MDMA-ASSISTED PSYCHOTHERAPY: NEW HOPE FOR TREATMENT-RESISTANT PTSD?

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Abstract

Review

Background Following a traumatic event, individuals can develop posttraumatic stress disorder (PTSD). While there are numerous therapy approaches, up to 58 per cent of patients remain treatment-resistant and continue to suffer from PTSD even after several treatment attempts. Thus, the development of novel treatment options is strongly needed to improve the care for this patient group and give them new hope for a life less impacted by PTSD. In the last decades, 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy has been investigated as a potential treatment for treatment-resistant patients.

Objective This review aims to outline the recent developments regarding research on MDMA-assisted psychotherapy to provide the reader with a feel for the potential and feasibility of this new form of treatment. Furthermore, the article aims to briefly delineate the current challenges faced by the field and address widespread doubts regarding the treatment.

Discussion MDMA-assisted psychotherapy consistently showed positive results in treatment-resistant PTSD patients and not only lessened the burden of disease for many but even clinically cured a substantial percentage of partaking patients. Common doubts about the abusive potential of MDMA, as well as dangerous adverse effects, seem to be largely dismissible, and the carried-out studies have given a comfortable framework of how future clinical use could be accomplished. Issues remain regarding the small size of patient cohorts that have so far been included in trials. This shortcoming could introduce a bias in the research results and could result in rare side effects being overlooked.

Conclusion MDMA-assisted psychotherapy is unlikely to be implemented as a first-line treatment for PTSD; nevertheless, it appears to be a promising new approach to treating treatment-resistant PTSD patients and is on track to gain FDA approval for this intent. The results are highly encouraging, and there is little evidence for substantial adverse effects or a high risk of abuse of MDMA in a medical context. Nevertheless, more research, especially studies with larger patient cohorts, is needed to better understand the involved risks and pitfalls of the treatment.

KEYWORDS: Posttraumatic stress disorder, treatment-resistant PTSD, MDMA, 3,4-methylenedioxymethamphetamine;

Posttraumatic stress disorder (PTSD) is a psychiatric condition that develops in about 25-30% of people encountering a single or repeating traumatic event(s) [1]. It is characterised by four clusters of symptoms, namely re-experiencing, negative alterations in cognition/mood, avoidance, and alterations in arousal and reactivity, including hyperarousal and sleep disturbance [2, 3].

Regarding the development of PTSD, the experience of an initial traumatic event X triggers substantial fear [4]. Following a popular model of PTSD development, this event X induces conditioning of the individual to fear a specific occurrence Y that is not directly causative of the fear itself [4]. Hence, a previously unconditioned event Y is associated with the anxiety felt in moment X, and, therefore, whenever that second event (event Y) occurs, the person is subject to the fear again [4]. This further results in avoidance of the trigger Y, which decreases anxiety and, therefore, negatively reinforces the notion that trigger Y is to fear and thus to be avoided [4]. Interestingly, in a rat model of PTSD, PTSD-like symptoms were only achieved when the rats were subject to social instability, additionally to the predatory threat, which is achieved by frequent switching of cage-mates [5]. This finding suggests that social instability is of great importance in PTSD development [5].

Neurobiologically, fear conditioning is controlled by an interplay of several brain structures [6]. The amygdala sends out signals (e.g. the X and Y events) incorporated with other inputs and induces a fear response. These stimuli from the amygdala can be inhibited by the medial prefrontal cortex [4]. In PTSD, the amygdala is hyperactive [7]. This could be, at least partially, rooted in a decrease in the size and activity of the medial prefrontal cortex [8]. Both have been described in twin studies where one twin was exposed to a traumatic event and consecutively did or did not develop PTSD [8]. The resulting fear-induced stress further inhibits the prefrontal cortex, hence, sustaining the fear response via a negative feedback loop [4]. Recently, increased inflammation in the brain in combination with cognitive dysfunction has also been proposed to underlie PTSD. However, more research is needed to fully elucidate its role in PTSD development [9].

