Debunking the myth of ‘Blue Mondays’: No evidence of affect drop after taking clinical MDMA

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Abstract

Background: Incorporating 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy has shown promise in recent years for treating various mental health conditions, particularly those involving trauma. However, concerns about declines in mood and cognition during the days following dosing, also known as ‘Blue Mondays’, have been raised as limitations to its clinical use. Although these changes have been well-documented among recreational users, there are critical confounds to these reports that limit generalizability to clinically administered MDMA.

Aims: Here, we aimed to evaluate the evidence basis for the negative side effects associated with MDMA as well as inform our understanding of the drug’s post-acute effects in a clinical context with an open-label study.

Methods: The current open-label study examined MDMA therapy for alcohol use disorder (AUD; N=14) and measured mood, sleep quality, illicit MDMA consumption and anecdotal reports after the acute drug effects had worn off.

Results: Participants maintained a positive mood during the week following drug administration in a clinical context. Relative to baseline, self-reported sleep quality improved at the 3- and 6-month follow-ups. Finally, no participants reported using or desiring to use illicit MDMA, and the anecdotal reports indicated that they perceived the treatment favourably.

Conclusion: The results support the overall safety and tolerability of clinically administered MDMA and, importantly, suggest that the ‘come downs’ previously associated with the substance may be explained by confounds in research relating to the illicit sourcing of the drug and specific environmental setting for recreational consumption.

Keywords
MDMA, ecstasy, psychotherapy, alcohol use disorder, come downs, Blue Mondays

Introduction

MDMA (3,4-methylenedioxymethamphetamine), sometimes known as ‘ecstasy’ when used recreationally, is an amphetamine derivative currently being explored as an adjunct in psychotherapy for posttraumatic stress disorder (PTSD; Mitchell et al., 2021) and alcohol use disorder (AUD; Sessa et al., 2021). However, there are a number of concerns about the safety of MDMA, including the alleged potential for neurotoxicity, misuse and cognitive/affective impairment after the acute effects have worn off (i.e. ‘hangovers’ or ‘Blue Mondays’). Here, we argue that many of the claims about the toxicity of MDMA and other negative phenomena associated with its use are based on its illicit sourcing (i.e. not clinical use evidence) and consumption in specific environmental settings which risk damaging medical research with clinical MDMA by association. We first give an overview of the history of MDMA and its therapeutic applications. We then detail assumptions about the adverse effects of MDMA as well as explore the evidence basis for these claims. Finally, we present novel data on the post-acute effects of clinically administered MDMA in a sample of patients with AUD and coalesce the results with discrepant findings from recreational and preclinical studies.

History and therapeutic applications

MDMA was first synthesized and patented by German pharmaceutical company Merck in 1912 as a precursor in a new synthesis for haemostatic substances but was never used. It was then resurrected by Alexander Shulgin in the 1970s when he self-experimented with a range of phenethylamine drugs and found that MDMA induced greater clarity of thought and empathy with others. Alexander’s psychotherapist wife, Ann Shulgin, then promoted its therapeutic potential, especially for couples counseling. Then still legal, MDMA began being used by psychedelic therapists in the United States, disseminated by psychotherapist Leo Zeff (Stolaroff, 2004), who referred to the drug as ‘Adam’. It
then leaked from the clinical community and became increasingly used in recreational settings where it was sold as an alternative to recreational psychedelics and stimulants, especially amphetamines and cocaine, and began to be called ‘ecstasy’ (Passie and Benzenhöfer, 2016). Its use in public contexts, particularly raves, attracted attention just when President Reagan was ramping up the War on Drugs and Nancy Reagan was spreading the ‘Just Say No’ campaign. The first claim of brain damage was made in the United States by Bob Schuster, a professor at University of Chicago, on the Phil Donahue talk show in early 1985, following a paper by George Ricaurte et al. (1985), showing supposed serotonegic neurotoxicity in rats exposed to methylenedioxymphetamine (MDA), not MDMA. Also on the Phil Donahue show was Gene Haislip of the Drug Enforcement Administration (DEA), who heard about neurotoxicity for the first time. Haislip subsequently used that information to emergency schedule MDMA in the summer of 1985.

