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Editorial

Exploring MDMA: From Neurotoxicity to Therapeutic Potential

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Editorial

MDMA or 3,4 methylenedioxymethamphetamine or commonly known as ecstasy is a ring-substituted amphetamine derivative and it has become a popular recreational drug used at "rave" and "techno" parties. The acute effects of MDMA include a relaxed, euphoric state that leads to emotional openness, empathy and decreased negative thoughts and inhibitions [1], hence its appeal as a recreational drug. MDMA was classed as an illegal drug in 1985 due to its high abuse potential, lack of clinical application and evidence that it can induce serotonergic nerve terminal degeneration in rat brain [2].

Due to the increased popularity of MDMA, for decades research has aimed to determine the acute and long-term effects of the drug on the brain and determine the extent to which MDMA disrupts normal brain functioning. The available human and animal data indicates that recreational use of MDMA is associated with loss of serotonin (5-HT) [3,4], its major metabolite (5-HIAA; [5]), its biosynthetic enzyme (TPH) and its presynaptic transporter (SERT; [6-9]. These losses are persistent after weeks of abstinence and thus are not only due to the short-term pharmacological effects of MDMA. There is sufficient both human and animal data to suggest that MDMA causes long-lasting decreases in 5-HT, 5-HIAA, TPH and SERT in a variety of brain regions (such as the hippocampus and frontal cortex). For example, neuroimaging evidence demonstrates that serotonin transporter binding in ecstasy users decrease throughout all cerebral cortices and hippocampus and that the decrease is related to the extent of drug use (i.e., years, maximum dose) while serotonin transporter binding is normal in other brain regions such as basal ganglia and midbrain [9]. It is therefore possible that MDMA has the potential to damage serotonergic axon terminals and produce a 5-HT distal axotomy. This evidence has been interpreted by several researchers and has been referred to as 'MDMA neurotoxicity'.

However, in recent years, several studies have questioned the neurotoxic potential of MDMA to 5-HT terminals. Such conclusions were based on results from western blot studies of the SERT protein showing no change in SERT protein abundance regardless of large decreases in 5-HT concentrations; what up to that date, had been considered a neurotoxic MDMA treatment in rats [10]. Another argument put forward by some researchers to question the 5-HT neurotoxic potential of MDMA is the failure of some studies to demonstrate changes in Glial Fibrillary Acidic Protein (GFAP) expression after several treatment regimens and thus neuronal degeneration [11,12]. Grob [13] and Kalia [14] also argue that the lack of reactive gliosis in animals exposed to MDMA suggests absence of MDMA-induced neurotoxicity. These findings therefore raise doubts among investigators as to whether MDMA "serotonergic neurotoxicity" involves distal axotomy or alternatively a long-lasting down regulation of 5-HT synthesis and SERT expression by the serotonergic neurons [15].

Despite the debate in the literature over the potential neurotoxicity of MDMA, what is clear is that there is a plethora of research to suggest that recreational use of ecstasy can be associated with neurocognitive deficits [16,17] and a growing body of research indicates that repeated use of recreational ecstasy use can have lasting impairments on memory ability [18-21] and several aspects of Executive Function [22-26].

In recent years, another debate has risen in the literature making MDMA once again a controversial drug; its therapeutic potential. It has been suggested that MDMA might be a useful therapeutic tool that can be used in psychotherapy with Post Traumatic Stress Disorder (PTSD) patients. Even though the therapeutic potential of MDMA has been long speculated, since in the 1980s the drug was used in psychotherapy to increase patients' self-esteem and help therapeutic communication, nowadays given its illegal status and evidence of neurotoxicity and neurocognitive impairments remains a controversial treatment. Due to MDMA's neurochemical properties such as acute increases in serotonin levels leading to euphoria and empathogenic properties [5] but also increases in levels of the neurohormone oxytocin [27] that are associated with prosocial effects [28], it has long been stipulated that MDMA could be a useful therapeutic tool in the treatment of chronic PTSD. The ability of MDMA to acutely induce a positive cognitive emotional state that reduces fear and helps to process traumatic material and better encode positive emotional experiences [29] might prove to be a useful way for PTSD patients to re-evaluate traumatic experiences with the assistance of a psychotherapist without overwhelming anxiety. Another possible therapeutic quality of MDMA, can be the release of oxytocin during acute administration of MDMA that can increase sociability but also diminish responses to threatening stimuli and enhance responses to rewarding social signals [28]. This way a client-therapist bond [30] can be achieved with greater feelings of trust facilitating the therapeutic alliance and achieve faster and long lasting improvements.

Prior to establishing MDMA as a drug of abuse in 1985, early reports of the effectiveness of MDMA use in psychotherapy were provided by Greer & Tolbert [31-33] in their publications describing MDMA-assisted psychotherapy in 80 patients. Greer and Tolbert [31] found that 90% of their patients reported positive experiences

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with lasting beneficial effects that remained at the one-year follow-up. More recently, rigorously-controlled clinical trials of MDMA-assisted psychotherapy in patients with PTSD have also shown some promising results for the effectiveness of this controversial drug in the treatment of chronic PTSD [34,35] that seem to be long lasting [36]. Oehen et al. [37] also investigated the safety and effectiveness of MDMA-assisted psychotherapy in a well-designed, randomized, double-blind, active placebo controlled trial in a small sample of treatment-resistant PTSD participants. Once again, findings were promising as they found evidence of the safety of 2 doses of MDMA (25 mg; 125 mg) but also improvement of self-reported PTSD symptoms that remained after one year follow-up. They failed, however to observe any reductions in the clinician-observed PTSD questioning the clinical usefulness of the drug.

Even though these studies are fairly promising and show some significant subjective improvements in PTSD symptoms, they fail to demonstrate the practical significance or magnitude of these significant (or lack of) improvements in PTSD patients and more rigorous statistical analysis need to be employed in order to draw solid conclusions on the therapeutic potential of this controversial drug. Furthermore, in order to evaluate the potential therapeutic value of MDMA in the treatment of chronic PTSD several concerns need to be addressed before MDMA can be fully accepted as a safe (and useful) drug for therapy [38]. As previously mentioned research has long documented that MDMA is associated with various deficits in neurocognitive function such as memory and higher cognition as well as a wide range of mood changes. For example, Curran & Travill [39] found that MDMA users reported a period of poor mood and anhedonia known as 'midweek blues' reflecting the residual effects of MDMA. Other studies also reported significant mood changes after MDMA use such as emotional excitation and sensitivity but also some negative undesired moods including anxiety, fear-of-loss of thought control [40] as well as depression and sleep disturbances [41]. Such negative moods, especially anxiety, were also reported in psychotherapeutic situations [33]. There is, therefore, a risk for patients experiencing some of the drug's adverse effects that if not dealt effectively i.e. with the help of an experienced psychotherapist might impede the therapeutic progress of the patient.

Even though there is some evidence to suggest that MDMA-assisted psychotherapy might be an effective treatment for chronic PTSD patients, incomplete clinical trials [34], small samples sizes, lack of estimates of practical significance and lack of evidence for long lasting (more than one year follow-ups) reductions in PTSD symptomatology make difficult to draw objective conclusions of the effectiveness of this treatment. Also, given the abundance of evidence for MDMA's neurotoxic potential and long-lasting effect on neurocognitive functioning and residual mood disturbances more rigorously-designed clinical trials are required in order to evaluate both the effectiveness but also the safety of MDMA administration in psychotherapy before accepting it as an established treatment.

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