Original Paper

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder

Journal of Psychopharmacology
1–9

DOI: 10.1177/0269881121991792
journals.sagepub.com/home/jop
SAGE

Ben Sessa[1], Laurie Higbed[1], Steve O'Brien[1], Claire Durant[1], Chloe Sakal[2], Daniel Titheradge[3], Tim M Williams[4], Anna Rose-Morris[4], Elsa Brew-Girard[4], Sam Burrows[4], Chantelle Wiseman[5], Sue Wilson[1], James Rickard[6] and David J Nutt[1,2]

Abstract

Background: 3,4-methylenedioxymethamphetamine (MDMA) therapy has qualities that make it potentially well suited for patients with addictions, but this has never been explored in a research study. We present data from the Bristol Imperial MDMA in Alcoholism (BIMA) study. This is the first MDMA addiction study, an open-label safety and tolerability proof-of-concept study investigating the potential role for MDMA therapy in treating patients with alcohol use disorder (AUD).

Aims: This study aimed to assess if MDMA-assisted psychotherapy can be delivered safely and can be tolerated by patients with AUD post detoxification. Outcomes regarding drinking behaviour, quality of life and psychosocial functioning were evaluated.

Methods: Fourteen patients with AUD completed a community alcohol detoxification and received an eight-week course of recovery-based therapy. Participants received two sessions with MDMA (187.5 mg each session). Psychological support was provided before, during and after each session. Safety and tolerability were assessed alongside psychological and physiological outcome measures. Alcohol use behaviour, mental well-being and functioning data were collected for nine months after alcohol detoxification.

Results: MDMA treatment was well tolerated by all participants. No unexpected adverse events were observed. Psychosocial functioning improved across the cohort. Regarding alcohol use, at nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox. This compares favourably to a previous observational study (the 'Outcomes' study) by the same team with a similar population of people with AUD.

Conclusions: This study provides preliminary support for the safety and tolerability of a novel intervention for AUD post detox. Further trials to examine better the therapeutic potential of this approach are now indicated.

Keywords
MDMA, alcohol use disorder, psychotherapy, alcoholism, psychedelics

Introduction

Alcohol use disorder

Drinking is a socially acceptable behaviour. The majority of people consume alcohol without significant problems, but a growing number drink in a harmful manner. Alcohol use disorder (AUD; (American Psychiatric Association (APA), 2013) encompasses a broad spectrum of clinical presentations related to harm associated with alcohol use. Approximately 24% of the adult population of England consume alcohol harmfully, with about 6% of men and 2% of women meeting the criteria for alcohol physical dependence. AUD is characterised by often serious withdrawal symptoms on the cessation of alcohol, drinking to avoid withdrawal symptoms, tolerance, the persistent desire to drink and continuing drinking despite negative consequences (NICE, 2011). The impact of alcohol misuse is widespread, encompassing alcohol-related illness and injuries, as well as significant social impact on family, friends and the wider community. Patients with AUD frequently have a past history of psychological trauma and commonly

[1]Imperial College London, Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, London, UK
[2]Drug Science, London, UK
[3]School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
[4]Avon and Wiltshire NHS Foundation Trust, Bath, UK
[5]Centre for Academic Mental Health, School of Medicine, University of Bristol, Bristol, UK
[6]Biotherapy Services, London, UK

Corresponding author:
Ben Sessa, Division of Brain Sciences, Faculty of Medicine, Imperial College London, Centre for Neuropsychopharmacology, Dorothy Hodgkin Building, Whitson Street, London, SW7 2AZ, UK.
Emails: bensessa@gmail.com; b.sessa@imperial.ac.uk

present with high levels of depression, social anxiety and social exclusion, having become dependent upon alcohol as a form of self-medication (Castillo-Carniglia et al., 2019). Furthermore, in the context of the current coronavirus disease 2019 pandemic, attention to the issue of the best management of AUD has become even more pertinent (Clay and Parker, 2020).

Traditional treatments for AUD include medical and psychosocial interventions. Pharmacological options include acamprosate, naltrexone, nalmefene and disulfiram, which reduce cravings and deter relapse respectively (Krampe et al., 2006; Paille and Martini, 2014; Rösner et al., 2010; Soyka and Rösner, 2008). Benzodiazepines are commonly prescribed as part of alcohol detoxification programmes (Lingford-Hughes et al., 2012). Large-scale studies of psychosocial interventions have emphasised the importance of psychotherapies and non-pharmacological supports (Anton et al., 2006; Miller and Wilbourne, 2002; Project MATCH Research Group, 1998; UK Alcohol Treatment Trial (UKATT) Research Team, 2005). In recent years, mindfulness techniques have been increasingly explored as a potential approach to assist recovery through interrupting the tendency to respond to stress with alcohol use and not to react automatically to cravings (Marcus and Zgierska, 2009).

3,4-methylenedioxymethamphetamine

3,4-methylenedioxymethamphetamine (MDMA) is a phenethylamine that raises levels of monoamine neurotransmitters in the brain. MDMA elevates mood, increases sociability and feelings of closeness to others, and can facilitate imagination and memory (Sessa et al., 2019). Evidence from neuroimaging studies shows a decrease in amygdala/hippocampus activity (Carhart-Harris et al. (2014) and an association between reduced amygdala activity and improved ability to process negative memories (Carhart-Harris et al., 2013). Together with changes in social cognition, interpersonal closeness and communication, these data support the proposition that MDMA could be of benefit as an adjunctive psychotherapeutic treatment for alcohol addiction and co-morbid psychological disorders (Sessa, 2018). The use of MDMA-assisted psychotherapy to manage post-traumatic stress disorder (PTSD) has been explored since the 1980s (Greer and Tolbert, 1998). More recently, long-term follow-up data from the first completed trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD has found statistically and clinically significant gains in symptom relief, with no subjects reporting harm from participation in the study (Mithoefer et al., 2010, 2013). The US-based research group, the Multidisciplinary Association for Psychedelic Studies (MAPS), has published favourable results of its Phase II studies (Mithoefer et al., 2019). MAPS is now in the Phase III stage of medicine development, with anticipated licensing and Food and Drug Administration approval in the USA expected by late 2022 to early 2023. European approval by the European Medicines Agency is anticipated by 2023.

