility, and empathogenic effects that may improve adherence and efficacy, as well as highlighting important safety considerations for further research.

Keywords

Anxiety or fear-related disorders; neuroscience; obsessive–compulsive disorders; psychological treatments; psychotherapy.

Obsessive–compulsive disorder (OCD) is a neuropsychiatric condition listed by the World Health Organization as one of the ten most debilitating worldwide.[1] The hallmark of OCD pathology lies in the distress caused by recurrent obsessive thoughts and repetitive compulsive actions, which can lead to significant social impairment and morbidity.[1] Pharmacologic management of OCD can involve high doses of selective serotonin reuptake inhibitors (SSRIs); however, these often yield inadequate treatment response and are associated with increased dose-dependent side-effects.[1]

The non-pharmacological standard of care for OCD includes exposure and response prevention (EX/RP). This therapeutic modality aims to uncouple the relationship between the obsessive thought and the compulsive action, by exposing the patient to distress from the obsession while resisting acting on the compulsive urge in a controlled environment.[2] EX/RP is deemed successful when it results in habituated and learned cessation of the obsession–compulsion distress loop. Although it is effective for many patients, up to 60% of those undergoing EX/RP experience partial relapse of symptoms.[2]

Deep brain stimulation is beneficial for patients with treatment-refractory OCD. However, there are several barriers to its acceptable implementation, including neuroanatomical variability and potential adverse effects.[1] Owing to these treatment limitations, there is a crucial need for more effective treatment modalities for OCD.

In February 2024, Lykos Therapeutics submitted a new drug approval application for 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy (MDMA-AT) to the Food and Drug Administration (FDA) for the treatment of post-traumatic stress disorder (PTSD).[3] In August 2024, the FDA rejected Lykos's MDMA-AT for PTSD and recommended further clinical trials to assess safety and efficacy. Preclinical research on MDMA has identified fear extinction learning and reopening of critical periods for social reward learning as mechanisms underlying the therapeutic effect of MDMA-AT.[4,5] In this article, we explore opportunities for the potential use of MDMA-AT to augment the effects of EX/RP, through fear extinction and reopening of critical periods, in the treatment of OCD.

Facilitated fear extinction in obsession–compulsion uncoupling during EX/RP

As described above, EX/RP enables extinction of the fear response associated with obsessive thoughts and leads to uncoupling of the obsession–compulsion anxiety relationship.[2] Poor adherence to between-session work for EX/RP often occurs and is associated with poor treatment response.[2] Subjective distress, anxiety and anticipatory fear due to the repetitive deconditioning used in EX/RP are probable contributors to poor adherence. An adjunct intervention that diminishes this anxiety and fear response could potentially facilitate better adherence to and efficacy of EX/RP.

MDMA has been found to consolidate fear extinction learning in both animal models and humans.[4,5] Preclinical data published by Young et al suggest that increased expression of brain-derived neurotrophic factor (BDNF) in the amygdala is associated with fear extinction in mice. Importantly, extinction enhancement is inhibited by blocking BDNF signalling, indicating that MDMA-mediated fear extinction is likely to occur through a BDNF-dependent pathway.[5] In 2022, Vizeli et al conducted a double-blind, randomised, placebo-controlled clinical trial in 30 healthy men and found that MDMA administration consolidated certain forms of fear extinction;[4] MDMA may potentiate the effects of psychotherapy by such a mechanism in trials of MDMA-AT for PTSD. These early findings are consistent with prior preclinical research on MDMA as a tool for fear extinction retention.[4] Although the neurobiological mechanism underlying this effect remains unclear, MDMA-mediated amygdala inhibition has been proposed.[5] As such, consolidated fear extinction observed with MDMA may potentiate the effects of EX/RP.[4] Indeed, this MDMA-mediated phenomenon may then enable the patient to experience a sense of safety while being exposed to the aversive obsessional thought, decrease anticipatory anxiety about EX/RP sessions, and potentially increase treatment adherence and response. Although this hypothesis is based on application of our mechanistic understanding of MDMA to OCD treatment, there is a need for research to further elucidate the mechanisms of action of MDMA and its transdiagnostic applications as an investigational treatment modality.

Metaplasticity and reopening of social reward learning critical periods facilitate psychological flexibility and generalisable learning

Recent research has shown that MDMA, along with ketamine, lysergic acid diethylamide, psilocybin and ibogaine, facilitates reopening of social reward learning critical periods in rats.[6] This effect may result from an increase in neurosynaptic metaplasticity,[6]

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which may explain the increased psychological flexibility and cognitive reappraisal observed following psychedelic administration. This phenomenon underlies psychedelic-assisted psychotherapy models, such as MDMA-AT for PTSD, whereby an increase in metaplasticity and reopening of social reward learning critical periods are thought to potentiate psychotherapeutic benefits. In the MDMA-AT clinical trials for PTSD, patients in the treatment group experienced improved outcomes compared with patients only receiving psychotherapy.[3] Although several questions pertaining to experimental design ought to be raised, such as the difficulty of achieving blinding, these results may indicate potentiation of psychotherapy by MDMA in PTSD treatment. In OCD treatment, failure to generalise the learning of obsession–compulsion uncoupling beyond the context of therapy sessions constitutes a barrier to EX/RP therapy.[2] MDMA-mediated metaplasticity and reopening of social reward learning critical periods could promote psychological agility, allowing generalisation of insights achieved in EX/RP. For example, integrating psychotherapy sessions in the days to weeks after the dosing session could facilitate generalisation of fear extinction learning and compulsion resistance explored during the session. Neurosynaptic metaplasticity is thus a hypothesised mechanism of MDMA-mediated EX/RP enhancement.

