Evaluating the attitudes of mental health professionals towards trials of MDMA: a randomised vignette trial

Dean J Wright, Ben Colagiuri, Nick Glozier

ABSTRACT

Objectives To compare attitudes of mental health (MH) professionals towards trials of methylenedioxyamphetamine-assisted psychotherapy (MDMA-AP), with a neutrally labelled pharmacotherapy trial.

Design A randomised controlled vignette study design, with experimenters blinded to group condition.

Setting Participants were recruited online via professional societies.

Participants Psychiatrists, psychologists and MH researchers from across Australia.

Interventions Participants were randomly allocated to read a vignette about a trial of either MDMA-AP or a neutrally labelled pharmacotherapy.

Outcomes Comparison of the difference in four attitudes towards MDMA-AP and control: How likely they were to (1) recommend participating, or (2) object to participating in the trial; (3) their predicted efficacy; and (4) concerns about the safety of the trial.

Results There were no overall differences between professional's attitudes towards MDMA-AP (n=51) and the control pharmacotherapy (n=43) trial vignettes. Psychiatrists were less likely to recommend participation in the MDMA-AP than the control trial (d=0.72, p=0.02), but did not differ in other attitudes. Psychologists and researchers did not differ in any attitudes. The correlation between professional experience and both: (1) concern about, and (2) strength of objection to, the trial, was higher for MDMA-AP, than control (d=0.60, p=0.01 and d=0.40, p=0.03, respectively).

Conclusions Psychiatrists, but not psychologists or researchers showed more hesitancy in recommending trials of MDMA-AP versus an unknown pharmacotherapy. Experienced MH professionals were more likely to have negative views about MDMA-AP trials than less experienced MH professionals. This may reflect the experience of prior unfulfilled pharmacotherapy innovation or exuberance associated with fewer years of practice. Research into, and implementation of, MDMA-AP may face barriers with certain MH professionals, which will need to be addressed if MDMA-AP continues to show promise as an efficacious treatment.

Trial registration number The study design was registered with the ANZCTR (ACTRN12620001068954).

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a debilitating illness with high personal, social and economic costs. Current treatments for PTSD have high drop-out rates and, for people with severe presentations, outcomes are poor.1-5 The recommended pharmacological treatments for PTSD display small reductions in PTSD symptoms.4-7 Exposure-based psychotherapies, like prolonged exposure (PE), are considered first-line treatments for PTSD.1 These therapies involve exposure and desensitisation to traumatic memories and generally show moderate to large reductions in Clinician-Administered PTSD Scale (CAPS) scores, compared with inactive controls.5 8-11 However, the process can be highly distressing, leading to high rates of attrition (drop-out range=0–45%; mean=23%), with 25%–50% showing no clinical improvement.1 Thus, novel treatments...
for PTSD are needed to help those who do not respond to currently available treatments.

3,4-Methylenedioxymethamphetamine-assisted psychotherapy (MDMA-AP) represents a novel approach to treatment, using acute administration of MDMA to enhance the psychotherapeutic process. All trials of MDMA-AP use an active psychotherapy control group, who receive an inactive placebo drug and the same psychotherapy as the treatment arm. The use of an inactive placebo means most participants to become unblinded once they consume MDMA, due to its significant psychoactive effect; thus, there is likely to be some uncontrolled placebo effect of MDMA-AP. This has been raised as a serious methodological concern with trials of many repurposed psychoactive compounds. To date, one phase-III and six phase-II trials of MDMA-AP have been conducted in people with chronic, treatment-resistant PTSD across eight countries in North America, Europe and the Middle East. Across all trials of MDMA-AP, there was only one serious adverse event (SAE) potentially attributable to MDMA. Trial data indicate that MDMA-AP is effective compared with active psychotherapy controls, with large between-groups reductions in CAPS score (range: d=0.91–1.17). A meta-analysis of phase-II results shows MDMA-AP to be as efficacious as PE. Notably, half of the PE studies used inactive psychotherapy controls, which not only increases between group differences, but again can also leave participants unblinded to treatment condition in much the same way that an inactive drug control can. Furthermore, none were investigated in treatment-resistant populations. Thus, it seems possible that MDMA-AP may show higher effect sizes than PE, if evaluated in equivalent populations with similar controls. Furthermore, the MDMA-AP studies showed significantly lower drop-out rates (13% vs 27%) and higher patient-rated outcomes than PE (d=0.87 vs 0.77). Thus, current studies show MDMA-AP is more tolerable and equally, if not more efficacious than PE, the current best treatment for PTSD. Furthermore, long-term follow-up of phase-II studies show remission rates increased 3 years after treatment finished, implying robust long-term effects.

