ANZJP

Australian & New Zealand Journal of Psychiatry
2021, Vol. 55(8) 741–743
DOI: 10.1177/00048674211032112

Out of the night-time and into the day: Ketamine and MDMA as therapies for mental disorders

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Ketamine and 3,4-methylenedioxymethamphetamine (MDMA) used to be in the news for all the wrong reasons. They were party drugs, used imprudently and reported as presenting dangers to the physical and mental well-being of users. Now we read about them as potential treatments for mental disorders. What has happened?

Both ketamine and MDMA are old drugs, with apparent new uses. They have similarities in the way they are used recreationally, but they have taken different pathways to consideration as therapies.

Ketamine is further along the pathway to mental health application than is MDMA. It was first synthesised in 1962 at Parke-Davis (now Pfizer), and its utility as an anaesthetic agent was apparent early. Ed Domino, the clinical pharmacologist who first tested ketamine in humans, described how these first participants reported their experiences: 'While in recovery [they] said, "Jesus, I'm in outer space. My God, I don't have any arms or legs, I'm floating, man what a high! Oh my God!"' (Denomme, 2018). His wife coined the term 'dissociative anaesthetic' to describe these unusual properties, with the participants' descriptions providing an early indication of ketamine's appeal for recreational users.

Ketamine's use as a clinical agent and as a drug whose effects were enjoyed in social settings continued in parallel for decades. In the meantime, researchers were focusing on the brain mechanisms of depression. In the 1990s, there was an emerging interest in the role of the glutamatergic system, and evidence that increased glutamate transmission had toxic brain effects that precipitated and perpetuated depression. Researchers proposed that a drug that had antagonist effects at glutamate receptors – a drug like ketamine – might therefore have antidepressant properties. The first test of this hypothesis, a small study published in 2000, showed that a single dose had antidepressant effects (Berman et al., 2000), and research has confirmed that repeated dosing over 2–4 weeks alleviates depressive symptoms (Singh et al., 2016) – although for how long remains an open question.

MDMA is, perhaps surprisingly, the older of the two drugs. It was first synthesised in 1912 by Merck, who developed it as a precursor to a clotting agent. It was not tested on either animals or humans and was patented and then forgotten. It emerged again in the 1970s, with pharmacists searching for new amphetamine-type drugs. One of those who took an interest was Alexander Shulgin, a research pharmacologist who had government approval to synthesise novel compounds. He first reported his experience with MDMA in 1977 (Benzenhöfer and Passie, 2010). Impressed with it, he introduced MDMA to his psychologist friends, who started using it with their clients in therapy sessions. The popularity of MDMA as a recreational drug increased rapidly after that, and in response, the use and manufacture of it was criminalised in 1985. Clinical and research work came to an abrupt halt.

A small group of therapists who had used MDMA with their clients before its criminalisation maintained their belief in MDMA's therapeutic potential, particularly for people with post-traumatic stress disorder (PTSD). The model they proposed was therapy focused – in which the use of MDMA was said to create a 'window of tolerance' for traumatised patients to work through their experiences in an open and supportive environment. Rick Doblin, and the organisation he established to advocate for MDMA's rescheduling (the Multidisciplinary Association for Psychedelic Studies [MAPS]), has funded a series of studies of MDMA-assisted psychotherapy for PTSD. A recent double-blind phase 3 trial, developed jointly with the US Food and Drug Administration (FDA), showed that MDMA-assisted psychotherapy was more effective for PTSD symptoms than the same psychotherapy delivered with placebo (Mitchell et al., 2021). In that study, participants had three MDMA-assisted therapy

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sessions, spaced about a month apart, with non-drug therapy ('integration') sessions following each dosing session. The effects of the treatment on PTSD symptoms were statistically and clinically significant.

A different way of thinking about medication treatments

These treatments provide new perspectives on how we think about drug treatments for mental illnesses. Mostly we prescribe medications that patients take each day for many months, or not infrequently, for years. In other parts of medicine, while daily drug treatment is standard (although often for shorter periods), short-term intermittent treatment protocols are not unusual: consider chemotherapies for cancers and intravenous immunoglobulin for autoimmune disorders. In psychiatry, the paradigm that these treatments most resemble is electroconvulsive therapy (ECT). The two to three treatments provided each week for four weeks are very close to protocols for ketamine administration. Could short courses of these drugs propel recovery in much the same way that ECT does?