Potential risks associated with MDMA as an adjunct to psychotherapy

Rarely, users of clinical MDMA experience an increase in anxiety associated with derealisation-type experiences (Mithoefer et al., 2010). Acute neurocognitive effects include a transient reduction in verbal and visual memory, which tend to resolve after the drug has worn off (Kuypers and Ramaekers, 2007). MDMA misuse potential needs to be borne in mind when proposing giving the drug to a population with pre-existing addiction issues. However, in studies where MDMA has been administered clinically in a therapeutic setting to healthy volunteers without any previous experience with ecstasy, subjects did not express a wish to use it outside of the clinical setting (Mithoefer et al., 2013). Taken together, these findings suggest that clinically administered MDMA is not likely to result in problematic use (Jerome et al., 2013). In order to monitor the risk of patients using MDMA outside of the study, we monitored their use or desire to use illicit ecstasy with specific questions pertaining to this issue asked in the final (session 10) therapy session.

Clinical MDMA increases blood pressure, heart rate and body temperature (Harris et al., 2002) and causes jaw tightness, bruxism, reduced appetite, poor concentration and impaired balance (Mithoefer et al., 2010). Despite historical reports of neurocognitive deficits in recreational ecstasy users, contemporary studies have failed to demonstrate any significant long-term neurotoxicity associated with recreational ecstasy when use of other recreational drugs is controlled for (Hanson and Luciana, 2010; Selvaraj et al., 2009). There have been no reports of long-term neurotoxicity or neurocognitive impairments when pure MDMA has been administered in a controlled clinical setting (Mithoefer et al., 2013).

Methods

Approvals and drug source

This trial, sponsored and approved by Imperial College London, received a favourable opinion from the Central Bristol Research Ethics Committee of the National Research Ethics Service and 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 obtained from Sterling Pharmaceuticals (Newcastle) and formulated into the investigational medicinal product (62.5 mg MDMA in gelatine capsules) by the Pharmacy Manufacturing Unit at Guy's and St Thomas' NHS Foundation Trust (London, UK).

Study design

This was an open-label, within-subjects, safety and tolerability feasibility study in 14 patients aged 18–65 years with AUD who had recently undergone detoxification. All patients received MDMA-assisted therapy. The main outcome measures were the number of patients completing the eight-week psychotherapy course, the number accepting the second booster dose of MDMA on drug-assisted days and adverse events. Secondary outcome measures included changes in drinking behaviour (measured by units per week consumed at three, six and nine months since completion of detoxification), measures of mental well-being, psychosocial functioning, quality of life and concomitant drug use.

Patients with a primary diagnosis of AUD who were seeking detoxification – with or without medical assistance – were recruited from the North Somerset Substance Misuse Service (Addaction). Patients received an eight-week course of recovery-based therapy

comprising 10 psychotherapy sessions. On two of these (sessions 3 and 7), patients were dosed with open-label MDMA during a six- to eight-hour assisted therapy session. On each dosing session, participants received an initial oral dose of 125 mg MDMA, followed two hours later by a booster dose of 62.5 mg MDMA. The booster dose served to prolong the experience, allowing for greater time for psychotherapy under the influence of the drug.

Other sessions (sessions 1, 2, 4, 5, 6 and 8–10) comprised one-hour psychotherapy sessions, employing aspects of motivational interviewing and 'third-wave' cognitive–behavioural approaches. Patients remained in the study for approximately 10 months.

Inclusion criteria

The inclusion criteria were as follows:

- Informed consent.
- Primary diagnosis (as defined by DSM-IV) of AUD.
- Successful alcohol detoxification (no longer consuming any alcoholic substances).
- Between 18 and 65 years old.
- Able to identify in advance a supportive significant other(s) who could accompany them to study visits if required and be contacted by the study team in the event that the patient could not be contacted.
- Proficient in speaking and reading English.
- Agree to comply with requirements of protocol.

Exclusion criteria

The inclusion criteria were as follows:

- Lacking capacity.
- History of, or a current, primary psychotic disorder, bipolar affective disorder type 1 or personality disorder.
- A serious suicide risk as determined by the Columbia-Suicide Severity Risk Scale (C-SSRS).
- Relevant abnormal clinical findings at screening visit judged by the investigator to render the subject unsuitable for study, including but not limited to a history of cardiac disease, hypertension and stroke, severe liver disease, a history of epilepsy or a history of malignant hyperthermia (central core disease).
- Regular user of ecstasy (material represented as containing MDMA), for example more than five times in the last five years or at least twice in the six months prior to the start of the study.
- Currently taking or unwilling/unable to stop any medications likely to interact with MDMA in the opinion of the investigators during the eight-week MDMA-assisted therapy.
- Regular use of/dependence on other drugs such as benzodiazepines, synthetic cannabinoids, cocaine and heroin.
- Female participants of childbearing age/potential must use an effective form of birth control for at least six days after administration of MDMA, and must not be pregnant and/or breast-feeding until the end of the treatment phase.
- For males with partners of childbearing age/potential, participants must themselves confirm use of an effective form of birth control for at least six days after administration of MDMA and confirm their partner will also.
- Taken part in a study involving an investigational product in the last three months.
- Patients who might face additional risks from immunosuppression (e.g. patients with immunological diseases or patients with active infection or history of infections within four weeks of MDMA administration).