Given the promising phase-III results, there is a chance MDMA-AP will be licensed for medical use by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2022. Australia has been lagging in trials of psychedelic research using MDMA, psilocybin and lysergic acid diethylamide (LSD) with only one current trial to our knowledge. Over recent years, a call-to-action has been made in Australian journals to engage in this field of research. Some researchers described experiencing resistance when attempting to establish trials of MDMA-AP in Australia, stating a proposed study was ‘vetoed by the deputy vice-chancellor’ of a university, before the application reached the ethics committee.

The current study seeks to assess whether there is bias among psychiatrists, psychologists, general practitioners (GPs) and mental health (MH) researchers, towards MDMA-AP research. We aimed to evaluate the attitudes of MH professionals towards a trial of MDMA-AP, by comparing them to attitudes towards a neutrally labelled pharmacotherapy trial, using a randomised, controlled vignette design. Secondary aims sought to understand if profession, age and experience, moderated any differences in attitudes.

METHODS

Design

A randomised controlled design was used to assess the differences in attitudes towards a trial of MDMA-AP compared with a trial of a neutrally labelled pharmacotherapy, labelled ‘JB-4801-AP’. Participants were blinded to the existence of a comparator vignette condition. BC coded and blinded experimental and control group data, prior to DW conducting the statistical analysis.

Participants

We aimed to recruit Australian MH professionals who may potentially be involved in the provision of, or research into, MDMA-AP in the future. This included registered psychiatrists, GPs and psychologists, and MH researchers. Sampling and recruitment

Participants were recruited through distribution of an advertisement and study URL to all psychiatrists, psychologists and MH researchers registered with peak professional bodies in Australia, and all GPs and MH professionals in Australian Primary Health Networks (see figure 1). The ad stated we were seeking to evaluate the ‘attitudes of psychiatrists, general practitioners, psychologists and mental health researchers towards new mental health treatments’ (full advertisement in online supplemental figure 1). Recruitment occurred from February 2020 to October 2020. Recruitment finished after achieving the required power for primary analyses. Only four GPs completed the study and thus, they were removed from the analysis. No incentives were provided for participation.

Procedure

Interested professionals were directed to an online survey, hosted within the online data collection software, Qualtrics (Qualtrics; Provo, Utah, USA). They were instructed to read the Participant Information Statement and Participant Consent Form. Once consented, participants started the survey and could not amend their previous answers after they progressed to the next stage. Participants were first required to answer demographic questions: age, gender, profession and years of experience. Participants were then randomised to either MDMA or control conditions, stratified by profession, using the Qualtrics algorithm. They were then instructed to read a vignette and answer questions about their views on the vignette. Participants were then asked potential moderator questions on a separate page, to avoid biasing previous answers.
Vignette interventions
Participants were asked to read a vignette of a hypothetical patient with a diagnosis of treatment-resistant PTSD, who is seeking advice about participating in a clinical trial assessing a novel pharmacotherapy treatment (see online supplemental methods 1). The vignettes were identical except for the descriptions of the treatments: (1) MDMA-AP group described as: ‘Methylenedioxyamphetamine (MDMA)-assisted psychotherapy for the treatment of PTSD, as part of a phase 3 clinical trial. MDMA is commonly known as the active chemical from the party drug ‘ecstasy’; 2) Control group described as: ‘JB-4801-assisted psychotherapy for the treatment of PTSD, as part of a phase 3 clinical trial. JB-4801 is a new drug being developed by the University’. Both vignettes said, “preliminary studies have suggested this treatment has worked for a high proportion of people with PTSD and has very low chance for negative side-effects”.

