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Effects of Selective Serotonin Reuptake Inhibitor Use on 3,4-Methylenedioxymethamphetamine–Assisted Therapy for Posttraumatic Stress Disorder

A Review of the Evidence, Neurobiological Plausibility, and Clinical Significance

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Abstract:

Background: Among the renewed applications of psychedelic medicines in psychiatry, 3,4-methylenedioxymethamphetamine (MDMA)–assisted therapy for posttraumatic stress disorder (PTSD) has demonstrated the most promise in early small-scale studies. Recent exploratory analyses from prior clinical trials of MDMA-assisted therapy for PTSD have suggested that recent use of selective serotonin reuptake inhibitors (SSRIs)—the only medication class with United States Food and Drug Administration (FDA) approval to treat PTSD—can significantly dampen the efficacy of this novel therapy. Although psychedelic medicines are not yet FDA approved, MDMA is very likely to be the first to achieve FDA approval—perhaps within the next 2 years. Given this timeline, the field would benefit from more knowledge about potential interactions between this novel therapy and our current treatments.

Methods: This brief report reviews selected literature in the basic and clinical neurosciences relevant to the interaction of SSRIs and MDMA.

Findings: The possibility that SSRI use could dampen future responses to MDMA-assisted therapy for PTSD raises many important questions about the biological mechanisms as well as ethical implications around the most appropriate way to counsel patients. In this brief report, we compare the evidence for SSRIs and MDMA-assisted therapy in the treatment of PTSD and discuss what is known about the neurobiological interactions between these 2 medicines.

Conclusions: There is strong neurobiological plausibility for the hypothesis that chronic SSRI use dampens response to MDMA-assisted therapy, although current knowledge in the field is limited and primarily relates to acute pharmacodynamic interactions. Our commentary highlights the urgent need for future work dedicated to addressing this important clinical topic.

Key Words: MDMA, 3,4-Methylenedioxymethamphetamine, SSRI, selective serotonin reuptake inhibitors, PTSD, posttraumatic stress disorder, interaction, efficacy, MDMA-assisted therapy, psychedelic

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The treatment of posttraumatic stress disorder (PTSD) has long been an area of weakness in the field of psychiatry. The current evidence-based treatments for this common and disabling condition include medications and trauma-focused psychotherapies such as cognitive processing therapy and prolonged exposure therapy. The trauma-focused therapies have demonstrated efficacy at reducing symptoms, but with high dropout and nonresponse rates, they fail to be a viable pathway to recovery for most people with PTSD.[1] Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, are the only medications United States Food and Drug Administration (FDA) approved for the treatment of PTSD. The SSRI fluoxetine and serotonin norepinephrine reuptake inhibitor venlafaxine have also been studied and, along with sertraline and paroxetine, are recommended as first-line pharmacotherapy in existing guidelines for the management of PTSD. These medications have demonstrated success at reducing some of the symptoms of PTSD significantly more than placebo, but the effect sizes are modest with low remission rates.[2] Additional medications are frequently relied on to manage symptoms, such as those used for nightmares, sleep, and anxiety. Despite this variety of therapies available, the overall evidence we have demonstrates that for most individuals with PTSD, the current treatments are insufficient to address the burden of suffering and disability.

It is within this context that many in the field of psychiatry and the general public are responding with excitement to recent studies demonstrating the safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA)–assisted therapy for PTSD.[3–10] Based on impressive results from phase 2 studies, the FDA has designated MDMA-assisted therapy for PTSD a "breakthrough therapy." This designation enables expedited development and review of drugs that are intended to treat a serious condition based on preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over available therapies. Thus far, there has only been 1 phase 3 trial of MDMA-assisted therapy in a small number of patients with severe PTSD. However, the large effect size seen in this positive study has bolstered hope for this novel therapy.[10] If the results of a second, ongoing phase 3 trial continue to demonstrate superior efficacy for MDMA-assisted therapy and the pathway to FDA approval is made clear, psychiatrists will be faced with many questions around eligibility, access, therapeutic approaches, cost, and safety protocols. One such question that we should be seeking to answer now is how this novel therapy may interact with our current first-line medication treatments for PTSD (eg, SSRIs). This brief report seeks to summarize the data suggesting recent antidepressant use may diminish the response to MDMA-assisted therapy, describe the biological plausibility of SSRIs interfering with the effects of MDMA, and introduce the clinical and ethical implications that may arise if current use of an FDA-approved medication reduces the efficacy of a potentially superior, but not yet accessible, breakthrough therapy.

