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Review article

MDMA and PTSD treatment
"PTSD: From novel pathophysiology to innovative therapeutics"

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ABSTRACT

There is a range of therapies to treat Post Traumatic Stress Disorder (PTSD) but treatment resistance remains high, with many sufferers experiencing the chronic condition. Engagement in trauma-focused psychotherapy is difficult for some patients with PTSD, especially those with extreme affect dysregulation associated with recall of traumatic memories. In recent years there have been a number of neuroscientific and clinical studies examining the potential role for adjunctive drug-assisted psychotherapy using 3,4,-methylenedioxmethamphetamine (MDMA) as a treatment for PTSD. re-visiting of a novel approach to trauma-focused psychotherapy with Used just two or three times, under careful medical supervision and specialised psychotherapy support MDMA appears to facilitate the recall of traumatic memories without the user feeling overwhelmed by the negative affect that usually accompanies such memories. This therapeutic approach began in the 1980s and was subsequently shelved in the midst of public health concerns surrounding the recreational use of the drug ecstasy. When pharmaceutical grade MDMA is used in a clinical setting it does not share the same risk profiles as ecstasy. Recent phase one neurophysiological studies and phase two clinical studies are showing promise as a potential new approach to managing treatment-resistant PTSD.

Contents

1. Introduction

Post Traumatic Stress Disorder is a common mental illness associated with high levels of self-harm, completed suicide and co-morbidity, including depression, anxiety and substance misuse Ferry et al., 2008. There are high levels of treatment-resistance, with over half of sufferers enduring significant impairments in functioning; including struggling with relationships, parenting, financial, employment and socialisation difficulties even after treatment [42]. One reason for treatment resistance is that PTSD sufferers are often so overwhelmed by the negative memories of their trauma that they cannot engage in a therapy that focuses on it [63]. There are high levels of treatment dropouts and many attempt suicide or self-medicate with illicit drugs or alcohol to block out their feelings [8]. There are, of course, multiple complex interrelated factors within the individual with PTSD, within the dynamics of the psychotherapeutic relation and from many socioaffective phenomenon that may have independent and interdependent effects on treatment response in PTSD. Nevertheless, a drug that temporarily reduces

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the fear response whilst increasing trust and empathy in the therapeutic relationship could be a useful adjunct to psychotherapy.

2. MDMA and the core features of PTSD

MDMA is a ring-substituted phenethylamine with a unique psychopharmacological profile. Considered alongside the core features of PTSD (hypervigilance, re-experiencing phenomena, affect dysregulation and, crucially, fear and avoidance associated with recall of traumatic memories), the psychopharmacological characteristics MDMA make it well suited as an adjunct for assisting trauma-focused psychotherapy [48]. The acute effects of MDMA typically include euphoria, increased extroversion, and empathic social interaction [60]. MDMA reduces the sense of fear that accompanies the recall of traumatic memories, strengthens the therapeutic alliance and decreases avoidance behaviour, whilst remaining in a clear-headed and alert state of consciousness [15,32,37] (Table 1).

The drug exerts its main effects through release of pre-synaptic 5-hydroxytryptamine at 5-HT_{1A} and 5-HT_{1B} receptors, leading to reduced depression and anxiety and increased positive mood [20]. There is increased activity at the 5-HT_{2A} receptors, which causes alterations in the perceptions of meanings [34,4], allowing an individual to think about past experiences in new ways and develop new insights [49]. MDMA also stimulates the release of dopamine and noradrenaline, which raise levels of arousal [64,65], producing a stimulating effect that increases motivation to engage in therapy. And effects at the alpha 2-adrenoceptor provide a paradoxical sense of relaxation [33], which reduces hypervigilance.

Although not a consistently replicated finding, cortisol has been found to be deficient in PTSD [62] but essential to facilitate normal fear extinction. Through release of noradrenaline and cortisol it has been suggested that MDMA improves levels of emotional arousal and improves fear extinction learning [21,56]. Furthermore, MDMA has been shown to release oxytocin [14], which is released from the brains of breast-feeding mothers, and facilitates emotional attachment, improves feelings of trust and empathy [5]. The net result of these effects is that MDMA puts the PTSD sufferer into the "optimal arousal zone" for psychotherapy where they are appropriately alert and motivated to engage in the psychotherapeutic process, not overly stimulated as to be hypervigilant and in a psychological state in which they are able address their traumatic memories [17].