AUD was identified using the DSM-IV SCID interview. Screening comprised of written informed consent, an evaluation of the patient's physical and mental health background, a psychiatric interview (MINI) and assessments of depression and anxiety severity using the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder Assessment (GAD-7) questionnaires. Severity of AUD was established using the Severity of Alcohol Questionnaire (SADQ) and the Short Inventory of Problems for Alcohol (SIP) questionnaire. Patients received a thorough physical health check comprising an electrocardiogram, routine blood tests, blood pressure, heart rate and physical examination. Following screening, eligible patients underwent the process of detoxification either by gradually cutting down alcohol consumption over many weeks or with a medically assisted detoxification regime. The majority of participants were also taking medications for anxiety and/or depressive symptoms (e.g. selective serotonin reuptake inhibitors). According to the inclusion/exclusion criteria, associated medications known to attenuate the effects of MDMA were subsequently gradually reduced and stopped under medical supervision ahead of the first MDMA session. A further 'baseline' visit clarified successful detoxification using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) questionnaire before eligible participants entered the eight-week course of psychotherapy. This entailed weekly 60-minute outpatient non-drug psychotherapy sessions delivered by two clinicians (B.S. and L.H.) trained in delivering MDMA-assisted psychotherapy by the USA-based organisation MAPS.

Dosing with MDMA occurred twice during the eight-week course on weeks 3 and 6. Physiological changes, observer and subject ratings of distress (Subjective Units of Distress (SUDS)) and the intensity of MDMA's acute psychoactive effects were measured throughout the drug-assisted session. Acute anxiety was managed primarily psychologically, but sedative medication (oral lorazepam) was available. Participants remained overnight in the treatment centre after each drug-assisted session, overseen by medically trained 'night sitters' who were on hand to support participants as required but instructed to avoid delivering any psychotherapeutic interventions.

Participants were seen the morning after each drug-assisted session for an integration psychotherapy session, and then telephoned daily for six days to assess changes to mood, suicidal risk factors (using the C-SSRS) and quality of sleep (using the Leeds Sleep Evaluation Questionnaire). Following the end of the eight-week therapeutic course, participants carried out additional follow-up questionnaires. They were then seen again at three, six and nine months (since baseline) for longer-term follow-up data collection.

Data analysis

All data were recorded on paper case report forms and then digitized into MS Excel spreadsheets. Analysis and graphing were

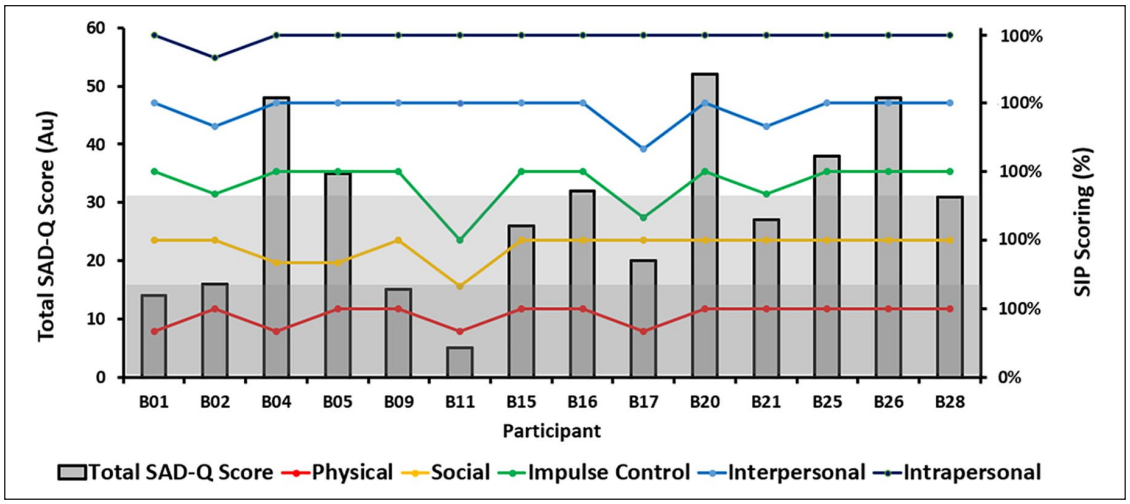

Figure 1. Severity of Alcohol Questionnaire (SADQ) measures alcohol dependency (Au = arbitrary units). Short Inventory of Problems for Alcohol (SIP) is a 15-question measure of self-noted consequences of drinking. Both were observed at screening. SIP categories are separated each between 0% and 100% on the second *y*-axis. A score of 31 or higher indicates severe alcohol use disorder (AUD) severity. A score of 16–30 indicates moderate AUD severity (light-grey area). A score lower than 16 indicates mild AUD severity (dark-grey area). Four SADQ questions were unanswered, in which case, mean substitution was applied using the average row value for the relevant time period and participant. B05, B16, B20 and B21 had one question missing each.

performed using GraphPad Prism Prism version 8.4.3 (GraphPad Software LLC, La Jolla, CA) or MS Excel. As this was a non-randomised, controlled, open-label study, no hypothesis testing was performed. When calculating timeline follow-back results, alcohol consumption levels at last observation were used in the case of drop-outs or when participants had undertaken a second detoxification (Hamer and Simpson, 2009).

Results

Demographics

Thirty-six participants attended face-to-face screening visits, and 14 were enrolled (8 males and 6 females; $M_{age} = 48$ years). All were white British. Four were employed, nine were unemployed and one was retired. The average age of first alcohol use was 13 years old. The average age when alcohol became problematic was 34 years old. Nearly two-thirds (64%) of participants reported a history of alcohol-related blackouts, 14% had experienced alcohol withdrawal–induced seizures, 86% of participants reported having experienced risky or vulnerable incidences due to alcohol and 75% of participants had had forensic/offending behaviour secondary to their alcohol use.

Severity of AUD criteria at screening and baseline

As per the inclusion criteria, all eligible patients scored above the diagnostic threshold on the DSM-5 SCID questionnaire for AUD. We also measured AUD severity using the SIP questionnaire and the SADQ questionnaire (Figure 1), with most eligible participants in the moderate to severe range. At the baseline visit (within one week of detox completion), 100% of eligible participants had successfully completed detoxification, which was assessed using the CIWA scale.