3,4-METHYLENEDIOXYMETHAMPHETAMINE–ASSISTED THERAPY FOR PTSD

Over the past decade, an impressive body of research has emerged suggesting MDMA-assisted therapy for PTSD is a safe,

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well-tolerated, and effective intervention for chronic PTSD. 3,4-Methylenedioxymethamphetamine is usually classified as an entactogen due to its commonly observed prosocial effects and distinct pharmacology compared with classical psychedelics. Its primary mechanism of action involves reversal of vesicular and cell-membrane monoamine transporters, resulting in significant increases in the synaptic concentrations of serotonin and, to a lesser extent, norepinephrine and dopamine. 3,4-Methylenedioxymethamphetamine also has some direct agonist activity at various neurotransmitter receptors, with downstream effects on release of oxytocin, cortisol, prolactin, and vasopressin.[11]

To survey the clinical evidence of MDMA-assisted psychotherapy, we searched for registered clinical trials on ClinicalTrials.gov using the diagnosis term "PTSD" and additional term "MDMA," along with synonyms; we restricted our results to trials which were completed, suspended, terminated, withdrawn, or of unknown status. When performed on June 2, 2022, this search yielded 14 clinical trials: 11 completed studies, 2 studies that were terminated (poor accrual, insufficient data collection, and high staff turnover), and 1 study that was withdrawn before recruitment began. The 11 completed studies assessing the safety and efficacy of MDMA-assisted therapy for PTSD involved clinicians in 5 countries and more than 200 participants.[3–10] In these studies, participants received MDMA in one or a handful of nondirective, supportive psychotherapy sessions, with multiple nondrug sessions preceding and following each drug session for preparation and integration. Across more than 600 experimental sessions, MDMA was found to be safe and well tolerated, with only one serious adverse event deemed possibly related to drug administration (increase in premature ventricular contractions without significant long-term sequalae).[12] Mild treatment-associated adverse events were more common in the MDMA arm of the phase 3 study, with the most common being muscle tightness, decreased appetite, and nausea.[10]

A pooled analysis of 6 of the initial phase 2 studies showed that by the end of treatment, the active groups (receiving MDMA doses of 75, 100, or 125 mg) had significantly greater improvement on the Clinician Administered PTSD Scale (CAPS)-IV as compared with the active-placebo groups (receiving MDMA doses of 0–40 mg), with a large between-group Cohen *d* effect size of 0.8. Using loss of PTSD diagnosis as the criterion for remission, 54% of participants in the active groups achieved remission compared with 25% in the active-placebo groups.[13] Long-term follow-up data from the same 6 studies found a large within-subjects effect size of $d = 1.58$ at treatment exit (1–2 months after the last active dose MDMA session) compared with baseline, which further improved between treatment exit and long-term follow-up (approximately 1 year later) with a small effect size of $d = 0.23$.[14] A recent meta-analysis including 10 phase 2 trials found a large overall effect size of $d = 0.93$ when comparing active MDMA intervention versus control groups, with a relative risk for remission of 2.96 (95% confidence interval, 1.63–5.39) indicating a nearly 3-fold higher chance of remission in the MDMA group.[12] Finally, in the only phase 3 study to date, Mitchell and colleagues demonstrated significant improvement in PTSD symptoms with MDMA-assisted therapy.[10] As with all prior studies, the population had chronic PTSD with significant symptom burden, indicated by a baseline CAPS-V of 44.1, greater than 97% having received prior psychotherapy, and an average illness duration of 14.1 years. After 3 MDMA sessions and associated nondrug therapy sessions, which took place over 18 weeks, 67% of the participants achieved remission compared with 32% in the placebo group, with a large effect size of $d = 0.91$.[10] Taken together, this emerging literature provides strong support for the use of MDMA-assisted therapy in the management of chronic PTSD that failed to respond adequately to prior medications or therapy.

