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Clinical and non-clinical use of MDMA

PERSPECTIVES

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3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, has shown promising results in the treatment of post-traumatic stress disorder (PTSD). In clinical trials, the use of MDMA in combination with psychotherapy differs substantially from its illicit recreational use.

MDMA is a central nervous system stimulant that is chemically similar to methamphetamine and the psychedelic compound mescaline. MDMA is classified as an entactogen, a term derived from Greek and Latin, referring to its capability to enable a 'touching within' (1). MDMA affects monoamine release and inhibits uptake, particularly of serotonin (2). Animal studies have also demonstrated effects on neuroplasticity (3).

MDMA's distinctive pharmacological profile has led to interest in its use in psychotherapeutic settings. Prior to its emergence as a recreational drug in the rave scenes in the United States and Europe, and its prohibition in 1985, MDMA was used in combination with psychotherapy. Acute psychological effects include enhanced levels of trust and self-compassion, which can prompt emotional therapeutic breakthroughs that are otherwise difficult to achieve in conventional psychotherapy (2). Following MDMA-assisted therapy, lasting personality changes have been reported, including increased openness and reduced neuroticism, alongside improved emotion regulation and the ability to maintain meaningful relationships (4). The therapeutic framework for MDMA-assisted therapy emphasises the combination of MDMA and psychotherapy rather than either component in isolation (5). Key elements include the therapeutic alliance, as in other forms of psychotherapy, but with greater

emphasis on a non-pathologising approach to the patient and the content of the therapeutic process, as well as the mobilisation of an inherent capacity for healing and growth, also referred to as 'inner healing intelligence' (5).

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MDMA-assisted therapy for post-traumatic stress disorder

MDMA in combination with psychotherapy has been investigated in six phase II trials and two phase III trials as a treatment for post-traumatic stress disorder (PTSD) (2). Overall, the phase II trials demonstrated a statistically significant reduction in PTSD symptoms compared with the control group, with a further statistically significant reduction in symptoms observed at long-term follow-up one year after treatment completion (6). Both phase III trials showed statistically and clinically significant reductions in PTSD symptoms in the MDMA group compared with the group receiving the same psychotherapy and a placebo (7, 8).

In both the phase II and phase III trials, approximately two-thirds of participants in the MDMA group no longer met the diagnostic criteria for PTSD following treatment (6–8). The dropout rate in the phase III trials was 9.3 %, which is substantially lower than the rates of up to approximately 50 % reported for gold-standard PTSD treatments such as prolonged exposure therapy or cognitive processing therapy (9). This suggests improved tolerance of MDMA-assisted therapy. A regulatory approval application submitted to the US authorities was nevertheless rejected, with a requirement for a third phase III trial (10). In its assessment, the authorities highlighted three main concerns: insufficient reporting of 'positive' side effects such as euphoria, a lack of long-term follow-up beyond 18 weeks, and a high proportion of participants with prior MDMA experience (up to approximately 40 %), which could introduce selection bias and unblinding.

MDMA trials are methodologically challenging, not least because the strong psychoactive effects make blinding difficult to maintain. In addition, participants are often recruited through self-selection, which can result in a sample characterised by expectancy bias (2).

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MDMA-assisted therapy for depression

An investigator-initiated, publicly funded phase II trial has been conducted in Norway, which includes 12 participants with major depressive disorder and a current depressive episode of moderate to severe severity (11). As this was an initial exploratory investigation intended to inform future trials, the study employed an open-label design without a control group. The trial met its primary objectives of feasibility and safety, with adequate recruitment and no participant dropouts or serious adverse events. The findings also indicated potential therapeutic effects, with both statistically and clinically significant improvements from baseline to post-treatment, as measured by reductions in depressive symptoms (Montgomery-Åsberg Depression Rating Scale, MADRS) and functional impairment (Sheehan Disability Scale, SDS). Nine of the 12 participants met the criteria for both treatment response and remission at the initial post-treatment assessment, and one participant relapsed. Follow-up data demonstrated lasting reductions in depressive symptoms and functional impairment seven months after the start of the trial (12).