The lifetime prevalence of PTSD has been established in numerous studies in the last three decades and shows an interesting pattern based on geographic location. In the United States, several conducted studies found a prevalence of approximately 8%, whereas European studies consistently established a prevalence of 1.3% [10]. Notably, there is a big difference between the sexes, with PTSD being more common among women than men [10]. This variation

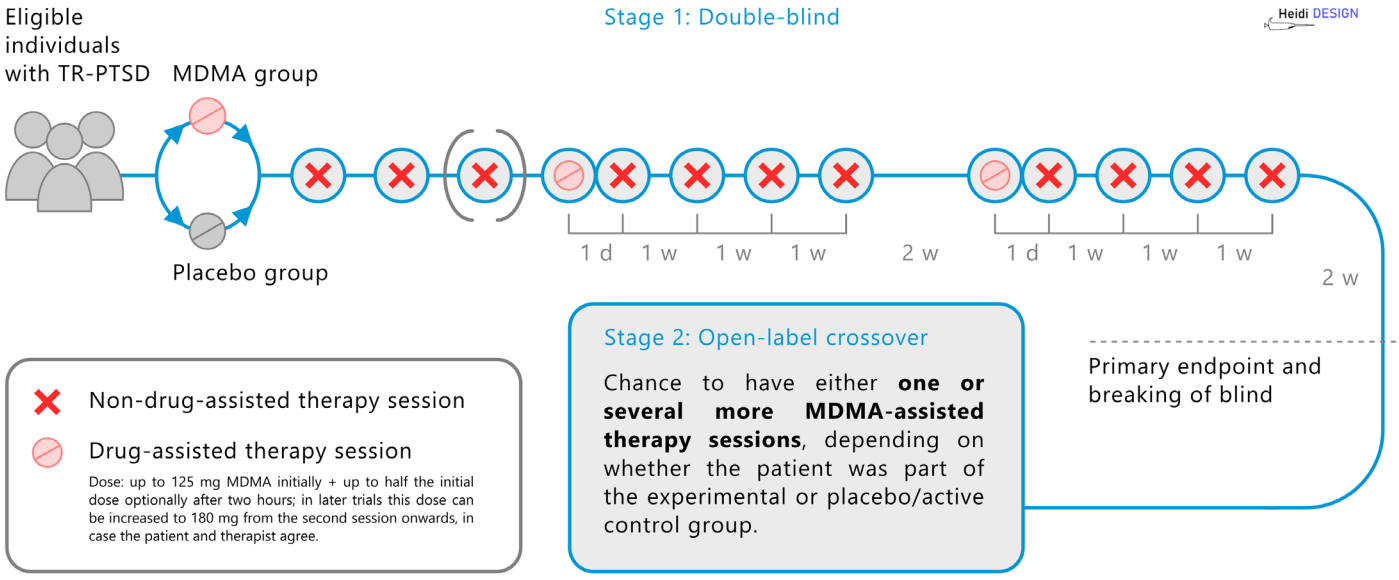

Figure 1: Study design of the clinical trials regarding MDMA-assisted psychotherapy to treat treatment-assisted PTSD. *The figure shows a simplified version of the study design used, with slight variations, in all so far concluded clinical trials. Generally, the study takes place in two stages; the first being the double-blinded phase, while the second one is an open-labelled phase, where placebo group members can switch into the MDMA group. The study subjects are chosen based on various in- and exclusion criteria, the most important being that all have undergone and failed psychotherapy previously, thus, suffering from treatment-resistant PTSD (TR-PTSD). The eligible patients are then classified randomly in a control group, receiving the placebo, and in one or more MDMA groups, receiving MDMA at concentrations between 30 and 125 mg. The substance administration as well as all therapy sessions and the scoring at the primary endpoint take place under double-blinding conditions. All study participants receive two to three preparational therapy sessions before taking part in one of two substance-assisted therapy sessions of about six to eight hours. The substance-assisted therapy sessions are directly followed by an overnight stay in the hospital, a non-drug-assisted therapy session the following day, and daily phone contact with the therapist for the next week, as well as three weekly non-drug assisted therapy sessions. At the end of stage one, the patients are scored according to the Clinician-Administered PTSD Scale to determine the extent of their dysfunctionality due to their PTSD. Next, the double-blinding is broken, and patients of the control group (and in the case of the phase II trials, patients receiving lower doses of MDMA) are offered the possibility to switch to the treatment group and receive further MDMA-assisted therapy sessions. The details on this phase have been omitted from the figure due to clarity and can be found in the individual descriptions in the literature. Furthermore, the studies include an observational period of about two to twelve months.*

is consistent with other stress disorders, although little is known about the underlying reason [10]. The possibility that PTSD only develops delayed following a traumatic event further complicates the identification and treatment of the patients; however, there is evidence that patients profit from treatment, even when this treatment is only given late into their condition [1, 11].