In the wake of the banning of MDMA, a scientific research organization in the United States, the Multidisciplinary Association for Psychedelic Studies (MAPS), was formed to carry out research into clinical uses of the drug (Doblin, 2002). MAPS is currently leading Phase III trials for MDMA-assisted therapy for PTSD. To date, the findings have been promising and federal approval is targeted in the United States and Europe within the next few years. In a pooled analysis of six Phase II trials, researchers found a large effect size and two-thirds of participants no longer met diagnostic criteria for PTSD at the 12-month follow-up (Jerome et al., 2020). The recently released results from the Phase III trials complemented these findings, as 67% of patients in the MDMA group compared with 32% in the control group no longer met PTSD criteria at the 2-month follow-up, and there were no major safety issues documented with MDMA (Mitchell et al., 2021). Lengthier longitudinal outcomes from the Phase III studies are in the process of being collected but as of now unavailable. It should also be noted that MDMA therapy research to date has been limited by blinding issues (Bershad et al., 2019) and many challenges remain in translating laboratory findings to clinical settings (de Wit et al., 2021).

MDMA is thought to be a useful tool in therapy by transiently suppressing amygdala activity (Carhart-Harris et al., 2015), helping traumatized patients address repressed negative emotional memories without becoming overwhelmed by negative emotion (Sessa and Nutt, 2015). Furthermore, the acute prosocial and interpersonal effects of MDMA may facilitate therapeutic alliance, which is an important predictor of treatment adherence and outcomes (Hefets and Malenka, 2021; Mitchell et al., 2021). Yet, media-driven claims about the risks of MDMA have been a hindrance to the progress of clinical studies with the drug.

Risks

Risks that have been linked to MDMA include neurotoxicity, post-acute cognitive and affective impairment, and potential for abuse. Concerns about the potential neurotoxicity of MDMA were made based on rodent work and this worry grew after Ricaurte et al. (2002) erroneously concluded that MDMA induced dopaminergic cell death in primates; however, it was later revealed that the subjects in Ricaurte’s study had been accidentally administered methamphetamine instead of MDMA. The study was retracted, but the paper left a lasting impression that MDMA leads to neurotoxicity. Its conclusions were used to support the Reducing Americans’ Vulnerability to Ecstasy (RAVE) Act in the United States, which inadvertently discouraged club owners from practicing harm reduction practices in order to avoid criminal liability – exacerbating negative side effects associated with recreational use. Among the MDMA scientific community, worry about dopaminergic cell death abated, but study into the drug’s effects on serotonin toxicity continued. However, in many studies that suggested neurotoxicity, dosages and patterns of administration were not analogous with human consumption, particularly when MDMA is orally administered in a therapeutic context (Baumann et al., 2007; De La Garza et al., 2007; Sessa and Nutt, 2007).

The potential for post-acute cognitive and affective impairment has been well-documented among recreational MDMA users (e.g. Curran and Travill, 1997; Verheyden et al., 2003). Acute post-MDMA lowered affect, occurring as the drug effects wear off, is often referred to colloquially as a ‘come down’. A delayed response several days later was originally termed ‘midweek low’ but is sometimes called ‘Blue Mondays’ or, at the most extreme, ‘Suicide Tuesdays’ (Sessa, 2019). However, there are a number of factors related to the conditions in which MDMA is used recreationally that may contribute to negative effects, including the contents of the illicit substance consumed, other substances consumed concurrently and the wider environmental context to that consumption. Importantly, these factors can be controlled in clinical settings and, therefore, many of the negative side effects observed with recreational use may not generalize to clinically administered MDMA. Next, we will elaborate further on these critical confounds to research with recreational MDMA users.

