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Evaluating the Attitudes of Mental Health Professionals Towards Trials of MDMA: A Randomized Vignette Trial

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<th>BMJ Open</th>
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<tr>
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<td>bmjopen-2021-060360</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Original research</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>12-Feb-2022</td>
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<td>Complete List of Authors:</td>
<td>Wright, Dean; The University of Sydney, Faculty of Medicine and Health, Central Clinical School; The University of Sydney, School of Psychology Colagiuri, Ben; The University of Sydney, School of Psychology Glozier, Nick; University of Sydney Brain and Mind Research Institute; The University of Sydney, Faculty of Medicine and Health, Central Clinical School</td>
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<td>Keywords:</td>
<td>PSYCHIATRY, Adult psychiatry &lt; PSYCHIATRY, MENTAL HEALTH</td>
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Evaluating the Attitudes of Mental Health Professionals
Towards Trials of MDMA: A Randomized Vignette Trial

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Keywords: MDMA; Posttraumatic Stress Disorder; Attitude; Bias; Psychedelic

Running title: MH Professional Attitudes of MDMA Therapy
Abstract

Objectives: Assess for bias in the attitudes of mental health (MH) professionals towards trials of MDMA-AP, comparing them with a neutrally labelled pharmacotherapy trial.

Methods: Psychiatrists, psychologists and researchers were recruited through direct marketing and randomly allocated to read a vignette about a trial of either MDMA-AP (n = 51) or the unknown pharmacotherapy (control; n = 43). Four key attitudes were assessed: How likely they were to (i) recommend participating, or (ii) object to participating in the trial; (iii) their predicted efficacy; and (iv) concerns about the safety of the trial.

Results: There were no overall differences of professional’s attitudes towards MDMA-AP and the control pharmacotherapy trial. Psychiatrists were less likely to recommend participation in the MDMA-AP trial than the control trial (d = .72, p = .02), but did not differ in other attitudes. Psychologists and researchers did not differ in any attitudes. The correlation between professional experience and both: (i) concern about, and (ii) strength of objection to the trial, was higher for MDMA-AP, than the control trial (d = .60, p = .01 & d = .40, p = .03, respectively).

Conclusions: Psychiatrists, but not psychologists or researchers show hesitancy in recommending trials of MDMA-AP vs an unknown pharmacotherapy. Experienced MH professionals were more likely to have concerns about, and object to, 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. The findings suggest that research into, and implementation of, MDMA-AP and other repurposed medicines may face barriers with certain MH professionals, which will need be addressed if such medicines continue to be a promising treatment avenue.
Article Summary

- By using a randomised controlled vignette design, we were able to be the first study to objectively assess for bias in mental health professionals towards MDMA-AP.
- The study was conducted in a sample of psychologists, psychiatrists and mental health researchers from across Australia, which enables inferences to be made about these populations, but reduces generalisability to other professions and health care systems around the world.
- By collecting demographic data related to profession, gender, age, experience, and political stance on drug use, alongside qualitative data from participants, we were able to understand the nature of biases towards MDMA-AP.
- We assessed for bias towards any pharmaceutical trials, increasing the certainty that our results reflect a specific bias towards MDMA-AP and not pharmaceutical trials more generally.
- The use of an unknown alpha-numeric control drug (JB-4801), rather than a currently used treatment (eg. Sertraline) increased the specificity of our conclusions about MDMA-AP, at the expense of a reduction in power and ecological validity.
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 [1-3]. 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 [4]. These therapies involve exposure and desensitization to traumatic memories and generally show moderate to large reductions in Clinician-Administered PTSD Scale (CAPS) scores, compared to 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 [12]. All trials of MDMA-AP use an active control group, which receives a placebo drug and the same psychotherapy as the treatment arm [12]. 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 [13-18]. Across all trials of MDMA-AP, there was only one serious adverse event (SAE) potentially attributable to MDMA with five SAEs in the control arm [17, 19]. Trial data indicate MDMA-AP is effective compared to active psychotherapy controls, with large between-groups reductions in CAPS score (range: $d=0.91-1.17$) [17, 19, 20]. A meta-analysis of phase-II results shows MDMA-AP to be as efficacious as PE [21]. Notably, half of the PE studies used inactive psychotherapy controls, and none investigated treatment-resistant populations. Thus, it seems reasonable to assume MDMA-AP would show higher effect sizes than PE, if evaluated in equivalent populations with similar controls. Furthermore, the MDMA-AP studies showed significantly lower dropout 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 [17, 19]. Furthermore, long-term follow-up of phase-II studies, show remission rates increased three years after treatment finished, implying robust long-term effects [22].
Given the promising phase-III results, there is a chance MDMA-AP will be licensed for medical use by the FDA and EMA in 2022 [18]. Australia has been lagging in trials of psychedelic research using MDMA, psilocybin and 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 [23-27]. 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 [26].

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

Methods

Design

A randomized controlled design was used to assess the differences in attitudes towards a trial of MDMA-AP compared to 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. The study design was registered with the Australian and New Zealand Clinical Trials Register (Trial Id: ACTRN12620001068954).

Participants

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

Participants were recruited through distribution of an advertisement and study URL to all psychiatrists, psychologists and mental health researchers registered with peak professional bodies in Australia, and all GPs and mental health professionals in Australian Primary Health Networks (PHNs) (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 Supplementary Figure 1). Recruitment occurred from Feb 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, UT, 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 randomized 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 Supplementary Methods 1). The vignettes were identical except for the descriptions of the treatments: 1) MDMA-AP group described as: “Methylenedioxymethamphetamine (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 Supplementary 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 Supplementary 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.