Physiological and tolerability effects during MDMA sessions

Of the 14 participants, 12 received both sessions of MDMA-assisted psychotherapy. So, in total, 26 drug-assisted psychotherapy sessions with MDMA were administered during the trial. Temperature, blood pressure and heart rate were measured at $t = 0$, before taking the medicine, then half-hourly up to $t = 2$ hours, then hourly thereafter for a minimum of six hours from the time of dosing (Figure 2).

Except for one participant, all of these physiological parameters remained within normal limits for all these sessions. As expected, we saw a mild transient rise in blood pressure, temperature and heart rate over the course of the MDMA session. No patients experienced sustained abnormal physiological disturbance, symptomatic experiences of raised blood pressure, heart rate or temperature or any other adverse events during MDMA sessions. No medical interventions were required in respect of these or any other physiological events during MDMA sessions. One participant experienced a transient abnormal rise in blood pressure after taking the initial dose of 125 mg MDMA, reaching 183/118 mmHg at two hours after dosing, attributed to the participant forgetting to take her regular antihypertensive medication on the morning of dosing. Although she was asymptomatic and no medical intervention was required, it was decided to withhold the two-hour supplemental dose. Her blood pressure subsequently spontaneously returned to normal in the following two hours, and she agreed with the study team to omit the booster dose of MDMA on that day. She did, however, receive her second MDMA session three weeks later (after taking her antihypertensive medication in advance appropriately), which was uneventful in terms of blood pressure. Another participant only received her first MDMA session. She subsequently relapsed back to heavy drinking in the context of personal psychosocial issues unconnected with the study, and therefore she chose not to have her second MDMA session.

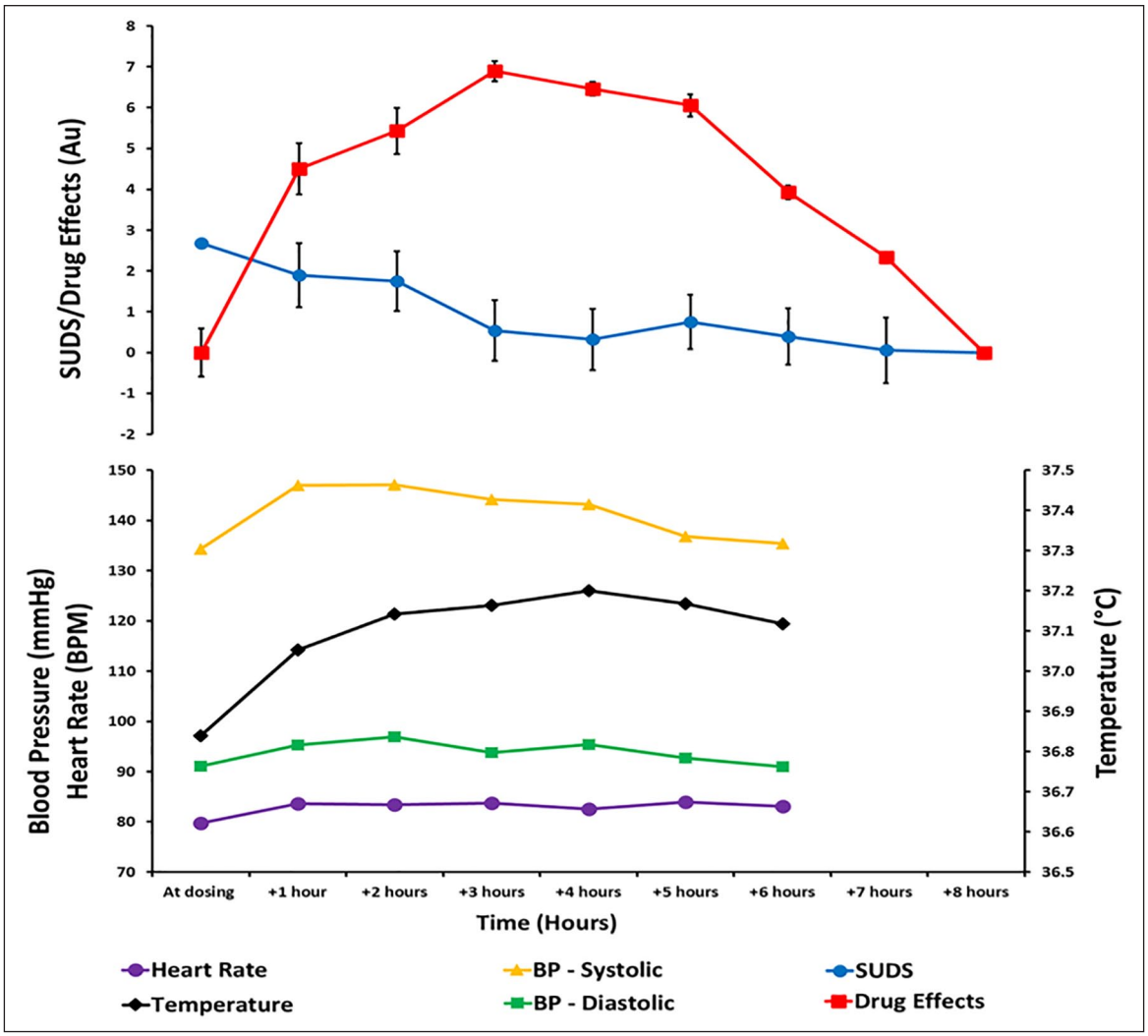

Figure 2. Pooled data of blood pressure, temperature, heart rate, observed drug effects and Subjective Units of Distress (SUDS) observed over the duration of the MDMA sessions. SUDS and drug effects observed over eight hours; physiological data observed over six hours following dosing. Mean data for each session are used, except in the case of missing data, where available session data are applied. Error bars (where applied) indicate ±standard error of the mean (SEM).