First, when used recreationally, a number of substances may be mis-sold by suppliers and mistakenly consumed as MDMA due to the nature of the market of illicit substances. For example, in UK drug checking services, approximately one-fifth of samples are identified through testing as other than the substance the user thought they had bought (Measham, 2019). The substances mis-sold as MDMA include inert household substances such as brown sugar mis-sold as MDMA crystal due to its similar appearance and psychoactive drugs such as substituted cathinones (e.g. N-ethylpentylone and eutylone) mis-sold as MDMA due to their similar appearance, smell and initial effects. These cathinones are a particular health concern because their unexpected, unwanted and often protracted stimulant effects include anxiety, confusion, insomnia, paranoia and at higher doses resulting from unintentional redosing, psychotic episodes (Measham, 2020).

Second, recreational MDMA consumption is often concurrent with consumption of other legal or illicit drugs, including alcohol, cannabis and other stimulants. In a convenience sample survey of festivalgoers, over nine in ten MDMA users also consumed alcohol on the fieldwork day and over three quarters of MDMA crystal users were also taking or planning to take at least one other illicit drug; two-thirds of ecstasy pill users were also taking or planning to take at least one other illicit drug (McCormack et al., 2021). A related issue is that the strength of an ecstasy pill is seldom known when purchased on the illicit market, rarely equates to a common adult dose of 100–120mg of MDMA, and can vary considerably, from zero up to over 350mg of MDMA (Safer Party, 2021). The average strength of ecstasy pills tested by the Dutch Drugs Information and Monitoring System in 2020...
was 166 mg of MDMA, about one and a half times a common starting dose (Drugs Information Monitoring System (DIMS), 2021).

Third, MDMA is most usually taken recreationally in the United Kingdom in nightlife settings (Measham et al., 2001). Concomitant potential dehydration, overheating, exhaustion and sleep and dietary disruption from extended periods of dancing in crowded venues without adequate ventilation may lead to mood swings and cognitive impairment in the following days. This therefore can confound the effects of MDMA with those resulting from lack of sleep, exhaustion, dehydration and interactions with other psychoactive drugs (whether taken intentionally or inadvertently), which may account for some of the post-acute cognitive and affective changes documented by MDMA users. Nonetheless, Vollenweider et al. (1998) reported that a third of healthy participants experienced slightly depressed mood during the 3 days after clinically administered MDMA compared with placebo, whereas another study that was placebo-controlled and examined healthy individuals found that clinically administered MDMA did not lead to changes in mood during the 3 days after dosing (Borissova et al., 2020).

**The current study**

Although MDMA has shown promise in clinical settings, claims regarding the substance’s potential negative side effects have slowed medical research with the drug. Many of these negative side effects might be explained by confounding variables with recreational use. Therefore, it is important to delineate what adverse reactions are direct effects of MDMA versus indirect effects of the context MDMA is often taken in recreationally. To inform this work, the current study evaluated the use of MDMA therapy for AUD ($N=14$) and measured mood, sleep quality, illicit MDMA use and anecdotal reports after the acute effects had worn off.

**Methods**

**Approvals and drug source**

The study was sponsored and approved by Imperial College London. It received a favourable opinion from the Central Bristol Research Ethics Committee of the National Research Ethics Service as well as from the Medicines and Healthcare products Regulatory Agency (MHRA). A Home Office licence for the storage and dispensing of Schedule 1 drugs was obtained. GMP MDMA was acquired from Sterling Pharmaceuticals (Newcastle) and formulated into the investigational product (62.5 mg MDMA in gelatine capsules) by the Pharmacy Manufacturing Unit at Guy’s and St Thomas’ NHS Foundation Trust (London, UK).

**Participants and design**

Individuals from the North Somerset Substance Misuse Service (formerly Addaction, now called We Are With You) with a primary diagnosis of AUD and who were seeking detoxification were recruited for the study. The trial was designed as a within-subjects, open-label safety and tolerability study of MDMA therapy for AUD. The primary outcome measures included the number of patients completing the 8-week psychotherapy course, the number accepting the second booster dose of MDMA on drug-assisted days, and adverse events. Full details of inclusion and exclusion criteria are described in Sessa et al. (2021).

**Measures**

The primary and secondary outcome measures related to acute safety and alcohol consumption are reported in Sessa et al. (2021). Here, we focus mainly on other outcome measures related to post-acute mood and sleep quality as well as illicit MDMA use and anecdotal reports.