PTSD can have drastic consequences for the quality of life of a patient and severely disrupt their lives; hence, successful treatment is crucial to lessen the burden [4]. Moreover, PTSD commonly appears alongside other psychiatric disorders, such as major depression and anxiety disorders, or physical comorbidities like cardiovascular disorders [4]. An association between PTSD and cancers and PTSD and gastrointestinal diseases has been proposed, albeit the research results remain inconclusive [4]. These comorbidities further underscore the importance of successful treatment of the patient.

Treatment options for PTSD

First-line treatment of PTSD conventionally consists of different forms of psychotherapy, all of which focus on confronting the trauma while in a safe space and processing the traumatic memories and accompanying feelings [1, 4]. More recently, also drug treatments alone (e.g. antidepressants like serotonin-reuptake inhibitors) or in combination with psychotherapy (e.g. antipsychotics) were proposed for PTSD, although for now, they remain second-line treatment options compared to psychotherapy alone [1].

Unfortunately, up to 58% of patients show PTSD symptoms even after first-line treatment, leaving a substantial part of patients without improvement [12]. A new treatment approach proposed for these treatment-resistant PTSD cases is repetitive transcranial magnetic stimulation in combination with psychotherapy [13]. In this non-invasive technique, repetitively changing electromagnetic fields are transmitted to the scalp of the patient [13]. If combined with psychotherapy, repetitive transcranial magnetic stimulation has been shown to have antidepressant effects and improve PTSD symptoms [13]. However, study designs varied considerably between the studies included in the analysis of Namgung *et al.*, and, thus, more research in this field is duly needed before the treatment can be made accessible to the majority of patients [13].

Another option of treating treatment-resistant PTSD is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy [14]. This review aims to give an overview of the current state of the field and outline the progress made regarding this new treatment variation.

MDMA-supplemented psychotherapy in PTSD

MDMA primarily acts to raise levels of serotonin, dopamine, and norepinephrine in the synaptic cleft between neurons by promoting their release and inhibiting their reuptake [14]. Psychological effects include enhancement in mood and well-being, as well as thought disorder and moderate depersonalisation [15]. These effects, in combination with a decrease in anxiety and an increase in

interpersonal closeness, could, potentially, substantially aid patients during psychotherapy targeting anxiety disorders like PTSD [14].

The worldwide first pilot study of MDMA-assisted psychotherapy got prematurely terminated in 2002 due to political opposition [16]. However, in 2010, the first clinical trial was concluded and showed promising results [16, 17]. The study was designed to be randomised and double-blinded and included 20 treatment-resistant PTSD patients (Figure 1) [17]. Twelve individuals received 125 mg MDMA (plus an optional dose of 62.5 mg after approximately two hours) for two therapy sessions of eight hours each. The remaining eight patients forming the smaller control group received a placebo [17]. Each individual substance-assisted therapy session was followed up with an overnight stay at a hospital as well as three regular therapy sessions, and the substance-assisted therapy sessions were one month apart [17]. The response rate was defined as >30% reduction of the individual "Clinician-Administered PTSD Scale" score, which is the gold standard of PTSD classification [17].

The results were encouraging, with MDMA-assisted therapy showing a response rate of 83% (10/12 patients) versus 25% (2/10 patients) in the control group [17]. This means that ten patients in the MDMA group no longer met the criteria for a PTSD diagnosis, whereas this was only the case for two patients in the placebo group [17]. Following the study's conclusion, control individuals were offered the possibility to crossover into the treatment group [17]. This group then showed a response rate of 100% [17]. A follow-up of 16 of the study participants concluded that this improvement was sustained for a median of 45 months, and the mean "Clinician-Administered PTSD Scale" score at the study exit was not significantly different from the "Clinician-Administered PTSD Scale" score at the end of the long-term evaluation [18].

A later study by Oehen and colleagues from New Zealand in 2013 failed at first glance to replicate these results and instead showed no improvement of MDMA-supplemented psychotherapy compared to placebo-supplemented psychotherapy [19]. However, a later re-analysis of the data pointed out that the previous interpretations were probably overly stringent as "the conclusion is based on improper reliance on statistical analyses inappropriately used on such a small sample" [20]. Thus, the results were, in fact, supporting the findings of Mithoefer *et al.* rather than contrasting them [20]. Recently, several phase II trials have been conducted, all of which had very similar study designs like the one concluded by Mithoefer *et al.* in 2010 (Figure 1) [21-23]. Not only was the severity of PTSD symptoms in patients reduced following MDMA-supplemented psychotherapy in these studies, but also, approximately twice as many patients of the MDMA group did no longer meet the criteria for PTSD compared to the control group. These results further strengthened the case of MDMA-supplemented psychotherapy as a treatment for treatment-resistant PTSD [22, 23].