Patients with PTSD often describe a sense of emotional numbing, with difficulties forming social contacts. MDMA appears to enhance the quality of social interactions and subsequently could improve the relationship between the patient and the therapist. A recent study showed participants given MDMA are more likely to use words relating to friendship, support and intimacy [7]. Another recent study showed that participants taking MDMA exhibited reduced social exclusion phenomena [18]. MDMA enhances levels of shared empathy and pro-social behaviour compared with placebo [26], with improved detection of happy faces and reduced detection of negative facial expressions, leading users to view their social interaction partner as more caring [61]. Furthermore, the positive effects of MDMA appear consistent across different environments, with subjects examined in San Francisco, Chicago and Basel demonstrating broadly similar pro-social outcomes [29].

2.1. Method of conducting MDMA psychotherapy

The consensus method that has emerged since MDMA Therapy's initial development in the 1970s uses the drug sporadically as an adjunct alongside non-drug psychotherapy sessions. A course of MDMA-assisted psychotherapy typically employs two therapists, usually a male and female co-therapist pair. There are usually between eight- and sixteen-weeks of psychotherapy sessions, only two or three of which will be MDMA-assisted, spaced several weeks apart. The non-drug sessions may last up to 90 min, whereas during

Table 1
A summary of how the effects of MDMA are related to the treatment of PTSD symptoms, with associated neurophysiological correlates.

MDMA Effects	Postulation of how MDMA effects relate to the treatment of symptoms associated with PTSD	Neurobiological Correlates	Associated studies
Reduces depression and anxiety	Provides patient with an experience of positive mood and reduced anxiety in which to engage in therapy.	Release of pre-synaptic 5-hydroxytryptamine at 5-HT_{1A} and 5-HT_{1B} receptors.	[20]
Stimulates alterations in the perceptions of meaning.	Provides patient with an opportunity to see old problems in a new light.	Increased activity at the 5-HT_{2A} receptors	[34,4]
Raises levels of arousal.	Stimulating effect increases motivation to engage in therapy	Release of dopamine and noradrenaline	[64,65]
Increases relaxation.	Reduces hypervigilance associated with PTSD	Increased alpha 2-adrenoceptor activity.	[33]
Improves fear extinction learning.	Allows patient to reflect upon traumatic memories during psychotherapy without being overwhelmed.	Release of noradrenaline and cortisol	[21,56,19]
Increases emotional attachment and increases feelings of trust and empathy.	Improved relationship between patient and therapist. Provides patient with capacity to reflect on traumatic memories.	Multiple factors, including release of oxytocin.	[14]
more likely to use words relating to friendship, support and intimacy	improve the relationship between the patient and the therapist, which can generate discussion about wider aspects of patient's social and emotional relationships.	Multiple factors, including release of oxytocin.	[7]
Produces reduced social exclusion phenomena.	Opportunity to reflect upon patients' wider social functioning.	Multiple factors, including release of oxytocin.	[18]
Improved detection of happy faces and reduced detection of negative facial expressions.	Enhances levels of shared empathy and pro-social functioning.	Increased PFC activation and decreased amygdala	[27,61]
Reduced subjective fear response on recall of negative memories.	Opportunity to reflect upon painful memories of trauma during psychotherapy.	Decreased cerebral blood flow in the right amygdala and hippocampus.	[10]

the drug-assisted sessions the patient will be with the therapists for up to eight-hours. In preparation sessions explanations are given about how MDMA works, the expected effects and risk and the patient's trauma history is explored. An assessment of physical health, alcohol breath test and urine drugs screen and pregnancy test, if applicable, are carried out. During the MDMA-Assisted sessions measurements of heart rate, blood pressure and temperature are taken at baseline and throughout the session.

A typical initial dose of MDMA for the drug-assisted sessions would be 125 mg. For the first 90 min, the participant is encouraged to lie down with eyeshades on, with little communication whilst they acclimatise to the psychological and physical effects of the drug. The psychotherapy that ensues over the coming hours is largely client-lead; though the facilitators might gently guide the participant into discussion of particular issues regarding their trauma. The patient is encouraged to 'go inside' and 'be with' the traumatic memories and there might be long periods of non-verbal activity in which they lie back with eyeshades. Music plays an important role; with the pace and tones of the chosen music used to enhance emotional release in line with the developing MDMA experience. Two hours after receiving the initial dose of MDMA the patient may be offered a further supplemental dose of half the original dose (62.5 mg MDMA), to prolong the effects of the drug and allow for further time for psychotherapy Mitheofer 2011.

Patients are not encouraged to get up and move around during the drug-assisted session. Physical touch from the therapists is often employed as a therapeutic tool, with carefully managed professional boundaries, to allow the participant to externalise their psychological pain. Typically, after a minimum of five hours after the initial dose, the drug effects are wearing off. To date most MDMA therapy studies have required that patients subsequently remain in the treatment centre overnight after their session. However, future planned studies (including the author's own studies with MDMA) will allow the patient to return home as long as they are safe to leave and are accompanied by a supervising significant other.