Subjective Units of Distress (SUDS) and participant report of drug effects were also measured hourly throughout the MDMA sessions (Figure 3). Most subjects predictably reported mildly raised SUDS scores at the beginning of the sessions before taking MDMA – consistent with expected anxiety ahead of dosing – which subsequently reduced during the course of the session as the positive effects of MDMA emerged. Participants gave their own subjective score (0–10) of whether they felt drug effects, and the therapists also recorded their own objective score of how 'altered' the participant appeared. There was no significant difference between observers' and participants' drug effects scores. Drug effects rose expectedly over the first two hours, with a notable further increase after the booster dose was given at $t=2$ hours, and a subsequent plateau and then decline over the following six hours. By the end of the MDMA session day, all drug effects had returned to baseline. No participants reported any significant neurocognitive impairments associated with receiving MDMA in the weeks and months following participation in the study.

Changes in drinking behaviour

Whilst changes in drinking behaviour were not a primary outcome measure, we nevertheless collected data in respect of units of alcohol consumed per week in the month before participants' detoxification, immediately after detox ('baseline'), throughout the eight-week MDMA therapy course and for up to nine months after detox. Of the 14 eligible participants who underwent the course of MDMA-assisted psychotherapy, at the nine-month follow-up end point, 11 participants were drinking fewer than 14 units of alcohol per week (including nine who were totally abstinent from alcohol), and three participants had relapsed to drinking more than 14 units of alcohol per week. On average, participants were drinking 130.6 units of alcohol per week in the month before detoxification, and no units at the point of detox. After nine months, the average amount of consumed alcohol had risen back to 18.7 units per week (Figure 3).

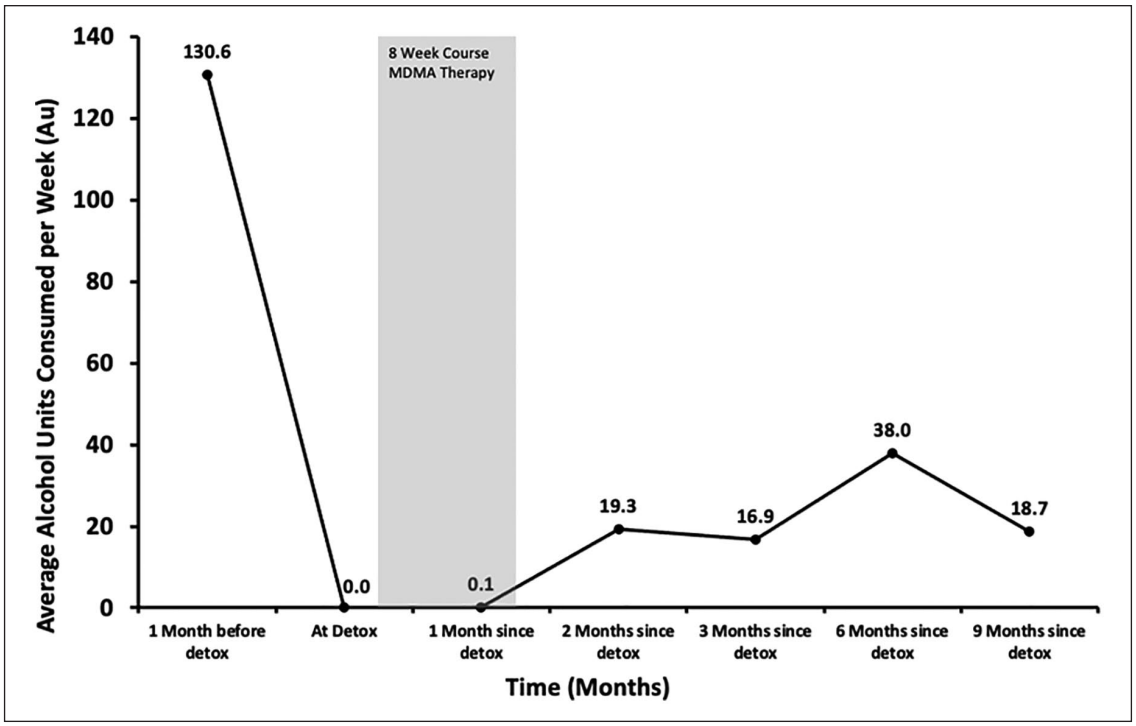

Figure 3. Timeline follow back (TLFB) assesses drinking behaviour prior to and following the study. Data are collected daily by self-reporting and reviewed at one month prior to detox, immediately following detox and at one, three, six and nine months follow-up. A full data set was not available for three of the participants. One participant dropped out of the study at three months, and two patients failed to provide data at the nine-month follow-up. Two participants had a second detox since starting the study. For these participants, TLFB drinking behaviour data were carried forward from the point of drinking levels before the second detox.

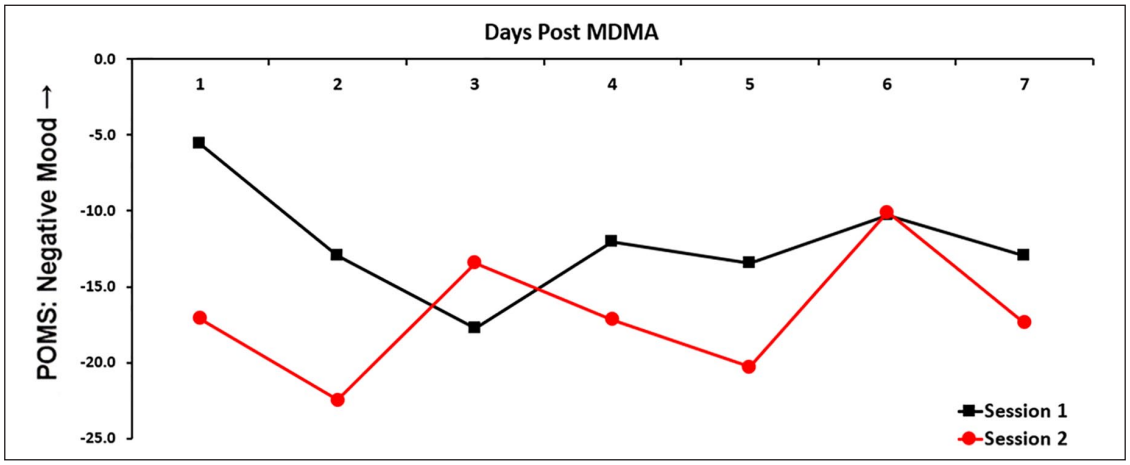

Figure 4. Profile Of Mood States (POMS). Individual composite scores of mood disturbance observed daily over a week following dosing. Mean data shown for both MDMA sessions. In the case of absent data for either session, the available data for the remaining session are used.