Mood was assessed using the Profile of Mood States (POMS) once a day for 7 days following each of the two MDMA dosing sessions. The POMS is a 65-question mood inventory with seven subscales (e.g. Tension, Anger, Fatigue, Depression, Esteem-related Affect, Vigour and Confusion) in which participants respond using a 5-point Likert-type scale ($0 =$ Not at all, 4 = Extremely). Given that two of the items are reverse scored (e.g. Esteem-related Affect and Vigour), lower POMS total score reflects a positive mood, whereas a higher score is indicative of negative mood. The POMS has high internal consistency, test–retest reliability and external validity (Gibson, 1997; Terry et al., 2003).

The Pittsburgh Sleep Quality Index (PSQI) was administered at baseline, 3 months post-MDMA administration and 6 months post-MDMA administration to assess changes in sleep quality. Lower scores reflect better sleep quality with this measure. The PSQI includes seven subscales (e.g. Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping Medication and Daytime Dysfunction) as well as a total sleep quality score. It has been shown to have high test–retest reliability and external validity (Backhaus et al., 2002).

Illicit MDMA cravings and use were assessed with two binary responses (e.g. yes or no) asking if participants had ‘Taken illicit MDMA or Ecstasy?’ or ‘Had any desire to take illicit MDMA or Ecstasy?’ These questions were asked during session 10 (i.e. final therapy session) and at the 3-, 6- and 9-month follow-ups. Finally, during all non-dosing session days, patients were asked a series of open-ended questions regarding their expectations and experience with MDMA therapy (e.g. ‘How do you feel about MDMA-assisted psychotherapy sessions?’, ‘How did MDMA-assisted psychotherapy compare to other interventions you have experienced?’, ‘How confident are you in your ability to remain abstinent from alcohol?’, ‘How have you felt about taking part in the study in general?’).

**Procedure**

Full details of the procedure can be found in Sessa et al. (2021). In brief, patients with a primary diagnosis of AUD were enrolled into an 8-week recovery-based therapy course that included 10 psychotherapy sessions. During sessions 3 and 7, patients were dosed with MDMA during an extended 6- to 8-h therapy session. They initially received an oral dose of 125 mg of MDMA, followed by a booster dose of 62.5 mg 2 h later during both sessions. Patients remained in the treatment centre overnight during dosing days and were monitored by a ‘night sitter’, who was instructed to...
to provide support as needed but to avoid delivering any therapeutic interventions. Non-dosing therapy sessions (e.g. 1, 2, 4–6, 8–10) included 1 h of psychotherapy incorporating motivational interviewing and recovery-based therapy.

Patients completed phone interviews once a day the week after each dosing session to assess post-acute effects of MDMA on mood. They also completed assessments 3 months and 6 months following completion of the 8-week programme to assess changes in sleep quality and illicit MDMA use and cravings.

Data analysis

All data were recorded on paper case report forms and then transferred into Microsoft Excel spreadsheets. Analyses were performed using SPSS Statistics Software version 26 and graphing used GraphPad Prism version 8.4.3 (GraphPad Software LLC, La Jolla, CA) or Excel. Following each of the two dosing sessions, participants completed the POMS once a day for 7 days; these two data sets were averaged for each participant. POMS Total scores were then analysed using a one-way analysis of variance (ANOVA) with seven levels of Day (Days 1–7 post-MDMA). PSQI Total scores were analysed using a separate one-way ANOVA with three levels of time (Baseline, 3 months post-MDMA and 6 months post-MDMA). The effect of Time was significant, 11 = 7.09, p < 0.01, such that baseline PSQI scores (M = 9.57, SD = 4.07) were significantly higher than at the 3-month (M = 7.07, SD = 4.53) and 6-month (M = 7.14, SD = 4.72) follow-ups, indicating an improvement in sleep quality following MDMA therapy (Figure 2; Table 2).

Illicit use

During session 10 and at the 3-, 6- and 9-month follow-ups, participants were asked to indicate (e.g. yes or no) if they had ‘Taken illicit MDMA or Ecstasy?’ or ‘Had any desire to take illicit MDMA or Ecstasy?’: 0% of patients reported ‘yes’ to either of these questions at any time point.