3,4-METHYLENEDIOXYMETHAMPHETAMINE–ASSISTED THERAPY VERSUS SSRIS FOR PTSD

The results of these prior studies and the FDA breakthrough therapy designation suggest that MDMA-assisted therapy is far more effective than the currently available pharmacotherapy for PTSD.[2] In 3 studies on the effectiveness of paroxetine in the treatment of PTSD, overall effect sizes were moderate at 0.45 to 0.56, whereas the 2 positive studies (out of four) for sertraline had small effect sizes of 0.31 to 0.37. The effect sizes for MDMA-assisted therapy from the phase 2/3 studies above were thus 2 to 3 times larger than for current pharmacotherapies. These comparisons in favor of MDMA-assisted therapy are further supported by an analysis of participants in the MDMA clinical trials who had previously taken SSRIs. Of the 105 participants examined, 64 (61%) had previously taken paroxetine, sertraline, or both. Of the 38 who had previously taken an SSRI and were randomized to high-dose MDMA groups, 20 (53%) achieved remission from PTSD at the primary end point, suggesting that MDMA-assisted therapy was effective in these patients when SSRIs were not.[15] Despite the limited efficacy of SSRIs in the treatment of PTSD, they are still among the most widely used medications for the disorder.[2] In addition, although there have yet to be any head-to-head studies comparing MDMA and SSRIs in the treatment of PTSD, comparison of their respective literature suggests that MDMA-assisted therapy is likely at least as effective, if not more effective, than SSRIs. Moreover, MDMA-assisted therapy seems to achieve superior efficacy with one or a few acute medication administrations, rather than the daily dosing of SSRIs with the potential adverse effects this schedule produces. These observations raise the question of how current or former SSRI use might impact the efficacy of MDMA-assisted therapy, a treatment that is potentially far more efficacious and durable and which is likely to be FDA approved within the next 5 years.

CURRENT SSRI USE AND MDMA

Anecdotal reports for decades have suggested that current SSRI use can significantly dampen or abolish the subjective effects of MDMA and serotonergic hallucinogens,[16–22] although this was not always observed.[23] Controlled studies beginning in the 2000s began to shed further light on this phenomenon by examining the impact of SSRI and MDMA coadministration in healthy controls. The SSRIs citalopram, paroxetine, and fluoxetine were all shown to reduce most of the psychological effects of MDMA when given as pretreatment, either orally for 3 to 5 days[24–26] or intravenously for 90 minutes[27,28] before MDMA oral dosing. The psychological effects of MDMA that were attenuated by SSRIs included positive mood/euphoria, alterations in thought process and content, extraversion/self-confidence, and dissociative phenomena. Not all psychological effects of MDMA were attenuated by SSRIs, however; effects on emotional excitability, sensitivity, and anxiety remained even with SSRI pretreatment.[25,29] Selective serotonin reuptake inhibitors also reduced the effects of MDMA on various physiological parameters, including increases in blood pressure, heart rate, temperature, and pupil diameter.[24–29] In addition to altering the pharmacodynamic effects of MDMA, SSRI pretreatment changed MDMA pharmacokinetics, putatively through a cytochrome P450-2D6 interaction. Pretreatment with paroxetine caused a 30% increase in MDMA plasma concentration,[26] whereas citalopram pretreatment prolonged the subdued effects of MDMA from 3 to 5 hours.[29] Studies in animal models support the idea that such attenuation of MDMA's effects via acute SSRI pretreatment occurs primarily through blockage of the serotonin reuptake transporter (SERT). Serotonin reuptake transporter–knockout animals have a marked reduction in MDMA-mediated serotonin release and subsequent

depletion and neurotoxicity.[30,31] Pretreatment of rats with SSRIs similarly attenuated MDMA-mediated increases in extracellular serotonin and led to preservation of serotonin metabolite concentrations and SERT binding that is normally depleted by MDMA after 1 week.[32–35] Taken together, this literature suggests that acute blockage of SERT by SSRIs leads to marked reductions in the physiological and psychological effects of MDMA.

