Neuroscience Letters 649 (2017) 176–180

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Review article

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

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ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 2 July 2016
Accepted 5 July 2016
Available online 6 July 2016

Keywords:
MDMA
PTSD

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.

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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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http://dx.doi.org/10.1016/j.neulet.2016.07.004
0304-3940/

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]