Ethics

This study was approved via the University of Sydney, Human Research Ethics Committee in December
2019 (Project #2019/872).

Sample Size Calculations

An a priori power analysis for a two-tailed t-test used to assess the primary outcomes was performed
using G*Power 3 [28]. It contained the following parameters: Power range = 0.80-0.95; a small-
moderate effect size (d=0.3); alpha = 0.05. The total number of participants required for such
parameters ranged from 82 (β = 0.8) to 134 (β = 0.95). Power analysis for ANOVA used to assess
secondary outcomes contained the following parameters: Power range = 0.80-0.95; a moderate effect
size ($F=0.3$); alpha $= .05$. 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**

Experimenters were blinded prior to conducting statistical analyses. 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. Sidak's method was used to correct for multiple
comparisons [29]. The relationship between age, experience and attitudes, were compared between
vignette conditions by converting linear binomial correlations to $z$-scores using an online calculator [30].
In all cases, significance was set at $p<0.05$. Data was analysed using IBM SPSS Statistics for Windows,
Version 25.0 (IBM, Armonk, NY, USA). Figures were created using GraphPad Prism 9.1.2 (GraphPad
software, Inc., LA Jolla, CA) and ggplot2 package conducted in R [31, 32].

**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 ($M_{\text{DIFF}} = 5.42$, $SE = 2.57$) and more
experienced ($M_{\text{DIFF}} = 5.42$, $SE = 2.57$), than those in the control vignette condition ($F(1,87) = 4.44,$
$p = .038$; & $F(1,84) = 4.05$, $p = .047$, 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 ($X^2 (2, 92) = 8.86$, $p = .012$). There were
significant main effects of profession with both age and experience ($F(2,87) = 5.71$, $p = .005$; and $F(2,84)$
= 8.78, $p < .001$, respectively). Psychiatrists were also significantly older than both psychologists ($M_{\text{DIFF}}$
= 8.9 years, $SE = 3.23$, $p = .020$) and researchers ($M_{\text{DIFF}} = 11.6$ years, $SE = 3.50$, $p = .004$). Similarly,
psychiatrists were more experienced than both psychologists ($M_{\text{DIFF}} = 8.94$ years, $SE = 3.23$, $p = .020$)
and researchers ($M_{\text{DIFF}} = 11.6$ years, $SE = 3.50$, $p = .004$), and psychologists were more experienced
than researchers ($M_{\text{DIFF}} = 6.82$ years, $SE = 2.61$, $p = .011$). 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).

**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) ($F(2, 88) = 4.120, p = .020$). Post hoc tests show psychiatrists were less likely to recommend participating in a trial with MDMA-AP, than control ($M_{\text{DIFF}} = 2.97, SE=1.08, p = .021$). There was no main effect of vignette condition ($F(1, 88) = 3.80, p = .054$) or profession ($F(2, 88) = 1.38, p = .257$), 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 ANCOVAs 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 (Supplementary Figure 2).
Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Psychiatrist</th>
<th>Psychologist</th>
<th>MH Researcher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>MDMA</td>
<td>Total</td>
<td>Control</td>
</tr>
<tr>
<td>Number of Participants</td>
<td>51</td>
<td>43</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>Male:Female (male %)</td>
<td>14:36</td>
<td>13:29</td>
<td>27:65</td>
<td>4:5</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>44.3*</td>
<td>50.0*</td>
<td>46.9</td>
<td>53.6</td>
</tr>
<tr>
<td>Years of experience (SD)</td>
<td>13.8*</td>
<td>17.4*</td>
<td>15.5</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Note: There were two non-binary participants in total, one a psychologist in each condition. They were removed from chi-square analyses, as most groups had zero non-binary participants. Gender, trainee and stance on decriminalisation were assessed via chi-square analysis. Age and years of experience were assessed using two-way ANOVA grouped by vignette condition and profession. Main effect of vignette condition: * p < .05. Main effect of profession: † p < .05, †† p < .01, ††† p < .001.
Exploratory analysis of Attitudes across: Gender, Age, Experience, Stance on Decriminalisation & 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 ($r = .495; p < .001$), than concerns about the control vignette and years of experience ($r = -.056; \text{Fisher} r \text{ to } z: d = .60, p = .005$; see Figure 4). Similarly, there was a significantly higher correlation of years of experience with the objection to MDMA-AP ($r = .285; p = .067$), than with the objection to control ($r = -.106; \text{Fisher} r \text{ to } z: d = .40, p = .031$).

When looking at concerns about pharmaceutical trials in general, there was a significantly higher correlation with concerns about the control trial ($r = .583; p < .001$), than with concerns about MDMA-AP ($r = .233; \text{Fisher} r \text{ to } z: d = .43, p = .045$). There was also a significantly higher correlation of concerns about all pharmaceutical trials with objection to the control trial ($r = .392; p = .004$), than with objection to MDMA-AP ($r = -.123; \text{Fisher} r \text{ to } z: d = .54, p = .012$). 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 Supplementary Figure 3. There were no significant effects of gender across any of the attitudes (Supplementary Figure 4).
Table 2. Correlations of attitudes with age, experience, and concerns about drug trials, within and across treatment arms.