Anecdotal responses

Responses to the open-ended questions that were asked about expectations, quality of the MDMA sessions and aftereffects were generally positive. Other than some initial worry before dosing reported by one participant (e.g. ‘I am not pretty confident I will tolerate MDMA. Big thanks to Laurie and Ben explaining [sic]’ the only answer judged to be negative in valence was in response to the use of music during therapy sessions, to which one participant wrote, “Did not like female singer on one of the tracks, not sure why”’. A list of representative questions and responses are included in Table 3.

Discussion

Research into the potential therapeutic applications of MDMA has increased significantly in recent years, yielding findings that may mark important innovations for psychiatry. Yet, concerns about potential side effects of the substance have led to negative stigma and slowed medical research. As elaborated on previously, many of the predominant risks documented in earlier studies might be explained by confounding factors with recreational use rather than being direct effects of MDMA per se. That is, when used recreationally, MDMA can be contaminated with other substances and is often taken in conditions that may lead to exhaustion, sleep deprivation and dehydration. Therefore, it may be these factors, rather than MDMA itself, that lead to cognitive and affective decline in the days following dosing. To rule out these confounds, the current study administered MDMA in a clinical setting and measured mood and sleep quality after the

Results

Demographics

Thirty-six participants were screened through face-to-face visits, of which 14 were enrolled in the study (8 males and 6 females; M_age = 48 years; all white British). Four participants were employed, nine unemployed and one was retired. Approximately two-thirds (64%) of participants reported a history of alcohol-related blackouts, 14% had experienced alcohol withdrawal-induced seizures, 86% reported having experienced risky or vulnerable incidences due to alcohol and 75% had forensic/offending behaviour secondary to their alcohol use.

Acute safety

Given that some of the post-acute side effects documented with recreational MDMA users may be due to acute physiological overarousal (e.g. overheating, tachycardia), we first briefly review the acute physiological effects that followed administration of clinical MDMA (see Sessa et al., 2021, for full details). Except for one participant who experienced an abnormal increase in blood pressure after forgetting to take their antihypertensive medication the morning of dosing, all physiological parameters remained within normal limits (Figure 1). There was an expected mild rise in blood pressure, temperature and heart rate over the course of the MDMA sessions. However, no patients experienced sustained physiological disturbances, and no medical interventions were required in respect to any physiological events during MDMA sessions. The Subjective Units of Distress (SUDS) scale indicated that participants overall rated the acute MDMA experience as positive and non-distressing.

POMS

POMS Total scores were analysed using a one-way ANOVA with seven levels of Day (Days 1–7 post-MDMA administration). The effect of Day was non-significant, F(6, 7) = 0.143, p > 0.05, indicating no mood changes in the days after dosing (Table 1). Participants overall maintained a positive mood during the week after MDMA administration (i.e. indicative of an afterglow effect; Table 1).

PSQI

PSQI Total scores were analysed using a one-way ANOVA with three levels of Time (Baseline, 3 months post-MDMA and 6 months post-MDMA). The effect of Time was significant, F(2, 11) = 7.09, p < 0.01, such that baseline PSQI scores (M = 9.57, SD = 4.07) were significantly higher than at the 3-month (M = 7.07, SD = 4.53) and 6-month (M = 7.14, SD = 4.72) follow-ups, indicating an improvement in sleep quality following MDMA therapy (Figure 2; Table 2).
drug had worn off as well as evaluated anecdotal reports and subsequent illicit consumption. We found that rather than a ‘come down’, participants maintained a positive mood during the week after each MDMA session with no significant mood fluctuations. Relative to baseline, sleep quality was improved at the 3- and 6-month follow-ups. Finally, no participants reported seeking or desiring illicit MDMA after being exposed to the substance in the study, and the anecdotal reports indicated that participants perceived the treatment positively.