The Multidisciplinary Association for Psychedelic Studies (MAPS) [36] has developed a treatment manual to assist trainee MDMA psychotherapists conducting studies (https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMAAssistedPsychotherapyTreatmentManualVersion+8_25May16_Formatted.pdf). An important aspect of delivering effective MDMA-assisted psychotherapy is that the therapist is familiar with the effects of the drug themselves, in order to feel confident working with their patients in the MDMA mental state. MAPS therefore provides training courses in which trainee therapists are required to take MDMA under the supervision of trained MDMA Therapists.

2.2. The neurophysiology of MDMA

At a simplified level PTSD can be conceptualised as an imbalance between the activity of the fear centres of the brain, principally the amygdala, and the parts of the brain where one can logically reason, rationalise and overcome that fear response – principally the prefrontal cortex (PFC). Amygdala over-activation has been correlated with anxiety, depressive disorders and PTSD in both adults and children. The amygdala is required for accurate social judgments of others based on their facial expression [1] and studies with healthy volunteers have found facial expressions of emotion to be a useful probe for amygdala function [59]. Oxytocin has been found to markedly dampen fear-related amygdala activity, causing a decrease in stress response and social anxiety [30,13,5]. This has been demonstrated through MDMA reducing the negative evaluations of aversive conditioned stimuli such as fearful faces [41]. Healthy volunteers given MDMA were better able to detect positive facial expressions than negative ones Hyesk et al. [26]. Studies have shown that MDMA causes increased PFC activation and decreased amygdala activation when given to healthy controls and in response to observing angry faces, when measured by PET Gamma, 2000 and fMRI [6].

Exposing the PTSD patient to traumatic memories therapeutically is difficult, if not impossible for some patients. However, studies have shown MDMA's capacity for fear extinction learning [19]. And recent UK-based study team at Imperial College London used BOLD-fMRI to show that when healthy subjects recalled negative memories on MDMA, compared to placebo, their subjective fear response was diminished and this correlated on neuroimaging to reduced amygdala activation [10]. The same study team used fMRI arterial spin labeling (ASL) and seed-based resting state functional connectivity (RSFC) to produce spatial maps displaying changes in cerebral blood flow (CBF) and RSFC after MDMA administration in healthy subjects. Decreased CBF in the right amygdala and hippocampus was correlated with the subjective positive psychological effects of MDMA. The RSFC results complemented the CBF results, with decreases in connectivity between the prefrontal cortex and increases between the amygdala and hippocampus [9]. The author is starting a UK-based study at Cardiff University on clinical patients with treatment-resistant PTSD, measuring BOLD and ASL outcomes alongside subjective responses to fear paradigms on MDMA versus placebo.

2.3. Previous clinical studies with MDMA

Very little published research exists from the use of MDMA by therapists in the 1970s and 1980s – and none that has the quality of double-blind placebo control studies. However there are accounts of successful case reports and informal therapy outcome studies [57]. One such report describes the therapeutic methods and the subjective reports of 29 patients administered MDMA as part of individual, group and couples therapy in the early 1980s [22]. In this report there were no significant physical complications from taking the drug and the majority of subjects reported positive individual improvements after their therapy. In a later review of 80 patients the same study team described the methods and experimental techniques that facilitate a successful drug-assisted session and suggested that further, controlled studies occur [23].

Between 1988 and 1993 there was a relaxation of laws in Switzerland allowing a small group of psychotherapists to legally deliver psychotherapy with MDMA (and other psychedelic drugs such as LSD and 2C-B). Results, though anecdotal, were largely positive, with few adverse effects. Some of those Swiss therapists continued in underground practice after restrictions halted research, whilst elsewhere political restrictions slowed research progress [55].

In 2010 psychiatrist Michael Mithoefer, working with MAPS, published the first randomised controlled study testing MDMA-assisted psychotherapy against placebo on 25 subjects with treatment-resistant PTSD [37]. Compared to 15% of placebo subjects, 85% of patients with PTSD no longer met the criteria for the disorder after a single course of MDMA-assisted psychotherapy, which involved taking MDMA three times during a 16-week course of weekly psychotherapy sessions. A subsequent long-term follow-up study of the same cohort showed that, with no further MDMA intervention, the original results were sustained four years later; with 85% of the cohort remaining PTSD-free [38]. Another double blind placebo-controlled study, in Switzerland with just 12 subjects, missed statistical significance ($P = 0.066$), suggesting some therapeutic action, but showed self-reported improvement and an effect size of 1.1 that was similar to Mithoefer et al. 2010 [11].