CHRONIC SSRI USE AND MDMA

3,4-Methylenedioxymethamphetamine–assisted therapy trials have required participants to taper off all antidepressants, likely in part due to the known acute interactions between antidepressants and MDMA such as those noted previously. Although lifetime SSRI use was not a significant covariate with treatment response in the phase 3 study,[10,13] those participants who were required to taper off antidepressants just before entering the phase 2 MDMA studies were found to have significantly reduced response to the active intervention.[36] A similar subgroup comparison between a taper and nontaper group has not been published using the phase 3 clinical trial data.[10]

Feduccia and colleagues[36] analyzed pooled data from four of the phase 2 studies of MDMA for PTSD, examining the impact of recent antidepressant use among the participants in the active treatment groups. Participants who were required to taper off antidepressants (n = 16) were compared with those who were not on antidepressants before the trial and thus did not have to taper (n = 34). Of the 16 taper participants, 12 tapered off 1 medication, 3 tapered off 2, and 1 tapered off 3. The number of participants tapering off each medication included 10 on SSRIs, 3 on serotonin norepinephrine reuptake inhibitors, and 9 on other antidepressants; taper lengths were not recorded but were generally advised to be in the order of weeks. The minimum time from stopping medications to the first MDMA session was 5 half-lives of the drug(s) and any active metabolites, with an average of 25 days (range, 4–70 days). Because of the small sample size, the authors could not draw any conclusions regarding the effects of specific subclasses of antidepressants.

The authors found that participants who did not have to taper an antidepressant showed a significantly greater response to the intervention, with larger reductions in CAPS-IV and depression severity scores as well as higher rates of PTSD remission (64%) compared with the taper group (25%). The nontaper group was also observed to have higher maximum blood pressure readings during MDMA administrations, and there was a nonsignificant correlational trend between length of antidepressant abstinence and maximum blood pressure readings (r = 0.31–0.32, P = 0.07–0.09). The period of antidepressant abstinence showed no correlation with change in CAPS-IV scores.[36]

Because the participants were required to be off medications for greater than or equal to 5 drug half-lives, it is unlikely that the observed decreased efficacy in the taper group can be attributed to acute antidepressant-MDMA interactions, such as the blocking of SERT by SSRIs. The authors postulated a few other potential explanations for the observed findings. Consideration was given to antidepressant prescriptions indicating more severe disease, although baseline depression and PTSD symptom scores were equivalent in the taper and nontaper groups. The effect of antidepressant withdrawal symptoms on outcome scores was also considered an unlikely explanation of the results because the taper and nontaper groups who received active placebo (MDMA doses <75 mg) reportedly showed similar responses; however, these data were not shown. This led the authors to hypothesize that the observed decrease in efficacy of MDMA-assisted therapy in those who tapered antidepressants may be related to neurobiological changes associated with long-term antidepressant use. These changes could include downregulation of various membrane proteins, especially SERT and 5-HT receptors.[36] It is also possible that prior use of antidepressants was correlated with comorbidities, such as anxiety and substance use disorders, which could have contributed to the observed differences in response. Although current substance use disorder diagnoses were part of the exclusion criteria for all studies, and there was no association between elevated substance use screening scores and treatment outcomes, this hypothesis was not formally tested.[10,13,14]

NEUROBIOLOGICAL CHANGES ASSOCIATED WITH ANTIDEPRESSANT USE

A large body of research has examined the effect of antidepressant administration on the expression of neural proteins that play a role in monoamine signaling. Early attempts to elucidate the antidepressant mechanism of SSRIs implicated desensitization of 5-HT_{1A} autoreceptors secondary to acute increases in synaptic serotonin concentrations after SERT blockade. Although later research would suggest alternative mechanistic explanations for antidepressant effects, there is nonetheless strong evidence for receptor-level changes induced by SSRIs.[37,38] Studies in mice and rats are largely convergent in the finding that 2 to 3 weeks of daily SSRI administration leads to a significant reduction in SERT expression in multiple brain areas, changes in expression patterns of 5-HT_1 and 5-HT_2 receptors, and desensitization of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus.[39–46] There was not complete consensus in these findings,[47–51] however, perhaps because of differences in how SSRIs were administered[44] or residual SSRI affecting binding assays.[52] Nonetheless, imaging work in humans also found evidence of downregulation and/or desensitization of SERT and 5-HT_{1A} autoreceptors.[38,53] Comparisons between patients recently started on antidepressants and those who were antidepressant naive or abstinent for years further suggested that the reductions in 5-HT_{1A} activity may last months to years after cessation of the medication.[38] These changes in receptor densities after SSRI use may help explain the reduced efficacy Feduccia and colleagues[36] observed in the patients who had to taper antidepressants before MDMA-assisted therapy.