Empathogenic effect of MDMA-AT may promote self-compassion, healing from the ego-dystonic experience of OCD and potential interpersonal mediation of family accommodation

OCD involves ego-dystonic awareness of the irrational nature of one's own thoughts and actions, which can lead to significant guilt and shame.[1] As such, OCD can disrupt a patient's self-concept; this is also correlated with disease severity and treatment resistance.[7] OCD therapies that reduce a patient's fear of self and negative self-image are associated with clinical improvement.[7]

MDMA is an empathogen[8]: in MDMA-AT, its oxytocin-mediated effect may foster heightened self-compassion during the session and mitigate the negative self-conceptualisation that characterises OCD. MDMA-mediated empathogenic effects may thereby enhance psychotherapeutic interventions that aim to decrease fear of self and negative self-image.

Family accommodation, the process whereby patients include family members in compulsive behaviours, is an important factor maintaining OCD symptomatology and is positively correlated with illness severity.[9] Family-based EX/RP, a family therapy modality, has yielded some clinical improvement in patients with family accommodation.[9] In MDMA-AT, oxytocin-mediated pro-social effects may increase empathy in interpersonal dynamics[8] and could potentially be leveraged to enhance family-based EX/RP, thereby disrupting patterns of family accommodation among adult patients with OCD.

Considerations in research on the transdiagnostic use of MDMA-AT for PTSD and OCD

There are several important future directions when exploring MDMA-AT for OCD treatment. First, psychotic disorders may co-occur with OCD[1] or initially be misdiagnosed as OCD. MDMA-AT clinical trials currently exclude patients with comorbid psychotic disorders; therefore, diagnostic rigour is important in studies of MDMA-AT for OCD.[3] Moreover, although MDMA-AT was found to be safe and well-tolerated in the Multidisciplinary Association for Psychedelic Studies phase 3 clinical trials for PTSD treatment, there is a need for further research to explore the safety profile and potential long-term neurotoxicity of MDMA-AT. Specifically, more research is warranted to assess the potential of MDMA for misuse. In addition, patients with moderate-to-severe OCD are often prescribed high-dose SSRIs, a practice that warrants further investigation of the potential interaction between MDMA-AT and commonly prescribed psychopharmacologic OCD treatments. Importantly, Lykos's phase 3 clinical trials involved participants being tapered off other psychiatric medications before the trial interventions.[3] Given that MDMA has serotonergic effects in the central nervous system, further research ought to elucidate the potential risk of serotonin syndrome when it is administered alongside SSRIs.

Importantly, 20–30% of patients with PTSD have comorbid OCD, and more than 50% of patients diagnosed with OCD report a traumatic experience.[7] With MDMA-AT for PTSD nearing FDA approval, future studies ought to assess whether patients with comorbid PTSD and OCD who respond to MDMA-AT for PTSD also experience improvement in OCD symptoms. Moreover, future clinical trials ought to determine whether PTSD is a predictor of OCD treatment response to MDMA-AT. The answers to such questions will be crucial to determining the potential transdiagnostic therapeutic efficacy of MDMA-AT. They would also provide an indication of potentially shared neurobiological mechanisms of comorbid PTSD and OCD that may respond to MDMA-AT.

Several other psychedelic compounds are under evaluation with respect to their transdiagnostic use. Esketamine has been approved by the FDA since 2019 to treat refractory depression, and ketamine is currently in studies for treatment of alcohol use disorder and alcohol withdrawal syndrome. Thus, psychedelic compounds have emerged as important treatment modalities with potential transdiagnostic therapeutic efficacies. Coupled with connectomics and neuroimaging studies to analyse neurobiological predictors of treatment response, psychedelic therapies may offer novel neurobiological insights into the pathophysiology of common comorbidities in psychiatric illness, such as ketamine for depression and alcohol use disorder, and MDMA-AT for OCD and PTSD.

In this article, we have proposed a framework to explore how the mechanistic effects of MDMA-AT could potentially help overcome several treatment limitations of EX/RP for OCD, as well as research safety considerations regarding the potential transdiagnostic clinical use of MDMA-AT for OCD. With the FDA advising additional investigation of MDMA-AT, researchers ought to further characterise mechanisms of action for PTSD treatment and explore the potential transdiagnostic application of this new treatment modality for other psychiatric indications.

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Author contributions

Z.S. conceived the original idea for this article, led the drafting of the article and incorporated feedback. A.S.K. provided important intellectual contributions and text edits to the article. A.S.K. supervised the drafting and revision of the article. Both authors revised the article

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Declaration of interest

A.S.K. reports royalties as editor of a McGraw Hill textbook on transgender and gender diverse healthcare and as editor of an American Psychiatric Association textbook on gender-affirming psychiatric care.

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