The drugs take divergent paths in their integration with psychotherapy. The history of MDMA as a treatment has been closely tied to therapy. The therapy model is non-directive and supportive: with sessions occurring before MDMA is administered, during and afterwards. Proponents of the model argue that MDMA provides the conditions for therapeutic change to occur. That for a person who has experienced severe trauma, taking MDMA with the support of empathetic clinicians, and then discussing it with them afterwards, provides the conditions for the corrective emotional experience that will aid their recovery. There is less focus on the drug itself, and more on the drug–psychotherapy dyad.

There is not currently the same focus for ketamine. There is nothing about the experience that suggests that psychotherapy might not also be useful – and some researchers are looking at integrating therapy with ketamine treatments in much the same as for MDMA. But the focus with ketamine has been on delineating how ketamine might exert its antidepressant effects at a brain level: whether by virtue of its antagonistic actions on the *N*-methyl-d-aspartate (NMDA) receptor or by the actions of its metabolites on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. This is likely a result of its history – its therapeutic potential was promoted by the white-coated professors of prestigious clinical academic departments – than anything inherent in the drug's properties. But it raises the question: would the same low lighting, music and empathetic framing provided for MDMA improve ketamine's actions? Or conversely, would MDMA treatment do just as well when provided under the stark fluorescent lighting of a hospital clinic?

Warning signs

The journey of these drugs from the nightclub to the clinic sets off alarm bells for many clinicians. The drugs have strong psychoactive effects, and there is understandable concern about their potential to destabilise the fragile mental states of unwell patients. This is perhaps more of a concern for MDMA, where the doses used are similar to recreational doses, than it is for ketamine, where the clinical doses are comparatively much lower, and which has been used in clinical settings for much longer. The drugs have potentially serious side effects, with MDMA in rare cases causing serotonin syndrome and hyponatraemia, both potentially fatal.

We have cautionary tales from psychiatry and from other areas of medicine that might give us pause. Deep sleep therapy was another short-term treatment that was once heralded as an innovative new treatment for mental illnesses, with appalling consequences. More recently, the opioid epidemic resulted from medical practitioners prescribing medications indiscriminately to patients who were poorly monitored. Some worry that such fates await ketamine and MDMA should oversight of treatment programmes be lax.

Can we be sure that the drugs really work, given the difficulty in masking the allocation of clinical trial participants to drug or placebo? The drugs have such prominent psychoactive effects that blinding with placebo pill is almost impossible. Effective blinding can only really be provided by drugs with similar psychological effects, but which do not cause significant changes in the symptoms of interest. Recent ketamine studies have used midazolam as an active placebo (it produces changes to the sensorium without antidepressant effects), and this seems to have improved masking of treatment allocation. No such active placebo has been found for MDMA, and critics of the recent phase 3 trial have been quick to suggest this as the reason for its apparent robust effectiveness.

The role of psychiatry

There is contention about the role that psychiatry might play in exploring the therapeutic potential of these medications. Commercial ketamine clinics have started to emerge in North America, often led by anaesthetists who know a lot about ketamine, but little about depression. MDMA treatments are largely being led by psychologists and other therapists, with peripheral medical involvement. But both ketamine and MDMA are complicated drugs that have strong effects on the mental and physical states of patients, which psychiatrists are well positioned to assess and monitor. Careful selection of patients is critical, as is careful monitoring of their clinical course, oversight of which

psychiatrists are expert. Ketamine is some distance down the path from research to wider clinical application, which is likely to be propelled by the Therapeutic Goods Administration's approval of an intranasal preparation of the S-enantiomer of ketamine (esketamine). We must ensure that ketamine is used judiciously, and we should speak out if it is not. MDMA-assisted psychotherapy is still in the research phase. We should have an open mind to its clinical application, and we need to look carefully at what the research is telling us. If it looks to be effective and safe, we should consider whether we can integrate it as a treatment option for selected patients who are struggling with trauma-related symptoms. And if it does not, we should say so.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author has received competitive funding from the National Health and Medical Research Council and the Medical Research Future Fund to study ketamine as a treatment for mood disorders.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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