<table>
<thead>
<tr>
<th>MH Professional attitudes (10-point Likert Scale)</th>
<th>Strength of recommendation</th>
<th>Strength of objection</th>
<th>Predicted efficacy</th>
<th>Concerns for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>-.192</td>
<td>.174</td>
<td>-.277**</td>
<td>.275**</td>
</tr>
<tr>
<td>Control</td>
<td>-.060</td>
<td>-.018</td>
<td>-.118</td>
<td>.154</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.297</td>
<td>.295</td>
<td>-.420**</td>
<td>.435**</td>
</tr>
<tr>
<td>Difference between arms (Cohen's d) (.25)</td>
<td>1.15</td>
<td>1.50</td>
<td>1.54</td>
<td>1.45</td>
</tr>
<tr>
<td>Total</td>
<td>-.187</td>
<td>.127</td>
<td>-.371***</td>
<td>.233*</td>
</tr>
<tr>
<td>Control</td>
<td>-.081</td>
<td>-.106</td>
<td>-.266</td>
<td>-.056</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.275</td>
<td>.285</td>
<td>-.457**</td>
<td>.495***</td>
</tr>
<tr>
<td>Difference between arms (Cohen's d) (.20)</td>
<td>0.93</td>
<td>1.87†</td>
<td>1.03</td>
<td>2.80 ††</td>
</tr>
<tr>
<td>Total</td>
<td>-.203*</td>
<td>.241*</td>
<td>-.173</td>
<td>.424***</td>
</tr>
<tr>
<td>Control</td>
<td>-.271</td>
<td>.392**</td>
<td>-.133</td>
<td>.583***</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.152</td>
<td>-.123</td>
<td>-.218</td>
<td>.233</td>
</tr>
<tr>
<td>Fisher r to z:</td>
<td>0.58</td>
<td>2.51†</td>
<td>0.41</td>
<td>2.01†</td>
</tr>
<tr>
<td>Δz (Cohen's d) (.13)</td>
<td>(.58)</td>
<td>(.09)</td>
<td>(.43)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Statistically significant differences between treatment arm correlations were calculated by transforming r to z, using Fisher's method, then calculating the difference in z-score. Significant correlations: *p<.05; **p<.01; ***p<.001. Significant difference between correlations: †p<.05; ††p<.01.
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 to a trial using an unknown, neutrally labelled pharmacotherapy (JB-4801-AP; control). However, we did find two sub-groups 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 [33, 34]. Given such clinical experience and training within psychopharmacology, it makes sense psychiatrists were more cautious in recommending a repurposed illicit drug as a potential therapeutic tool.

The harms of recreational ecstasy use are low compared to other substances, such as alcohol and methamphetamine [35, 36], but at higher doses in uncontrolled recreational settings, it can lead to serious adverse events or death [37]. 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-square analysis shows psychiatrists were significantly more likely to make critical comments about MDMA-AP than researchers (Supplementary 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”, whilst 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” [38], with significantly fewer adverse events associated with MDMA-AP, than placebo [19]. MDMA-AP also displayed efficacy in patients with a history substance use disorders [17].

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 there is an experience-dependent bias towards MDMA-AP, with experienced professionals more cautious, and professionals with fewer years practice more optimistic.

Experienced professionals were more likely to have witnessed overhyped trial 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 [39]. 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 1980’s, MDMA was made illegal and many studies, mainstream news articles and government campaigns have highlighted the potential harms of chronic, high-dose recreational use, whilst studies on the safety and efficacy of therapeutic MDMA were halted [34]. 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, whilst 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 mental health 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. We also recruited fewer psychiatrists, than psychologists or MH researchers, which limited the power and sensitivity of our exploratory analyses. Fourth, 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. Fifth, 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 alphanumerical 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 [17]. 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 [6], 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 [1]. However, for patients to access MDMA-AP, it must first be accepted by the mental health community.

Researchers previously described experiencing resistance in setting up trials of MDMA-AP in Australia, which they hypothesised was due to stigmatising beliefs [23, 25]. The current study provides experimental evidence of bias in psychiatrists. There is also evidence of an experience-dependent bias towards 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. Regardless, Australia is falling behind the rest of the international research community in assessing and implementing this novel therapy. We hope this study may motivate MH professionals to evaluate their potential biases, enabling more effective local research and if trials continue to show efficacy, barriers to access may be reduced.

**Acknowledgements**

Thank you to all the participants who freely gave their time. Thank you to the following organisations for disseminating our research project to their members: RANZCP, ACPA, ASMR, and the APS. Thank you to the PHNs around Australia who passed on our research to professionals within their catchments. DW would like to thank Professor Caroline Hunt and Professor Suncica Lah for their support through the challenges that arose during the completion of this study.
Data Availability

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 on request from the corresponding author.

Declaration of Conflicting Interests

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

Author Contributions

DW, NG and BC designed the study. DW and NG recruited participants. DW conducted statistical analyses and wrote the paper. NG and BC provided feedback on the paper and amendments to the paper.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
References


**Figure 1.** Recruitment Flow Chart

**Figure 2.** Comparing the attitudes of mental health professionals towards 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.

**Figure 3.** Comparing the attitudes of psychiatrists, psychologists, and mental health (MH) researchers towards MDMA-AP and control, 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* = 9-28; significant simple effects: *p* < .05.