Assessments and outcomes
Participants were asked questions evaluating their attitudes towards the hypothetical clinical trial on a 10-point scale (see online supplemental methods 2). The four primary outcomes were: how likely they are to recommend participating in the trial; how strongly they would object to participating in the trial; the predicted efficacy of the trial; and concerns about the safety of the trial.

Participants were then asked: ‘how concerned are you about any pharmacological trial for mental health’; and ‘do you think recreational use of MDMA and psilocybin should be decriminalised’ also using 10-point scales, to assess if attitudes towards pharmaceutical and illicit drugs, moderated attitudes towards the vignette trials. Participants in the control condition were asked ‘What type of drug do they think JB-4801 is’ to assess if they were effectively blinded to the MDMA-AP condition. Participants were also given space to describe the rationale for their answers, if desired. A summary and analysis of qualitative responses can be seen in online supplemental table 1.

Patients and public involvement
Participants were not involved in the study design or in the setting of research objectives or outcomes of this study protocol.
Sample size calculations

A priori power analysis for a two-tailed t-test used to assess the primary outcomes was performed using G*Power 3. It contained the following parameters: power range=0.80–0.95; a small-moderate effect size ($\beta$=0.3); alpha=0.05. The total number of participants required for such parameters ranged from 82 ($\beta$=0.8) to 134 ($\beta$=0.95). Power analysis for analysis of variance (ANOVA) used to assess secondary outcomes contained the following parameters: power range=0.80–0.95; a moderate effect size ($\beta$=0.5); alpha=0.05. The total number of participants required for such parameters ranged from 111 ($\beta$=0.8) to 175 ($\beta$=0.95). The effect sizes were chosen to represent the minimal clinically significant difference.

Statistical analysis

BC deidentified the group condition within the raw data set, so that DW was blinded to treatment condition while organising, cleaning and analysing the data. The primary aims were assessed by comparing participant attitudes between vignette conditions using multiple independent samples t-tests. The secondary aims were tested by comparing participant attitudes across vignette conditions and professions using multiple two-way ANOVAs. Assumptions of normality were tested using visual inspection of Q-Q plots and distributions. For two-way ANOVA, assumptions for homogeneity of variances were assessed using Levene’s test. The secondary aims were tested by comparing participant attitudes across vignette conditions and professions using multiple two-way ANOVAs. Assumptions of normality were tested using visual inspection of Q-Q plots and distributions. The relationship between age, experience and attitudes were compared between vignette conditions by converting linear binomial correlations to z-scores using an online calculator. In all cases, significance was set at $p<0.05$. Data were analysed using IBM SPSS Statistics for Windows, V.25.0 (IBM). Figures were created using GraphPad Prism V.9.1.2 (GraphPad software, LA Jolla, California) and ggplot2 package conducted in R.

RESULTS

Sample characteristics

Table 1 describes the sample characteristics stratified by vignette condition and profession. Participants within the MDMA-AP vignette condition were significantly older ($M_{SD}=5.42$, $SE=2.57$) and more experienced ($M_{SD}=5.42$, $SE=2.57$), than those in the control vignette condition ($F(1,87)=4.44$, $p=0.038$; and $F(1,84)=4.05$, $p=0.047$, respectively). There were no statistically significant differences between vignette conditions on the number of trainees or the proportion of participants in favour of decriminalisation.

Psychiatrists were more likely to be male than psychologists ($X^2(2, 92) = 8.86$, $p=0.012$). There were two non-binary participants in total, one a psychologist in each condition. They were removed from analysis. Age and years of experience were assessed using two-way ANOVA grouped by vignette condition and profession. Main effect of vignette condition.
were significant main effects of profession with both age and experience ($F(2,87) = 5.71$, $p=0.005$; and $F(2,84) = 8.78$, $p<0.001$, respectively). Psychiatrists were also significantly older than both psychologists ($M_{DIF}=8.9$ years, $SE=3.23$, $p=0.020$) and researchers ($M_{DIF}=11.6$ years, $SE=3.50$, $p=0.004$). Similarly, psychiatrists were more experienced than both psychologists ($M_{DIF}=8.94$ years, $SE=3.23$, $p=0.020$) and researchers ($M_{DIF}=11.6$ years, $SE=3.50$, $p=0.004$), and psychologists were more experienced than researchers ($M_{DIF}=6.82$ years, $SE=2.61$, $p=0.011$). There were no statistically significant differences between professions on the number of trainees or the proportion of those in favour of decriminalisation.