Seven-day follow-up after MDMA sessions

Considerable medical literature and the popular press report the anecdotal observation of ecstasy users experiencing an acute 'come-down' effect and a drop in mood in the days after using the drug recreationally. In order to measure this prospectively with clinical MDMA, we measured participants' mood states by daily Profile Of Mood States measurements for seven days after each MDMA session (Figure 4). Positive scores represent depressed affect, zero represents no change in mood/affect and results below zero represent a positively felt mood. Average scores across both MDMA sessions for all 14 participants (26 MDMA sessions) revealed no evidence of any mood disturbance during the week after taking each session of clinical MDMA. Indeed, participants sustained a positive mood for seven days. This result contrasts with anecdotal reports from recreational ecstasy users.

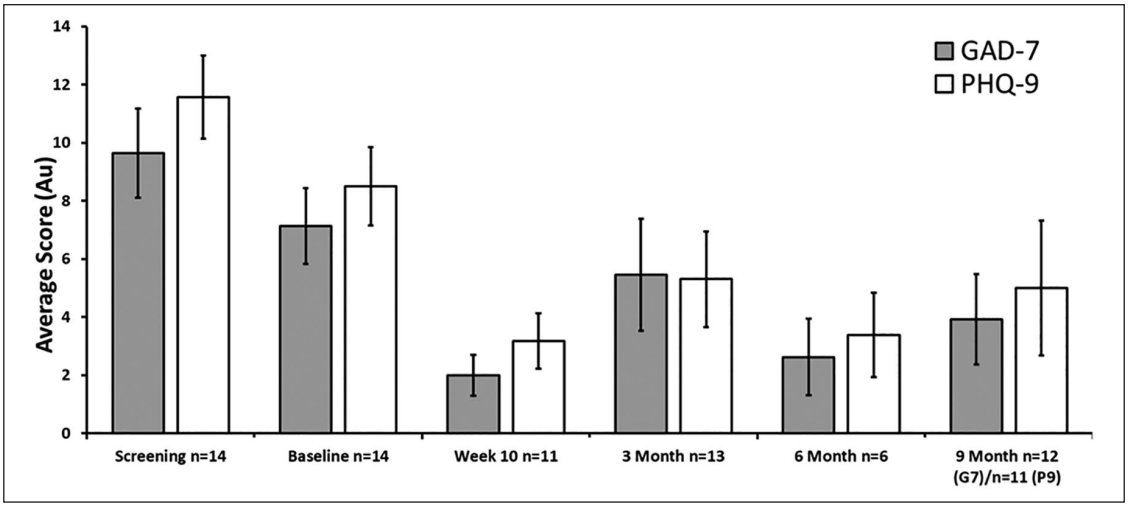

Figure 5. General Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9). Self-report scales for anxiety and depression, respectively. Recorded at screening, baseline and week 10, and then at three, six and nine months of follow-up. Greater scores report indication of heightened anxiety/depression. Error bars indicate ±SEM.

Other mental health measures and quality of life measures

Brief assessments of mood and anxiety were made at screening, baseline, after the eight-week MDMA therapy course and at the three-, six- and nine-month follow-ups using the PHQ-9 and GAD-7 rating scales, respectively (Figure 5). Scores demonstrated a reduction in both anxiety and depression after screening and baseline time points, followed by a transient rise in anxiety and depression scores three months after baseline, a further reduction at six months and a moderate rise again at nine months post detox.

Suicidality

Participants underwent the C-SSRS at screening, baseline, throughout the eight-week therapy course, in the week after each MDMA session and at the three-, six- and nine-month follow-up visits. No participants reported current suicidal ideation, intent or plans or self-harm behaviour during the course of the study

Adverse events

The acute effects of MDMA-assisted psychotherapy were well tolerated by participants. No unexpected adverse events occurred. No participants reported any desire to use illicit ecstasy/illicit MDMA following receiving clinical MDMA as part of this trial. No psychotic symptoms were observed in any of the patients.

A variety of further data were collected, including changes to the quality of sleep, quality of life measures and changes to compassion and empathy scales, which will be published in forthcoming papers.

Discussion

In this first safety and tolerability study, we demonstrate that MDMA-assisted psychotherapy could be useful in treating AUD, probably through its capacity to enhance the psychotherapeutic process or indirectly through augmenting the treatment of comorbid psychological conditions commonly associated with AUD (Jerome et al., 2013).

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of harmful use of alcohol. Recreational MDMA users have reported improved intrapersonal attitudes and prosocial attitudes towards the self, which could be a mechanism by which the drug enhances psychotherapy, especially for patients with pre-existing histories of trauma (Stolaroff, 2004). Similarly, Mithoefer et al. (2010) described MDMA's capacity to 'make yourself present in the moment' – a core concept of mindfulness. Drug-assisted psychotherapies with the 'classic' psychedelic compounds LSD and psilocybin utilise the induced subjective mystical/spiritual effects of the psychedelic experience and have found the depth of this experience is strongly associated with maintained recovery from harmful substance use (Sessa and Johnson, 2015). However, not all patients are able or willing to tolerate the classic psychedelic experience, and compliance is a critical aspect of addiction therapy. Whilst there is also an, albeit minimal, subjective spiritual/mystical experience associated with MDMA (Sumnall et al., 2006), it is generally better tolerated than the classic psychedelics, with fewer perceptually disturbing effects compared to LSD and psilocybin. Therefore, MDMA offers an alternative opportunity for enhanced psychotherapy in patients with AUD.