**Figure 4.** The relationship between experience and attitudes toward each vignette trial, measured on a 10-point scale. **A)** Level of safety concerns & **B)** strength of objection. Differences between correlations assessed using Fisher *r* to *z* transformations and comparisons; *n* = 43-51.
Sent recruitment advertisement to the following **Peak Bodies and research bodies**: Society for Mental Health Research (SMHR); Royal Australian & New Zealand College of Psychiatrists (RANZCP); Australian Psychological Society (APS); Australian Clinical Psychology Association (ACPA); Australian Association of Psychologists Incorporated (AAPI)

Sent recruitment advertisement to **all Primary Health Networks - 31 PHNs**

Sent to the following **Facebook Groups**: AAPI Facebook page; Australian Psychologists; Psychology Australia; GP, doctor, allied health job group

**Recruitment advertisement passed on to the members of organisation/group/networks**

**Peak Bodies**: SMHR, RANZCP, APS and ACPA all advertised via a direct email communication, through a monthly newsletter email, or in and ad on the website. It is unclear if an advertisement was sent through AAPI.

**PHNs**: 13 PHNs (42%) passed on recruitment (Hunter New England, Northern Sydney, North Coast NSW, South Western Sydney, Central and Eastern Sydney, Nepean Blue Mountains, Tasmania, Adelaide, Northern Territory, Northern Queensland, Brisbane South, Perth North, North Western Melbourne); 10 PHNs (32%) denied the request; and 8 PHNs (26%) did not clarify if recruitment was sent.

**Facebook Groups**: Psychology Australia was the only group to post the advertisement

**Number of participants who begun the survey** \( N = 141 \)

**Participants who gave informed consent & completed all the primary outcome attitudes** \( N = 100 \)

**After removing GPs and those without a listed profession** \( N = 94 \)

**Figure 1.** Recruitment flow chart

158x149mm (150 x 150 DPI)
Figure 2. Comparing the attitudes of mental health professionals towards 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.
Figure 3. Comparing the attitudes of psychiatrists, psychologists, and mental health (MH) researchers towards MDMA-AP and control, 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 = 9-28; significant simple effects: *p<.05.

169x194mm (150 x 150 DPI)
Figure 4. The relationship between experience and attitudes toward each vignette trial, measured on a 10-point scale. **A)** Level of safety concerns & **B)** strength of objection. Differences between correlations assessed using Fisher r to z transformations and comparisons; n = 43-51.
Email Template Used in Recruitment

Title: “Evaluation of attitudes towards novel mental health treatments at the University of Sydney.”

“To…

Researchers from The Brain and Mind Centre, University of Sydney are seeking to understand
the attitudes of psychiatrists, general practitioners, psychologists and mental health researchers
towards new mental health treatments, as part of a Clinical Masters research project.

The survey will take 5 minutes to complete.

If you’re interested in learning more about the study and taking part, please CLICK THIS LINK

Thank you for your attention.

Warm regards,

…

(02) 9114 4343

email address

University of Sydney HREC project number [2019/872].”
Supplementary Figure 1. The advertisement image used to recruit participants, alongside the written template.
Supplementary methods 1 - Vignettes

Vignette – Experimental condition

PLEASE READ THE ENTIRE STORY BEFORE MOVING ON TO ANSWER THE QUESTIONS.

Lisa is a 32-year-old primary school teacher. Three years ago, her ex-partner raped Lisa at knifepoint. A year later, Lisa was experiencing frequent vivid nightmares and would often have only a few hours sleep. Lisa noticed that she was “on edge” most of the day, withdrawing socially, and found it harder to focus on teaching her students. Lisa then began seeing you for treatment for post-traumatic stress disorder (PTSD). Lisa initially underwent exposure-based CBT for a period of 12 weeks. Lisa failed to see much improvement from this and started medication. Over the past 2 years, Lisa has tried two different types of antidepressant and had further CBT and EMDR therapy. Lisa continues to experience frequent nightmares, insomnia and high levels of daytime anxiety. Lisa has now ceased all psychiatric medications.

In her appointment today, Lisa has brought in a flyer for a clinical trial being conducted at a University. It states they are testing the effects of “Methylenedioxymethamphetamine (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’. The leaflet states that 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. Lisa is interested in participating in this trial and wants to know what you think.
Vignette – Control condition

PLEASE READ THE ENTIRE STORY BEFORE MOVING ON TO ANSWER THE QUESTIONS.

Lisa is a 32-year-old primary school teacher. Three years ago, her ex-partner raped Lisa at knifepoint. A year later, Lisa was experiencing frequent vivid nightmares and would often have only a few hours sleep. Lisa noticed that she was “on edge” most of the day, withdrawing socially, and found it harder to focus on teaching her students. Lisa then began seeing you for treatment for post-traumatic stress disorder (PTSD). Lisa initially underwent exposure-based CBT for a period of 12 weeks. Lisa failed to see much improvement from this and started medication. Over the past 2 years, Lisa has tried two different types of antidepressant and had further CBT and EMDR therapy. Lisa continues to experience frequent nightmares, insomnia and high levels of daytime anxiety. Lisa has now ceased all psychiatric medications.