**Comparison of attitudes towards MDMA-AP versus control**

There was no overall difference between the responses to the vignettes in the level of concern about the trial; how strongly professionals objected to participating in the trials; how strongly professionals recommended participating in the trials; and the predicted efficacy of the trials (see figure 2).

**Figure 2** Comparing the attitudes of mental health professionals towards methylenedioxymethamphetamine-assisted psychotherapy (MDMA-AP) and control, as measured on a 10-point scale. (A) Safety concerns about; (B) strength of objection to; (C) predicted efficacy of; and (D) strength of recommendation for, the vignette trials. Error bars represent mean±SEM; n=43–51.
Comparison of psychiatrist, psychologist and researcher attitudes towards MDMA-AP versus control

There was a significant interaction between vignette condition and profession on the likelihood respondents would recommend participating in the trial (see figure 3) \((F(2, 88) = 4.120, p=0.020)\). Post hoc tests show that psychiatrists were less likely to recommend participating in a trial with MDMA-AP than control \((M_{\text{off}}=2.97, SE=1.08, p=0.021)\). There was no main effect of vignette condition \((F(1, 88) = 3.80, p=0.054)\) or profession \((F(2, 88) = 1.38, p=0.257)\), on the likelihood respondents would recommend participating in the vignette trials. There was no difference in the concerns for safety; the strength of objection; or the predicted efficacy of the trials, within or across professions.

Given the differences in age and experience across professions, we conducted sensitivity analysis using several analysis of covariance (ANCOVA) controlling for age, experience, stance on decriminalisation and gender. There were no significant covariates, and in all cases a significant interaction of profession and treatment arm remained (online supplemental figure 2).

Exploratory analysis of attitudes across: gender, age, experience, stance on decriminalisation and concern about drug trials

We assessed correlations of attitudes with age, experience and level of concerns about all drug trials, within and across vignette conditions (table 2). Correlations were then compared between vignette conditions, using Fisher \(r\) to \(z\) transformations and comparisons. There was a significantly higher correlation of concerns about MDMA-AP and years of experience \((r=0.495; p<0.001)\), than concerns about the control vignette and years of experience \((r=-0.056, p>0.05)\) (Fisher \(r\) to \(z\): \(d=0.60, p=0.005\); see figure 4). Similarly, there was a significantly...
higher correlation of years of experience with the objection to MDMA-AP ($r=-0.285$; $p=0.067$), than with the objection to control ($r=-0.106$, $p=0.05$) (Fisher $r$ to $z$: $d=0.40$, $p=0.031$).

When looking at concerns about pharmaceutical trials in general, there was a significantly higher correlation with concerns about the control trial ($r=0.583; p<0.001$), than with concerns about MDMA-AP ($r=0.233; Fisher r$ to $z$: $d=0.43$, $p=0.045$). There was also a significantly higher correlation of concerns about all pharmaceutical trials with objection to the control trial ($r=0.392; p=0.004$), than with objection to MDMA-AP ($r=-0.123; Fisher r$ to $z$: $d=0.54$, $p=0.012$). There were no significant differences between vignette conditions in correlations of age with any attitude. The differences in participant attitudes separated by stance towards decriminalisation and vignette condition can be seen in online supplemental figure 3. There were no significant effects of gender across any of the attitudes (online supplemental figure 4).

**DISCUSSION**

Our study was the first to experimentally assess bias in MH professional attitudes towards the emerging field of psychedelic psychotherapy, particularly MDMA-AP. Overall, there appeared to be no bias against MDMA-AP, compared with a trial using an unknown, neutrally labelled pharmacotherapy (JB-4801-AP; control). However, we did find two subgroups who showed some negative bias. First, experienced MH professionals were more likely to object to, and be concerned about, MDMA-AP, than MH professionals with fewer years practice. Second, psychiatrists were less likely than psychologists or researchers to recommend participating in MDMA-AP, than control.