Prior to carrying out the BIMA study, the same study team carried out a non-interventional observational study, following 14 participants through their treatment-as-usual post-alcohol detox (the 'Outcomes Study'; Sessa et al., 2020). The eligibility criteria and questionnaires used in the Outcomes Study were similar to the BIMA study in respect of assessment of AUD, severity of AUD, success of detoxification and follow-up of outcomes in respect of mental health issues and drinking behaviours – measured at three, six and nine months post detox but without the additional eight-week therapeutic course with MDMA-assisted psychotherapy,

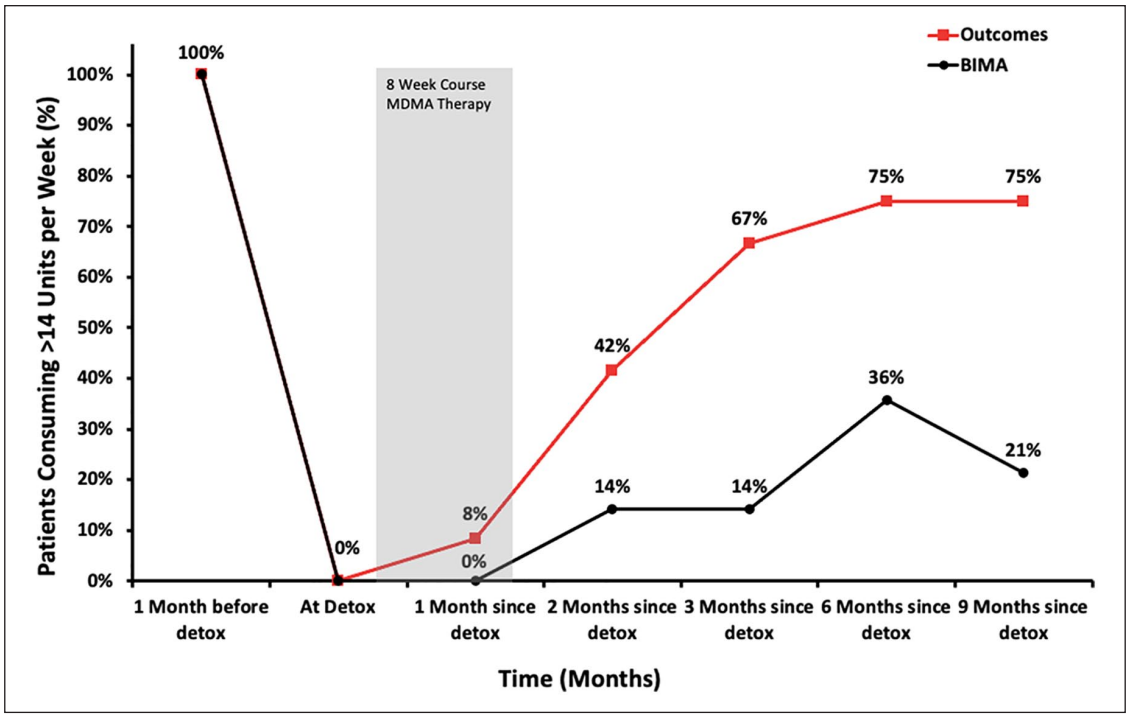

Figure 6. TLFB showing % of patients consuming more than the 14 recommended daily units of alcohol (Sessa et al., 2020).

which occurred post detox. Whilst it is not appropriate to compare these two studies statistically, as patients were not randomised into the studies, Figure 6 demonstrates the success of BIMA participants in terms of alcohol consumption over nine months compared to current best treatments available locally. Only 21% of participants who had undergone MDMA-assisted psychotherapy were drinking in excess of 14 units of alcohol a week in comparison with the 75% observed in the Outcomes Study.

Limitations

The BIMA study had a relatively small sample size. As directed by the MHRA, given that the study was exploring a first-time drug intervention in a previously unexplored clinical population, it was an open-label, non-placebo-controlled study. Therefore, all patients knew they would be getting MDMA. Whilst efforts were made to test objectively for alcohol use using regular breath alcohol analysis, review participants' medical notes throughout the study and carry out Gamma-GT blood tests post course, all data represented above were nonetheless reliant primarily on retrospective self-report. The study team considered other techniques to assess alcohol use objectively, such as worn alcohol sweat meters, but given that efficacy (drinking outcome) was not a primary outcome measure, this was concluded to be overly intrusive for this type of study.

Conclusion

In summary, this study demonstrates that MDMA-assisted psychotherapy can be safely delivered, is well tolerated and has the potential to enhance and intensify the psychotherapeutic processes in the treatment of patients with AUD. MDMA, given in a psychotherapeutic context, may reduce avoidance of emotionally distressing thoughts, images or memories of alcohol misuse while increasing empathy for the self and others. It may also address symptoms of other conditions that are frequently co-morbid with harmful use of substances, particularly those symptoms associated with a history of psychological trauma.

A logical next step would be to carry out a placebo-controlled randomised controlled trial in which the level of therapist contact is consistent between conditions. This would enable any between-group differences in clinical outcomes to be attributed to MDMA rather than to the psychological support provided.