In her appointment today, Lisa has brought in a flyer from a clinical trial being conducted at a University. “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. The leaflet states that preliminary studies have suggested this treatment has worked for a high proportion of people with PTSD and has very low chance for negative effects. Lisa wants to participate in this trial and wants to know what you think.
Supplementary methods 2 – Survey Questions

1. How likely are you to recommend that Lisa participates in this trial?
   Not at all 1-----------2-----------3-----------4-----------5-----------6-----------7-----------8-----------9-----------10 Definitely

2. How strongly would you object to Lisa participating in this trial?
   Not at all 1-----------2-----------3-----------4-----------5-----------6-----------7-----------8-----------9-----------10 Extremely

3. How likely do you think it is that MDMA-assisted psychotherapy will help Lisa?
   Not at all 1-----------2-----------3-----------4-----------5-----------6-----------7-----------8-----------9-----------10 Extremely

4. How concerned are you about the safety of this treatment?
   Not at all 1-----------2-----------3-----------4-----------5-----------6-----------7-----------8-----------9-----------10 Extremely

5. How concerned are you about people with mental health conditions taking part in ANY experimental drug trial?
   Not at all 1-----------2-----------3-----------4-----------5-----------6-----------7-----------8-----------9-----------10 Extremely

6. How did you come to these opinions?

7. Would you recommend that Lisa try other therapies before considering this trial? [tick all that apply]
   a. Psychodynamic therapy
   b. Other talk therapies
   c. Augmentation with antipsychotics
   d. Transcranial magnetic stimulation
   e. Neurofeedback
   f. Other

8. Do you think recreational use of some drugs like ecstasy (MDMA) and magic mushrooms (psilocybin) should be decriminalised? YES/NO
   a. Why?
Supplementary Table 1. Exploring qualitative responses that explain the rationale for mental health professionals’ attitudes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Control</th>
<th>MDMA</th>
<th>Total</th>
<th>Psychiatrist Control</th>
<th>MDMA</th>
<th>Total</th>
<th>Psychologist Control</th>
<th>MDMA</th>
<th>Total</th>
<th>MH Researcher Control</th>
<th>MDMA</th>
<th>Total</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>51</td>
<td>43</td>
<td>94</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>28</td>
<td>21</td>
<td>49</td>
<td>14</td>
<td>14</td>
<td>28</td>
<td>A) More responses in MDMA than control; B) Psychologists gave more responses in MDMA than control</td>
</tr>
<tr>
<td>Number of Responses</td>
<td>23 A (45%)</td>
<td>34 A (79%)</td>
<td>57 (61%)</td>
<td>6 (67%)</td>
<td>5 (63%)</td>
<td>11 B (39%)</td>
<td>18 B (85%)</td>
<td>29 (59%)</td>
<td>6 (43%)</td>
<td>11 (79%)</td>
<td>17 (61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive : Negative responses (%)</td>
<td>10:4 (71%)</td>
<td>19:8 (70%)</td>
<td>29:12 (71%)</td>
<td>4:1 (80%)</td>
<td>2:3 C (40%)</td>
<td>6:4 (60%)</td>
<td>3:3 (50%)</td>
<td>9:4 (69%)</td>
<td>12:7 (63%)</td>
<td>3:0 (100%)</td>
<td>8:1 C (89%)</td>
<td>11:1 (92%)</td>
<td>C) Researchers have more positive responses about MDMA, than Psychiatrists</td>
</tr>
<tr>
<td>Neutral responses (%)</td>
<td>11 (47%)</td>
<td>7 (21%)</td>
<td>17 (30%)</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td>1 (9%)</td>
<td>5 (55%)</td>
<td>5 (28%)</td>
<td>11 (38%)</td>
<td>3 (50%)</td>
<td>2 (18%)</td>
<td>5 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: “Positive responses” are those which describe low concerns, low objections, high predicted efficacy or high recommendation, whilst “Negative responses” are the inverse. Neutral responses state: they have no personal opinion; they would seek more information; or would help the patient find her own answer.

Chi-square statistics A: $X^2(1, N=94)=11.3, p<.001$; B: $X^2(1, N=49)=10.7, p=.001$; C: $X^2(1, N=14)=3.7, p=.05$
**Strength of Recommendation**

**A** Covariate: Age

![Graph showing the likelihood of recommending participation by profession for age as a covariate.]

- Psychiatrist
- Psychologist
- MH Researcher

- Error bars represent mean ± SEM; \( n = 8-28 \); significant simple effects: \( *p<0.05 \).

**B** Covariate: Experience

![Graph showing the likelihood of recommending participation by profession for experience as a covariate.]

- Psychiatrist
- Psychologist
- MH Researcher

- Error bars represent mean ± SEM; \( n = 8-28 \); significant simple effects: \( *p<0.05 \).

**C** Covariate: Decrim

![Graph showing the likelihood of recommending participation by profession for stance on decriminalisation as a covariate.]

- Psychiatrist
- Psychologist
- MH Researcher

- Error bars represent mean ± SEM; \( n = 8-28 \); significant simple effects: \( *p<0.05 \).

**D** Covariate: Gender

![Graph showing the likelihood of recommending participation by profession for gender as a covariate.]

- Psychiatrist
- Psychologist
- MH Researcher

- Error bars represent mean ± SEM; \( n = 8-28 \); significant simple effects: \( *p<0.05 \).