Safety profile in clinical versus non-clinical use

There are considerable differences between unregulated, non-clinical use of illicit MDMA and its use in controlled clinical trials (2). This applies, for example, to the risk of misuse and dependence – a distinction that is also well recognised for several commonly used medicines, including benzodiazepines, hypnotics and opioids (13).

In clinical settings, standardised doses of pharmaceutical-grade MDMA are administered, whereas illicit MDMA may contain variable quantities of the drug as well as other substances. The most common causes of death associated with non-clinical use are hyperthermia and hyponatraemia, both of which can be prevented through dose control, temperature regulation and fluid management (2). No cases of clinically significant hyperthermia or hyponatraemia have been reported in clinical trials (2).

In the two phase III trials, a total of two serious adverse events were reported, both in the placebo group and both related to suicidality (7, 8).

Risk of misuse and dependence

According to a report from the Norwegian Institute of Public Health, 6.5 % of Norwegians reported lifetime MDMA use and 1.4 % reported use in the previous year. The prevalence appears to be increasing slightly (14). Although MDMA has dopaminergic effects, animal studies indicate that chronic

administration of MDMA does not produce physical dependence (2). Experimental studies have shown that animals can self-administer MDMA, indicating some potential for misuse (2).

A one-year follow-up study of participants who had undergone MDMA-assisted therapy for PTSD found that 8 of 83 participants (9.6 %) had used MDMA outside the study, although six of these had also used MDMA prior to the study (6). Overall, the risk of developing dependence appears to be low when MDMA is used in a clinical setting, and preliminary data suggest a potential role for MDMA in the *treatment* of substance use disorders (2).

A new approach to treatment

This form of therapy represents a novel approach to the treatment of PTSD and depression, in which two to three day-long MDMA sessions are delivered as part of an integrated psychotherapeutic process. This differs from the current standard treatment with psychotropic medication or psychotherapy. If this treatment approach is approved for clinical use, new requirements will be imposed on the health service and clinicians delivering the therapy, including day-long treatment sessions and specialised therapist training (5). Although the therapy is resource-intensive, analyses from a phase III trial suggest that it may lead to long-term cost savings (15).

> ***«If this treatment approach is approved for clinical use, new requirements will be imposed on the health service and clinicians delivering the therapy»***

The harm potential of non-clinical use has been the subject of research for several decades, whereas its therapeutic potential has only recently been systematically investigated in controlled trials (2). It cannot be assumed that findings from a non-clinical context, such as risks of misuse and complications, are directly transferable to a clinical setting. Conversely, it is also uncertain whether the therapeutic effects observed in clinical trials can be reproduced outside a structured clinical framework (2).

The available data remain limited, and the extent to which potential regulatory approval and subsequent use as a treatment within the health service might increase illicit use outside clinical settings has not been investigated. Promising findings from clinical trials may already have contributed to increased non-clinical use, as observed for psilocybin in the United States, where use has risen in parallel with an increase in calls to poison control centres (16). Meanwhile, a Norwegian cross-sectional survey of individuals reporting a memorable MDMA experience found that these experiences were generally rated as positive, with rare and short-lived adverse effects (17).

A promising alternative

Several questions remain unanswered, particularly in relation to expectancy bias and challenges related to blinding. The rejection of the application to the US regulatory authorities underscores the need for rigorous and methodologically robust clinical trials before the therapy can be introduced in routine clinical practice. Switzerland and Australia have recently permitted MDMA-assisted therapy in health care outside clinical trials (18), and international developments should be closely monitored.

Given the burden of inadequately treated depression and PTSD, MDMA-assisted therapy seems to be a promising alternative with a favourable benefit–risk profile. In Norway, it will be essential to build on the clinical evidence base and ensure that any future clinical implementation takes place within a safe framework. If successful, MDMA-assisted therapy may become an important adjunct to existing treatment options for depression and PTSD.

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