In-line with our hypothesis that ‘come downs’ previously documented with MDMA may be confounded by recreational use, we found no evidence of affect drop after clinical MDMA. To the

<table>
<thead>
<tr>
<th>Days post-dosing</th>
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<th>Mean</th>
<th>SD</th>
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<th>95% CI</th>
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<td>Lower bound</td>
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<td>-10.7</td>
<td>21.4</td>
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<td>-23.0</td>
<td>1.6</td>
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<td>2</td>
<td>14</td>
<td>-17.2</td>
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<td>-6.6</td>
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<td>3</td>
<td>14</td>
<td>-15.2</td>
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<td>-3.6</td>
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<td>4</td>
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<td>-14.2</td>
<td>13.5</td>
<td>3.6</td>
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<td>-6.4</td>
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<td>5</td>
<td>14</td>
<td>-14.5</td>
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<td>6</td>
<td>14</td>
<td>-9.6</td>
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<td>5.5</td>
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<td>-62.0</td>
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CI: confidence interval.
contrary, participants exhibited a positive mood during the week after each MDMA session (i.e. an afterglow effect) with no significant negative mood fluctuations. This contrasts with the results of Vollenweider et al. (1998) who found that a third of healthy participants reported slightly depressed mood in the days following clinically administered MDMA. It could be argued the addition of therapy in the current study as well as improvements in substance misuse may have buffered against subacute mood drops; however, Borissova et al. (2020) found that even without therapy there were no mood drops after clinically administered MDMA. The results are consistent with other research indicating that euphoric and transformative experiences, such as those induced by MDMA, may be followed by periods of afterglow (Freye, 2009). The discrepant results with recreational studies could potentially be explained by the increased emphasis on preparation and set and setting in clinical environments. Altogether, the findings support that when administered clinically, patterns of usage can be managed, and potential risks associated with repeated dosing are reduced. Although our sample size may have been too small to detect an effect on this measure, the results are in line with findings from Phase II and III clinical trials for MDMA therapy for PTSD, which have found that only a small minority of participants reported seeking illicit MDMA after being exposed to the substance in the study (Jerome et al., 2020; Mitchell et al., 2021). Critically, our results provide novel evidence that MDMA therapy can be incorporated into populations characterized by substance misuse without leading to drug-seeking behaviours.

Limitations

Although the current study sought to rule out confounds that have obfuscated the previous MDMA literature, it is not without limitations of its own. First, as this was an exploratory trial for MDMA therapy for AUD, it was mandated by the MHRA that the

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**Table 2. ANOVA table for PSQI scores.**

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
<th>Mean</th>
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<th>SE</th>
<th>95% CI</th>
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<td>Lower Bound</td>
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<tr>
<td>Baseline</td>
<td>14</td>
<td>9.6</td>
<td>4.1</td>
<td>1.1</td>
<td>7.2</td>
<td>11.9</td>
<td>3</td>
</tr>
<tr>
<td>3 months post-MDMA</td>
<td>14</td>
<td>7.1</td>
<td>4.5</td>
<td>1.2</td>
<td>4.5</td>
<td>9.7</td>
<td>2</td>
</tr>
<tr>
<td>6 months post-MDMA</td>
<td>14</td>
<td>7.1</td>
<td>4.7</td>
<td>1.3</td>
<td>4.4</td>
<td>9.9</td>
<td>1</td>
</tr>
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CI: confidence interval.
study use an open-label design with a small sample size. However, the study was adequately powered to detect improvements in sleep quality as well as mood based on recreational studies with MDMA (Parrott and Lasky, 1998). Another limitation is that alcohol and illicit MDMA abstinence were measured by self-report rather than verified with biomarkers. Finally, future research is needed to test if the observed effects generalize to healthy individuals administered MDMA in a clinical setting or if the benefits reported here are indirectly facilitated by MDMA through improvements in substance misuse. Borissova et al. (2020) found that healthy individuals did not experience mood changes during the 3 days after clinically administered MDMA, but further studies are needed to see if the improvements in sleep quality reported here generalize as well.

**Conclusion**

Altogether, the current study supports that many of the post-acute risks that have historically been associated with MDMA may not be relevant when the drug is administered in a clinical setting. We conclude that there is no observable decline in mood after controlled dosing of MDMA in clinical settings.

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**Declaration of conflicting interests**

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