Such changes in SERT and 5-HT receptor expression may also help explain the phenomenon of antidepressant discontinuation syndrome. This syndrome occurs after discontinuation of an antidepressant medication and is characterized by a broad constellation of symptoms, including affective dysregulation, sleep disturbances, gastrointestinal disturbances, sexual disturbances, cognitive impairments, disequilibrium, sensory and perceptual disturbances, and general somatic or flu-like symptoms. Antidepressant discontinuation syndrome seems to be more common when discontinuing medications with shorter half-lives and is more common and severe when antidepressants are used at higher doses and over longer periods.[54] Withdrawal symptoms may affect 30% to 60% of antidepressant users, and while classic teaching has suggested the syndrome is mild and lasts in the order of weeks, some studies have found large proportions of patients reporting severe symptoms and withdrawals lasting greater than a year.[55] Antidepressant discontinuation syndrome can be challenging to detect, in part because of the significant symptom overlap with depression itself, and the first systematic review on the subject was not performed until 2015.[56] While most psychiatrists now agree the syndrome exists, there remains considerable debate around the potential severity, length, and overlap of the syndrome with depression relapse.[54–61]

The recent observation that tapering from antidepressants was associated with reduced efficacy of MDMA-assisted therapy adds a new dimension to this debate. Antidepressant discontinuation

syndrome likely represents a clinically relevant corollary to the observed decreases in SERT and 5-HT receptor densities after SSRI and other antidepressant use. Because it is well established that SERT and 5HT receptors are central to the mechanism of action of MDMA,[30,31] and blockage of specific serotonin receptors can attenuate the psychological effects of MDMA,[28] it seems reasonable to postulate that reductions in the density of SERT and 5-HT receptors after SSRI use would lead to attenuated effects of MDMA. In other words, neurobiological changes induced by SSRI use may help explain not only antidepressant discontinuation syndrome but also the decreased efficacy of MDMA in the treatment of PTSD.

CONCLUSIONS AND FUTURE DIRECTIONS

The potential for SSRI use to interfere with MDMA response has strong neurobiological plausibility, and evidence of a diminished physiologic and clinical response was present in the exploratory pooled analyses of phase 2 data of MDMA-assisted therapy for PTSD.[36] It is critical that we better understand the interactions between SSRIs (as well as other classes of antidepressants) and MDMA so that we can best provide guidance and informed consent to our patients—both at time of initiation as well as with continuation of antidepressant treatment. A recent systematic review on this topic comprehensively covers the field's current understanding of these interactions and underscores the many questions that remain.[62] Future randomized studies are needed that look closely at the relationship between chronicity of antidepressant treatment, dose of antidepressants, length of time off antidepressants, and response to MDMA-assisted therapy. If there is evidence that the use of SSRIs or other antidepressants may diminish a response to MDMA-assisted therapy, we need to carefully consider how we communicate this potential risk responsibly to our patients while keeping in mind the many uncertainties surrounding access for MDMA-assisted therapy.

With extensive media coverage of the emerging psychedelic-assisted therapy field, patients will increasingly turn to physicians to explain and navigate their treatment options. To uphold the ethical principles of respect for autonomy, beneficence, and nonmaleficence when we discuss medication treatment options for PTSD, we must be able to communicate our most up-to-date understanding of this complicated issue. Included in this discussion will be the potential benefits of medications for PTSD, which are modest but not insignificant, as well as the potential risks. Along with the typical discussion of adverse effects that we commonly engage in, a full discussion of the risks of PTSD pharmacotherapy might need to expand to include what we know about the potential risk of antidepressants reducing the efficacy of MDMA-assisted therapy. In the absence of rigorous research in this area, our patients will turn to unreliable resources such as Internet forums for guidance, exposing them to the associated risks of harm from misinformation and reduced trust in the treatment relationship.

People experiencing symptoms of PTSD have good reason to feel hopeful that more effective treatments may soon be available. Their likelihood of optimally benefiting from breakthrough treatments will depend on a better scientific understanding of how current first-line treatments interact with MDMA-assisted therapy and on our ability to communicate these complexities in ways that support the best course for each patient.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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