Together, these data have paved the way for phase III trials in the United States, Canada, and Israel, one of which has already been concluded [14, 23]. While the experimental data is still under review, data on adverse side effects have been made public in the MDMA Investigators Brochure of the Multidisciplinary Association for Psychedelic Studies (MAPS) [14]. MAPS strongly supports research into MDMA-assisted psychotherapy, as well as other psychedelics-related studies [14]. Most commonly reported side effects included muscle tightness, decreased appetite, and nausea, all of which resolved seven days after MDMA administration at the latest [14]. Prevalence of suicidal thoughts, suicidal behaviour, or substance abuse was equal to or, in the case of suicidal ideation, even reduced compared to the placebo group [14]. Altogether, research remains on track, and, following completion of the second phase III trial, MAPS plans to seek approval of the FDA for MDMA as a supplement to psychotherapy in treatment-resistant PTSD [14].

Challenges, indication, and use in other disorders

Despite the promising results gathered so far and the good pace at which research on MDMA-assisted therapy progresses, several challenges remain. One of the most prominent doubts refers to the abuse potential of MDMA, seeing as it is, for now, classified as an illegal substance. Several animal experiments explored the addictive potential of self-administration of MDMA. These studies outlined that MDMA does have the potential for abuse, although this seems to be less than for other illegal substances, such as cocaine or heroin [14]. Data on drug abuse by patients following their participation in MDMA trials highlighted only a small abuse potential, as not a single participant thought of abusing any illegal substance for at least 17 months post-trial [18]. Similar results were gathered from later phase II trials and the previously finished phase III trial [14, 22, 23]. Here, three subjects of the MDMA group acknowledged using cannabis post-trial. However, it has to be highlighted that the trial purposefully included treatment-resistant PTSD patients that may or may not have a mild-moderate substance abuse problem at the beginning [14]. Thus, cannabis use does not necessarily derive from the administration of MDMA during the trial [14]. Nevertheless, despite the apparent relatively low abuse potential, the addictive nature of MDMA will have to be kept in mind during treatment. Hence, the administration needs to be tightly regulated, and the patients need to be closely monitored. The so-far carried-out studies provide the clinicians with a well-thought-out framework of what future clinical implementation of MDMA-assisted psychotherapy could look like.

Another remaining challenge is that the outlined data stem exclusively from studies with small participant numbers. This could potentially introduce a bias and cause rare side effects not to become apparent. Moreover, larger cohorts allow for more diversity among participants, hence, improving the validity of the data. Thus, trials with higher patient numbers are strongly needed to guarantee the patients' safety and well-being.

Notably, the risks, extensive necessary surveillance, and related costs make the treatment unlikely to be implemented as a first-line treatment [24]. Instead, the treatment would be offered as a new chance for patients who fail to respond to other forms of treatment or do not wish to undergo pharmacological treatments using antidepressants. Apart from PTSD, the use of MDMA-assisted psychotherapy has also been discussed for other disorders [25, 26]. MAPS has so far conducted trials for several anxiety disorders, and a new one is planned for a combinational cohort of patients with anorexia nervosa and binge eating [14].

Conclusion

In the last two decades, research on MDMA-assisted psychotherapy has consistently gathered highly promising results concerning treatment-resistant PTSD patients and seems on its way into clinical practice. Importantly, MDMA-assisted psychotherapy is not aiming at replacing other first-line therapies for PTSD; rather, it would come into play where other treatments failed. Data on the toxicity and adverse effects of MDMA itself show the substance to be reasonably safe. However, due to its inherent addictive potential, strict regulations will be necessary to keep risks of abuse as low as possible. As MDMA is still widely regarded as an illegal substance,

research on it remains challenging, especially in the aspect of larger trials. However, precisely these studies will be necessary to improve the understanding of the potential risks as well as the benefits of MDMA in the context of assisting psychotherapy. The coming years could very well bring a fundamental change of mentality towards MDMA and its place as an assisting substance to psychotherapy, not only in PTSD therapy but also in the treatments of other anxiety disorders.

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