There have not, as yet, been any prospective studies comparing patients with PTSD randomized into either MDMA-Assisted Psychotherapy or the current mainstream recommended treatment (exposure therapy in combination with SSRI medication). However, a recent, in print, paper looked at effect sizes of the Mithoefer and Oehen studies and compared them against effect sizes for a large meta-analysis of traditional exposure therapy for PTSD. This comparison shows that MDMA-Assisted psychotherapy has larger effect sizes in terms of clinician-assessed outcomes and patient self-report outcomes, plus with fewer drop-outs in the PTSD studies compared to traditional treatments [2]).

2.4. Safety of MDMA

Hyperthermia, serotonin syndrome, hepatotoxicity and hyponatraemia have all been reported in non-medical settings [43,44,35] but given the prevalence of recreational ecstasy use these remain rare [46,3]. More common, though less severe, side effects of MDMA are that of insomnia, bruxism and acute facial dystonia. Much research has been done on the relative risks and safety of recreational ecstasy use. But care must be taken when comparing the morbidity and mortality statistics associated with the recreational use of ecstasy with the use of MDMA in a controlled, medically supervised setting [50,51]. A review of ecstasy research will not be described in this article.

MDMA possesses moderate abuse potential, but less so than that for other stimulants, e.g. amphetamine and cocaine [28]. Self-administration studies in monkeys and rats demonstrate some dependence potential [16,45] but the pattern of dosing amongst human recreational users shows that cases of MDMA addiction are rare.

There have been no deaths or serious adverse events in any of the clinical MDMA studies conducted since research began in the early 1980s [12].

3. Controversy and politics

Despite 25 years of ecstasy use in the UK mortality and morbidity rates remain low. There are few neurotoxicity concerns linked to the use of MDMA in a clinical setting. But there remains a negatively biased media depiction of ecstasy, which impairs medical research studies exploring potential MDMA treatments in psychiatry [54]. In 1992 a proposed study of MDMA-assisted psychotherapy for treating anxiety secondary to end-stage cancer was switched from MDMA to psilocybin after being twice rejected by the FDA [24,25].

Impediments to MDMA research include difficulties accessing high quality (GMP) MDMA and obtaining the necessary expensive and time-consuming Schedule One licenses required to store the compound. It is far easier to administer more toxic drugs such as methamphetamine, cocaine and heroin to patients as part of research studies than it is for MDMA [40]. In 2009 the UK government's Advisory Committee on the Misuse of Drugs (ACMD) was asked to provide a report about Ecstasy/MDMA. After consulting with experts in the fields of medicine, neuroscience and the criminal justice service, the ACMD concluded that Ecstasy/MDMA would be more appropriately placed in Class B, rather than Class A [39]. Despite these recommendations being made after extensive examination of peer-reviewed evidence the then Home Secretary disregarded the advice, saying to change the drug's classifications would be to "send the wrong message". The chief of the ACMD subsequently spoke out against the Home Secretary's decision and was sacked from his position as drugs advisor to the government, sparking a national debate about the negative influence of politics over medical research [53].

4. The future for MDMA research

Phase Two studies for MDMA-Assisted Psychotherapy for PTSD are nearing completion, with the addition of an RCT on post-combat veterans from the Iraq and Afghanistan wars. Further Phase Two MDMA-PTSD studies are underway in Canada, Israel and Australia in an attempt to replicate the results of the initial Mithoefer study. Phase Three studies for MDMA-PTSD are planned across multiple international sites from 2018 – including in the UK. The estimated date for gaining FDA approval for MDMA is the year 2021. The license will be linked to be MDMA prescribed as an adjunct for treating PTSD.

We are entering a new era of psychopharmacology research, in which psychotropic drugs are combined with psychotherapies to increase the effects of the latter. Increasingly substances such as MDMA – as well as other psychedelic drugs including psilocybin, ketamine and LSD – could hold significant potential as adjuncts to traditional treatment models [52]. And MDMA-Assisted Psychotherapy is not only restricted to PTSD. The author is starting a further UK study in 2016, using MDMA-Assisted Psychotherapy as a treatment for post-detox alcoholics; with the understanding that patients with addictions often present with high levels of premorbid trauma. Furthermore, because the psychobiology of MDMA is remarkably consistent in controlled settings, it could also be explored as a neural probe to increase our understanding of the neurobiology of higher order socioemotional states such as empathy and trust.

The future looks bright for MDMA science. Despite 100 years of modern psychiatry the specter of trauma continues to underpin the clinical presentation for most chronic mental health disorders. PTSD is one such disorder with high levels of treatment resistance. For the population of patients that could benefit from the novel approach to addressing trauma in a safe and efficient manner using MDMA, we owe it to these people to continue the valuable research in this field of medicine.

Conflicts of interest

None.

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