**Supplementary Figure 2.** Analysis of potential covariates with the strength of recommendation to participate in the vignette trials. There was no significant covariance of **A** Age; **B** Experience; **C** Stance on decriminalisation; or **D** Gender. After accounting for the covariance in each analysis, a significant interaction of profession and vignette condition on the strength of recommendation, remained. Error bars represent mean ± SEM; \( n = 8-28 \); significant simple effects: \( *p<0.05 \).
Stance Towards Decriminalisation

The Effect of Decriminalisation Stance on Attitudes Towards MDMA-AP versus Control

Those in favour of decriminalisation of recreational use of drugs like MDMA and psilocybin, were less likely to be concerned about MDMA-AP ($M_{\text{DIF}} = -2.3, \ SE = .74, \ p = .014$) and more likely to predict that MDMA-AP would be efficacious ($M_{\text{DIF}} = 2.3, \ SE = .57, \ p < .001$), than those against decriminalisation (Supplementary Figure 3). Furthermore, participants against decriminalisation were less likely to recommend MDMA-AP than controls ($M_{\text{DIF}} = 2.4, \ SE = .72, \ p = .008$), and those in favour of decriminalisation ($M_{\text{DIF}} = 2.3, \ SE = .72, \ p = .011$). There are significant interactions of stance towards decriminalisation and vignette condition for: the likelihood of recommending the trial ($F(1, 82) = 8.12, \ p = .006$); the predicted efficacy ($F(1, 82) = 7.90, \ p = .006$); and the level of safety concerns ($F(1, 82) = 5.27, \ p = .024$).

Interpretation of the Effects of Stance Towards Decriminalisation of Recreational Use

Professionals against decriminalisation of the recreational use of drugs, like MDMA and psilocybin displayed bias towards MDMA-AP. They were less likely to recommend MDMA-AP than the control trial, whilst those in favour of decriminalisation recommended MDMA-AP and control equally. There was also bias in both political groups, with the predicted efficacy of, and concerns about MDMA-AP biased according to the political stance on recreational use. It is unclear if beliefs about the efficacy and safety of MDMA-AP are motivating participants political beliefs or if their political alignment may bias their view towards the therapeutic use of MDMA.
Stance Towards Decriminalisation

A) Concerns for Safety

\[ P_{interaction} = .024 \]
\[ P_{ME \, decrim} = .029 \]

B) Strength of Objection

C) Predicted Efficacy

\[ P_{interaction} = .006 \]
\[ P_{ME \, decrim} = .003 \]

D) Strength of Recommendation

Supplementary Figure 3. Comparing the attitudes of those for and against decriminalisation, towards MDMA-AP and control, measured on a 10-point Likert 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; \( n = 9-28 \); significant simple effects: # \( p < 0.05 \); ## \( p < 0.01 \); ### \( p < 0.001 \).
Supplementary Figure 4. Comparing the attitudes of males and females, towards MDMA-AP and control, 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 = 9-28; significant simple effects: *p<0.05; **p<0.01; ***p<0.001.
# CONSORT 2010 checklist of information to include when reporting a randomised trial*

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td>1</td>
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<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions</td>
<td>2</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>4-5</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td>5</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>5, 7</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>6</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>N/A</td>
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<tr>
<td><strong>Randomisation:</strong></td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>6</td>
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<tr>
<td>Sequence generation</td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>6</td>
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<tr>
<td>Allocation concealment mechanism</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>6</td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>6</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>5</td>
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</table>

*For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
11b If relevant, description of the similarity of interventions

Results

Participant flow (a diagram is strongly recommended) 13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome

Participant flow (a diagram is strongly recommended) 13b For each group, losses and exclusions after randomisation, together with reasons

Recruitment 14a Dates defining the periods of recruitment and follow-up

Recruitment 14b Why the trial ended or was stopped

Baseline data

Baseline data 15 A table showing baseline demographic and clinical characteristics for each group

Numbers analysed 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Outcomes and estimation 17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

Outcomes and estimation 17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Ancillary analyses 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Harms 19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)

Discussion

Limitations 20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Generalisability 21 Generalisability (external validity, applicability) of the trial findings

Interpretation 22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

Other information

Registration 23 Registration number and name of trial registry

Protocol 24 Where the full trial protocol can be accessed, if available

Funding 25 Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
Evaluating the Attitudes of Mental Health Professionals Towards Trials of MDMA: A Randomized Vignette Trial

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<td>05-Oct-2022</td>
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Evaluating the Attitudes of Mental Health Professionals Towards Trials of MDMA: A Randomized Vignette Trial

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Keywords: MDMA; Posttraumatic Stress Disorder; Attitude; Bias; Psychedelic

Running title: MH Professional Attitudes of MDMA Therapy
Abstract

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

Design: A randomized 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 (i) recommend participating, or (ii) object to participating in the trial; (iii) their predicted efficacy; and (iv) 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= .72, p=.02), but did not differ in other attitudes. Psychologists and researchers did not differ in any attitudes. The correlation between professional experience and both: (i) concern about, and (ii) strength of objection to, the trial, was higher for MDMA-AP, than control (d=.60, p=.01 & d=.40, p=.03, respectively).

Conclusions: Psychiatrists, but not psychologists or researchers showed more hesitancy in recommending trials of MDMA-AP vs 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 be addressed if MDMA-AP continues to show promise as an efficacious treatment.

Trial registration: The study design was registered with the ANZCTR (Trial Id: ACTRN12620001068954).
**Article Summary**

- By using a randomised controlled vignette design, we were able to be the first study to objectively assess for bias in mental health professionals towards MDMA-AP.

- The study was conducted in a sample of psychologists, psychiatrists and mental health researchers from across Australia, which enables inferences to be made about these populations, but reduces generalisability to other professions and health care systems around the world.

- By collecting demographic data related to profession, gender, age, experience, and political stance on drug use, alongside qualitative data form participants, we were able to understand the nature of biases towards MDMA-AP.

- We assessed for bias towards any pharmaceutical trials, increasing the certainty that our results reflect a specific bias towards MDMA-AP and not pharmaceutical trials more generally.