In the vignette, MDMA-AP was described according to the available research and the control was described in the same terms as MDMA-AP. Thus, the caution of experienced MH professionals and the hesitation of psychiatrists to recommend MDMA-AP were likely due to prior beliefs held towards MDMA. Despite psychiatrists being older in our sample, neither age nor experience moderated the hesitation of psychiatrists in recommending MDMA-AP. Thus, we hypothesise this hesitation was related to factors inherent to the training or clinical experience of psychiatrists.

**Psychiatrists displayed some bias towards MDMA-AP trials**

In general, psychiatrists are more likely than psychologists and researchers to treat severe presentations, to understand psychopharmacology and the legislation surrounding medicines and drugs. Such legislation classically maintains a distinction between ‘medicines’ and ‘drugs of abuse’. Medicines are appraised considering their therapeutic potential and side-effect profile. Illicit drugs are assessed according to their potential for abuse, dependence and harm. Once a drug is deemed illicit, therapeutic research typically ceases, as was the case with MDMA for several decades. Given such clinical experience and training within psychopharmacology, it makes sense that psychiatrists were more cautious in recommending a repurposed illicit drug as a potential therapeutic tool.
The harms of recreational ecstasy use are low compared with other substances, such as alcohol and methamphetamine, but at higher doses in uncontrolled recreational settings, it can lead to SAEs or death. We hypothesise the caution of psychiatrists could result from generalising the harms associated with high-dose recreational use of MDMA, and possibly a lack of understanding of efficacy and safety aims of clinical research.

This hypothesis is supported by some of the qualitative responses given by psychiatrists. \( \chi^2 \) analysis shows that psychiatrists were significantly more likely to make critical comments about MDMA-AP than researchers (online supplemental table 1. One psychiatrist stated: “I am concerned about this sort of drug being given to patients with PTSD, who are already at an increased risk of substance abuse.” Another psychiatrist said they based their decision on ‘clinical experience’ and challenged the ‘spurious claim of a low chance of negative side effects’, while further noting the ‘cardiac and psychosis risks’. Such assertions do not align with the clinical research on MDMA. As highlighted in a memorandum by the Australian Psychiatrists’ professional college: ‘clinical trials [of MDMA-AP] have a demonstrated safety profile’, with significantly fewer adverse events associated with MDMA-AP, than placebo. MDMA-AP also displayed efficacy in patients with a history substance use disorders.

**Experience-dependent bias towards MDMA-AP trials**

Experienced MH professionals were more likely to object to, and be concerned about the MDMA-AP trial, than MH professionals with fewer years practice. There was no such association of experience and either concerns about, or objections to, the control trial. Furthermore, the concerns and objections participants had for MDMA-AP were not related to concerns about pharmaceutical trials in general, but to the use of MDMA, specifically. This implies that there is an experience-dependent bias against MDMA-AP, with experienced professionals more cautious, and professionals with fewer years practice more optimistic.

Experienced professionals are more likely to have witnessed lauded drug therapies, which after being approved for medical use, failed to live up to the hype. This is particularly relevant for therapies picked-up by mainstream media, where the nuanced, critical scientific discussion is replaced by overgeneralised conclusions, creating false expectations for vulnerable patients. MDMA-AP saw a spike in positive attention in the mainstream media over the past decade, which may have caused experienced MH professionals to be more cautious of hype. A similar rationale was described by a psychiatrist with 36 years of practice: “During my practice I have seen several new drugs introduced into clinical practice and then withdrawn for safety reasons, and others where significant side effects were only recognised after many years of use. Others have, with time, been found less effective than first suggested. So, I am cynical about new wonder drugs and the vulnerability of those with treatment resistant conditions (mental health or in medicine more generally).”

