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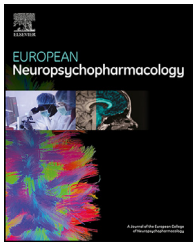

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INSIGHTS

Premise, promise and challenges of MDMA assisted therapy for PTSD

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From the COVID-19 pandemic, natural disasters, migratory crisis, to devastating wars across the world, exposure to traumatic experiences is widespread, often producing lasting neurobiological, behavioral and epigenetic changes, triggering different mental health problems including major depression, anxiety, substance use disorders and post-traumatic stress disorder (PTSD). The lifetime prevalence of PTSD ranges from 1.3% to 12% depending upon the studied population, with a heavy socioeconomic burden on patients and the society at large (Shalev et al., 2017).

In 1912 Merck pharmaceuticals developed 3,4-methylenedioxy-N-methylamphetamine (MDMA), a compound largely forgotten until Alexander Shulgin resynthesized it in 1976. Over the following years, hundreds of therapists administered MDMA and observed that in just a few sessions with the medication, patients achieved progress that normally took years. It didn't take long before this compound with entactogenic and activating effects leaked into the night scene and became popularly known as ecstasy. Subsequently in October of 1986, without any convincing academic arguments MDMA became classified as a Schedule I substance by the DEA, meaning that MDMA had no "accepted medical use" and thus research in this field was hugely restricted from that point onwards.

From the early 2000's the Multidisciplinary Association for Psychedelic Studies (MAPS) has been spearheading worldwide clinical research of MDMA-Assisted Therapy. Pooled data from all the MAPS-sponsored Phase 2 trials led to the FDA Breakthrough Therapy designation in 2017 and the expansion into multi-site Phase 3 trials. In 2021, positive results were obtained from the first randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial testing the efficacy and safety of MDMA-assisted psychotherapy for the treatment of patients with severe PTSD, showing a significant attenuation in CAPS-5 score compared with placebo, with as much as two thirds of patients in the MDMA arm no longer meeting criteria for PTSD after completing treatment (Mitchell et al., 2021). In addition, the safety profile of MDMA appears to be favorable as it did not induce adverse events of abuse potential, suicidality, or QT prolongation. In the U.S., Canada and Israel, MAPS has completed the second Phase 3 trial of MDMA-AT for the treatment of PTSD and recently announced positive top-line results from this trial, having met their primary and secondary endpoints. With this, MAPS will have conducted two successful Phase 3 studies and is planning to submit a new drug application (NDA) to the FDA in the 3rd quarter of 2023, and it is very likely they will receive regulatory approval within the next year and a half. In Europe and England, MAPS has trained therapists in seven countries (Netherlands, Czech Republic, Germany, Portugal, Spain, Norway, and England) in preparation for launching a Phase 3 trial in 2024. Regulatory approval by EMA might be possible thereafter as early as 2026.

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MDMA-AT sessions must be provided in an optimal environmental condition, delivered in a non-directive way and the therapist's role is to create a sense of safety and communicate trust in their patient's ability to explore their issues. Also, sessions before and after the MDMA administration are essential for preparation and subsequent integration of the emergent material after the sessions. Both the pharmacological effects and the subjective psychological experience of MDMA provide a selective impairment of the fear response whilst leaving other cognitive processes relatively spared (Mithoefer, 2017; Sessa et al., 2019). As proposed by Hasler, psychedelics and entactogens seem to act like a helioscope, which not only makes looking at the sun harmless but also intensifies colors and contours and prevents disturbing reflections. Transferred to psychedelics, this means that one has the possibility to see something through a different filter that could not be looked at under normal circumstances (Hasler, 2022). This mechanism of action could lead to a shift in the conventional pharmacological treatment paradigm, towards an integrative and individualized approach where both the pharmacological and psychotherapeutic interventions work synergistically to catalyze changes in the individual's entrenched pathological thought and behavioral patterns.

Like almost any effective approved treatment, MDMA-AT has inherent risks. Furthermore, risks increases in recreational settings, such as abuse potential and triggering of psychiatric disorders, specially for individuals with preexisting vulnerabilities (eg, psychotic disorders). In order to conduct post-approval risk evaluation and implement mitigation strategies we believe administration must be limited to certified centers, with defined safety screenings, and a centralized pharmacy for control. A key way to minimize potential harms and control for heterogeneous treatment results, will be making sure that the therapy is provided by trained therapists under supervision. Training of therapists to provide MDMA-AT is possibly one of the biggest challenges ahead and most likely the main limiting factor for wide-spread availability of this novel treatment in the near future. Although this might be challenging and costly, the potential advantages are clear: a recent cost-effectiveness analysis shows that increasing access to MDMA-AT to 25–75% of eligible patients with chronic and severe PTSD over 10 years could avert between 43,000 and 106,000 deaths, produce a gain of 3.3–8.2 million quality-adjusted life years, and lead to $109–$266 billions in net savings for the US healthcare system (Avanceña et al., 2022).

Findings from the phase 2 and 3 trials have shown that MDMA might revolutionize the treatment of PTSD and might provide much needed novel pharmacotherapy with therapeutic benefits beyond all current and existing pharmacotherapies, making MDMA the most promising novel adjunctive agent for PTSD psychotherapy (Gonda et al., 2022). A recent scientometric analysis shows a clear trend toward clinical testing of MDMA, psylocibin, ketamine and its enantiomers in treatment formats frequently associated with psychotherapy for several mental disorders (Solmi et al., 2022), and psychedelic-assisted therapies might become key in addressing the most urgent mental health challenges of our time and reducing needless suffering. On the other hand psychedelic research currently appears to be trapped in a hype bubble driven largely by interests from media and the industry (Yaden et al., 2022). At the same time, there has been recent debate over the lowering of standards by major medical journals publishing psychedelic related clinical trials (Hall and Humphreys, 2022). This combination might prove disastrous for the development and implementation of these new promising therapies, unless efforts are made to keep research to the highest ethical and scientific standards.

Declaration of Competing Interest

O.A. is a principal investigator for the phase IIB and III clinical trials in the MAPS sponsored MDMA-AT trials for PTSD. He has no other conflicts of interest to report in relationship with the present manuscript.

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