- The use of an unknown alpha-numeric control drug (JB-4801), rather than a currently used treatment (eg. Sertraline) increased the specificity of our conclusions about MDMA-AP, at the expense of a reduction in power and ecological validity.
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 [1-3]. 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 [4]. These therapies involve exposure and desensitization to traumatic memories and generally show moderate to large reductions in Clinician-Administered PTSD Scale (CAPS) scores, compared to 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 [12]. 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 [12]. 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 [13]. 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 [14-19]. Across all trials of MDMA-AP, there was only one serious adverse event (SAE) potentially attributable to MDMA with five SAEs in the control arm [18, 20]. Trial data indicate MDMA-AP is effective compared to active psychotherapy controls, with large between-groups reductions in CAPS score (range: d=0.91-1.17) [18, 20, 21]. A meta-analysis of phase-II results shows MDMA-AP to be as efficacious as PE [22]. 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 [18, 20]. Furthermore, long-term follow-up of phase-II studies, show remission rates increased three years after treatment finished, implying robust long-term effects [23].

Given the promising phase-III results, there is a chance MDMA-AP will be licensed for medical use by the FDA and EMA in 2022 [19]. Australia has been lagging in trials of psychedelic research using MDMA, psilocybin and 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 [24-28]. 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 [27].

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

**Methods**

**Design**

A randomized controlled design was used to assess the differences in attitudes towards a trial of MDMA-AP compared to 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. The study design was registered with the ANZCTR (Trial Id: ACTRN12620001068954).
Participants

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

Sampling and Recruitment

Participants were recruited through distribution of an advertisement and study URL to all psychiatrists, psychologists and mental health researchers registered with peak professional bodies in Australia, and all GPs and mental health professionals in Australian Primary Health Networks (PHNs) (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 Supplementary Figure 1). Recruitment occurred from Feb 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, UT, 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 randomized 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 Supplementary Methods 1). The vignettes were identical except for
the descriptions of the treatments: 1) **MDMA-AP group described as:** “Methylenedioxymethamphetamine (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 Supplementary 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 Supplementary 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**

An *a priori* power analysis for a two-tailed t-test used to assess the primary outcomes was performed using G*Power 3 [29]. It contained the following parameters: Power range = 0.80-0.95; a small-moderate effect size (*d*=0.3); alpha = 0.05. The total number of participants required for such parameters ranged from 82 (β = 0.8) to 134 (β = 0.95). Power analysis for ANOVA used to assess
secondary outcomes contained the following parameters: Power range = 0.80-0.95; a moderate effect size ($F=0.3$); alpha = .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 de-identified the group condition within the raw data set, so that DW was blinded to treatment condition whilst 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 only variable to violate normality was the strength of objection by treatment arm. Thus, we used the Mann-Whitney U test to compare differences between these groups. Sidak’s method was used to correct for multiple comparisons [30]. The relationship between age, experience and attitudes, were compared between vignette conditions by converting linear binomial correlations to z-scores using an online calculator [31]. In all cases, significance was set at $p<0.05$. Data was analysed using IBM SPSS Statistics for Windows, Version 25.0 (IBM, Armonk, NY, USA). Figures were created using GraphPad Prism 9.1.2 (GraphPad software, Inc., LA Jolla, CA) and ggplot2 package conducted in R [32, 33].

**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 ($M_{\text{dif}} = 5.42$, SE = 2.57) and more experienced ($M_{\text{dif}} = 5.42$, SE = 2.57), than those in the control vignette condition ($F(1,87) = 4.44$, $p=.038$; & $F(1,84) = 4.05, p = .047$, 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 ($X^2 (2, 92) = 8.86, p = .012$). There were significant main effects of profession with both age and experience ($F(2, 87) = 5.71, p = .005$; and $F(2, 84) = 8.78, p < .001$, respectively). Psychiatrists were also significantly older than both psychologists ($M_{\text{DIFF}} = 8.9$ years, $SE = 3.23, p = .020$) and researchers ($M_{\text{DIFF}} = 11.6$ years, $SE = 3.50, p = .004$). Similarly, psychiatrists were more experienced than both psychologists ($M_{\text{DIFF}} = 8.94$ years, $SE = 3.23, p = .020$) and researchers ($M_{\text{DIFF}} = 11.6$ years, $SE = 3.50, p = .004$), and psychologists were more experienced than researchers ($M_{\text{DIFF}} = 6.82$ years, $SE = 2.61, p = .011$). 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).

**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) ($F(2, 88) = 4.120, p = .020$). Post hoc tests show psychiatrists were less likely to recommend participating in a trial with MDMA-AP, than control ($M_{\text{DIFF}} = 2.97, SE=1.08, p = .021$). There was no main effect of vignette condition ($F(1, 88) = 3.80, p = .054$) or profession ($F(2, 88) = 1.38, p = .257$), 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 ANCOVAs 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 (Supplementary Figure 2).
Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Psychiatrist</th>
<th>Psychologist</th>
<th>MH Researcher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>MDMA</td>
<td>Total</td>
<td>Control</td>
</tr>
<tr>
<td>Number of Participants</td>
<td>51</td>
<td>43</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>(28)</td>
<td>(31)</td>
<td>(29.3)</td>
<td>(44.4)</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>44.3 *</td>
<td>50.0 *</td>
<td>46.9</td>
<td>53.6</td>
</tr>
<tr>
<td></td>
<td>(10.8)</td>
<td>(12.6)</td>
<td>(11.9)</td>
<td>(11.9)</td>
</tr>
<tr>
<td>Years of experience (SD)</td>
<td>13.8 *</td>
<td>17.4 *</td>
<td>15.5</td>
<td>18.5</td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td>(12.9)</td>
<td>(11.5)</td>
<td>(9.8)</td>
</tr>
<tr>
<td>Yes:No (yes %)</td>
<td>(14)</td>
<td>(7.8)</td>
<td>(10.6)</td>
<td>(11.1)</td>
</tr>
<tr>
<td></td>
<td>(55.6)</td>
<td>(48.8)</td>
<td>(52.3)</td>
<td>(44.4)</td>
</tr>
</tbody>
</table>