MDMA also has a long history of stigma in the mainstream media. Since the 1980s, MDMA was made illegal and many studies, mainstream news articles and government campaigns have highlighted the potential harms of chronic, high-dose recreational use, while studies on the safety and efficacy of therapeutic MDMA were halted. Thus, it is also possible the caution of experienced MH professionals who received their training many years ago...
was influenced by the stigma of the past, while professionals with more recent training were open to appraising MDMA-AP according to the current therapeutic research.

Limitations
Several potential limitations to the study are worth noting. First, the attitudes measured in this study were from a sample of Australian MH professionals. Therefore, the results may not generalise well to non-western countries. Second, there is a chance of selection bias, with professionals strongly for or against clinical trials, more likely to complete the study. We assessed for such bias, by asking participants how concerned they were about pharmaceutical trials in general. Concerns about clinical trials in general were normally distributed and did not help explain any of our key findings. Third, due to a difficulty in accessing GPs, we were unable to include them in this study. This has inhibited our ability to comprehensively assess potential barriers to access MDMA-AP. Fourth, we also recruited fewer psychiatrists, than psychologists or MH researchers, which limited the power and sensitivity of our secondary and exploratory analyses. There is a chance we missed smaller, but still clinically meaningful differences between our professional subgroups. Despite such issues, we still managed to show differences across professions. Fifth, there was potentially some measurement bias, due to issues with blinding. Two control participants guessed JB-4801 might be MDMA, and five guessed it may be a psychedelic compound. Although this is only a small proportion of the sample, these assumptions may have reduced the size of differences between treatment arms. Sixth, there may not have been enough of a difference between the vignettes to elicit the strength of attitudes and beliefs that may occur in a true clinical setting, with a patient. The finding of differential effects by arm in some subgroups suggests that the lack of main effect may be due this issue. Finally, the use of an unknown alphanumeric drug as a control (JB-4801) was likely associated with a level of hesitation or caution, which may have reduced between group differences. We considered using a control with higher ecological validity, such as an SSRI. However, SSRIs are less efficacious than MDMA-AP and thus would have been described differently in the vignette. Furthermore, SSRIs have a long history in psychiatry and inspire their own set of biased beliefs. Thus, by using JB-4801-AP, we lost ecological validity and potentially reduced between groups effects, but in doing so were more precise in assessing bias associated with the label ‘MDMA’.

CONCLUSION
One phase-III trial for MDMA-AP in the treatment of PTSD has now been completed. MDMA-AP displays strong effect sizes in the treatment of chronic, treatment resistant PTSD, including patients with childhood trauma, comorbid depression or substance use disorders. For the 70%–80% of patients who do not respond to SSRIs, the 25%–50% who show no clinical improvement from the first-line treatments, and the large number of patients who drop-out of distressing psychotherapies, MDMA-AP offers a promising alternative. However, for patients to access MDMA-AP, it must first be accepted by the MH community.

Researchers have previously described experiencing resistance in setting up trials of MDMA-AP in Australia, which they hypothesised was due to stigmatising beliefs. The current study provides some experimental evidence of bias in psychiatrists. There is also evidence of an experience-dependent bias against MDMA-AP. It is unclear if such biases fall within the naïve optimism of professionals with fewer years practice, or in those with more experience projecting the history of stigma onto the therapeutic use of MDMA. This study may motivate MH professionals to evaluate their potential biases, enabling more effective local research and, if trials continue to show efficacy, help address barriers to implementation.

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Contributors
DJW, NG and BC designed the study. DJW and NG recruited participants. DJW conducted statistical analyses and wrote the paper. NG and BC provided feedback on the paper and amendments to the paper. DJW is responsible for the overall content as guarantor.

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None declared.

Patient and public involvement
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Patient consent for publication
Not applicable.

Ethics approval
This study was approved via the University of Sydney, Human Research Ethics Committee in December 2019 (Project #2019/872). Participants gave informed consent to participate in the study prior to taking part.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available upon reasonable request. The data that support the findings of this study are stored on a secure server within the University of Sydney database, as required by HREC. It is available upon reasonable request from the corresponding author.

Supplemental material
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ORCID iDs
Dean J Wright http://orcid.org/0000-0003-0564-8482
Ben Colagiguri http://orcid.org/0000-0003-2157-2641
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