Acknowledgements

We also wish to express thanks to Minirigs – the Bristol-based electronics company that provided the stereo equipment for the experimental sessions. We are grateful to Dr Mendel Kaelen, who provided the playlists for the MDMA therapy sessions. Thank you to all the staff at the Clinical Research and Imaging Centre (particularly Jade, Cathy and Hannah). Enormous gratitude to the local staff and the research and development team at Addaction, without whose support this project would never have happened. In particular, we thank our expert user, Mr Kevin Speller. The staff at MAPS – especially Rick Doblin, Michael Mithoefer and Ilsa Jerome – provided essential support and guidance throughout the project – including provision of the IB and ongoing advice regarding MDMA pharmacology and therapeutic issues. We are grateful to Dr James Rickard, Chief Scientific Officer at Biotherapy Services, for providing pharmacy support, to Dr Tim White (at Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit, London, UK) for production of the IMP and to Dr Liz McCullough at BRI pharmacy for storing and dispensing the study medication. And finally, we are extremely grateful to the pool of local junior doctors who gave their time to act as post-MDMA night sitters after each of the participants drug-assisted sessions, including Sakal, C., (night sitters lead), Titheradge, D., Rose-Morris, A., Brew-Girard, E., Alderton, K.,

Burrows, S., Secker, A., Loysen, S., Hall, K., Lilford, P., Flowers, J., Wright, L., Roberts, R., Lawton, S., Meyer, A., Salter, E., Guy, J., Brown, R. and Rifkin-Zybutz, R. Most importantly, we extend enormous gratitude to the patients who participated in this study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The authors are grateful to the Alexander Mosley Charitable Trust for the entire funding of the study.

ORCID iDs

Ben Sessa https://orcid.org/0000-0002-1212-6060
Chantelle Wiseman https://orcid.org/0000-0002-0146-3969

References

American Psychiatric Association (APA) (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, DC: APA.

Anton RF, O'Malley SS, Ciraulo DA, et al. (2006) Combined pharmacotherapies and behavioural Interventions for alcohol dependence. The COMBINE study: a randomized controlled trial. *JAMA* 293: 2003–2017.

Carhart-Harris RL, Murphy K, Leech R, et al. (2014) The effects of acutely administered MDMA on spontaneous brain function in healthy volunteers measured with arterial spin labelling and BOLD resting-state functional connectivity. *Biol Psychiatry* 78: 554–562.

Carhart-Harris RL, Wall MB, Erritzoe D, et al. (2013) The effect of acutely administered MDMA on subjective and BOLD fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol* 17: 527–540.

Castillo-Carniglia A, Keyes KM, Hasin DS, et al. (2019) Psychiatric comorbidities in alcohol use disorder. *The Lancet Psychiatry*, 6: 1068–1080.

Clay JM and Parker MO (2020) Alcohol use and misuse during the COVID-19 pandemic: a potential public health crisis? *Lancet Public Health* 5: e259.

Greer GR and Tolbert R (1998) A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs* 30: 371–379.

Hamer R and Simpson P (2009) Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials. *Am J Psychiatry* 166: 639–641.

Hanson KL and Luciana M (2010) Neurocognitive impairments in MDMA and other drug users: MDMA alone may not be a cognitive risk factor. *J Clin Exp Neuropsychol* 32: 337–349.

Harris DS, Baggott M, Mendelson JH, et al. (2002) Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* 162: 396–405.

Jerome L, Schuster S and Berra Yazar-Klosinski B (2013) Can MDMA play a role in the treatment of substance abuse? *Curr Drug Abuse Rev* 6: 54–62.

Krampe H, Stawicki S, Wagner T, et al. (2006) Follow-up of 180 alcoholic patients for up to 7 years after outpatient treatment: impact of alcohol deterrents on outcome. *Alcohol Clin Exp Res* 30: 86–95.

Kuypers KP and Ramaekers JG (2007) Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected. *Psychopharmacology* 189: 557–563.

Lingford-Hughes AR, Welch S, Peters L, et al. (2012) BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *J Psychopharmacol* 26: 899–952.

Marcus MT and Zgierska A (2009) Mindfulness-based therapies for substance use disorders: part 1 (Editorial). *Subst Abus* 30: 263.

Miller WR and Wilbourne PL (2002) Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 97: 265–277.

Mithoefer MC, Feduccia AA, Jerome L, et al. (2019) MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six Phase 2 randomized controlled trials. *Psychopharmacology* 236: 2735–2745.

Mithoefer MC, Wagner TM, Mithoefer AT, et al. (2010) The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* 25: 439–452.

Mithoefer MC, Wagner MT, Mithoefer AT, et al. (2013) Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependence after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow- up study. *J Psychopharmacol* 27: 28–39.

NICE (2011) *Alcohol-use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence*. NICE clinical guideline 115. Available at: www.nice.org.uk/CG115 (accessed 1 June 2020).

Paille F and Martini H (2014) Nalmefene: a new approach to the treatment of alcohol dependence. *Subst Abuse Rehabil* 5: 87–94.

Project MATCH Research Group (1998) Matching alcoholism treatments to client heterogeneity: Project MATCH three year drinking outcomes. *Alcohol Clin Exp Res* 22: 1300–1311.

Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010) Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* CD004332.

Selvaraj S, Hoshi R, Bhagwagar Z, et al. (2009) Brain serotonin transporter binding in former users of MDMA ('ecstasy'). *Br J Psychiatry* 194: 355–359.

Sessa B (2018) Why MDMA therapy for alcohol use disorder and why now? *Neuropharmacology* 142: 83–88.

Sessa B and Johnson M (2015) Is there a role for psychedelics in the treatment of drug dependency? *Br J Psychiatry* 206: 1–3.

Sessa B, Higbed L and Nutt DJ (2019) A review of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. *Front Psychiatry* 10: 138.

Sessa B, Higbed L, O'Brien S, et al. (2020) How well are patients doing post-alcohol detox in Bristol? Results from the outcomes study. *J Alcohol Drug Depend Subst Abuse* 6: 021.

Soyka M and Rösner S (2008) Opioid antagonists for pharmacological treatment of alcohol dependence – a critical review. *Curr Drug Abuse Rev* 1: 280–291.

Stolaroff M (2004) *The Secret Chief Revealed: Conversations with a Pioneer of the Underground Therapy Movement*. Sarasota: Multidisciplinary Association for Psychedelic Studies, pp.45–49.

Sumnall HR, Cole J and Jerome L (2006) The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. *J Psychopharmacol* 20: 670–682.

UK Alcohol Treatment Trial Research Team (2005) Effectiveness of treatment for alcohol problems: findings of the randomised UK Alcohol Treatment Trial (UKATT). *BMJ* 311: 541–544.