Note: There were two non-binary participants in total, one a psychologist in each condition. They were removed from chi-square analyses, as most groups had zero non-binary participants. Gender, trainee and stance on decriminalisation were asssed via chi-square analysis. Age and years of experience were assessed using two-way ANOVA grouped by vignette condition and profession. Main effect of vignette condition: * p < .05. Main effect of profession: † p < .05, †† p < .01, ††† p < .001
**Exploratory analysis of Attitudes across: Gender, Age, Experience, Stance on Decriminalisation & 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 ($r = .495; p < .001$), than concerns about the control vignette and years of experience ($r = -.056, p > .05$) (Fisher $r$ to $z$: $d = .60, p = .005$; see *Figure 4*). Similarly, there was a significantly higher correlation of years of experience with the objection to MDMA-AP ($r = .285; p = .067$), than with the objection to control ($r = -.106, p > .05$) (Fisher $r$ to $z$: $d = .40, p = .031$).

When looking at concerns about pharmaceutical trials in general, there was a significantly higher correlation with concerns about the control trial ($r = .583; p < .001$), than with concerns about MDMA-AP ($r = .233; Fisher r to z: d = .43, p = .045$). There was also a significantly higher correlation of concerns about all pharmaceutical trials with objection to the control trial ($r = .392; p = .004$), than with objection to MDMA-AP ($r = -.123; Fisher r to z: d = .54, p = .012$). 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 *Supplementary Figure 3*. There were no significant effects of gender across any of the attitudes (*Supplementary Figure 4*).
Table 2. Correlations of attitudes with age, experience, and concerns about drug trials, within and across treatment arms.

<table>
<thead>
<tr>
<th>MH Professional attitudes (10-point Likert Scale)</th>
<th>Strength of recommendation</th>
<th>Strength of objection</th>
<th>Predicted efficacy</th>
<th>Concerns for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>-.192</td>
<td>.174</td>
<td>-.277**</td>
<td>.275**</td>
</tr>
<tr>
<td>Control</td>
<td>-.060</td>
<td>-.018</td>
<td>-.118</td>
<td>.154</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.297</td>
<td>.295</td>
<td>-.420**</td>
<td>.435**</td>
</tr>
<tr>
<td>Difference between arms (Cohen's d)</td>
<td>1.15 ( .25)</td>
<td>1.50т</td>
<td>1.54 ( .33)</td>
<td>1.45</td>
</tr>
<tr>
<td>Experience (Pearson r)</td>
<td>.127</td>
<td>-.371***</td>
<td>.233*</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-.187</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-.081</td>
<td>-.106</td>
<td>-.266</td>
<td>-.056</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.275</td>
<td>.285</td>
<td>-.457**</td>
<td>.495***</td>
</tr>
<tr>
<td>Difference between arms (Cohen's d)</td>
<td>0.93 ( .20)</td>
<td>1.87т</td>
<td>1.03т</td>
<td>2.80тт</td>
</tr>
<tr>
<td>Concerns - Any drug trials (Pearson r)</td>
<td>.241*</td>
<td>-.173</td>
<td>.424***</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-.203*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-.271</td>
<td>.392**</td>
<td>-.133</td>
<td>.583***</td>
</tr>
<tr>
<td>MDMA</td>
<td>-.152</td>
<td>-.123</td>
<td>-.218</td>
<td>.233</td>
</tr>
<tr>
<td>Fisher r to z:</td>
<td>0.58</td>
<td>2.51т</td>
<td>0.41</td>
<td>2.01т</td>
</tr>
<tr>
<td>Δz (Cohen’s d)</td>
<td>(.13)</td>
<td>(.54)</td>
<td>(.09)</td>
<td>(.43)</td>
</tr>
</tbody>
</table>

Note: Statistically significant differences between treatment arm correlations were calculated by transforming r to z, using Fisher’s method, then calculating the difference in z-score. Significant correlations: *p<.05; **p<.01; ***p<.001. Significant difference between correlations: тp<.05; ттp<.01.
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 to a trial using an unknown, neutrally labelled pharmacotherapy (JB-4801-AP; control). However, we did find two sub-groups 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 [34, 35]. Given such clinical experience and training within psychopharmacology, it makes sense psychiatrists were more cautious in recommending a repurposed illicit drug as a potential therapeutic tool.

The harms of recreational ecstasy use are low compared to other substances, such as alcohol and methamphetamine [36, 37], but at higher doses in uncontrolled recreational settings, it can lead to serious adverse events or death [38]. 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-square analysis shows psychiatrists were significantly more likely to make critical comments about MDMA-AP than researchers (Supplementary 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”, whilst 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” [39], with significantly fewer adverse events associated with MDMA-AP, than placebo [20]. MDMA-AP also displayed efficacy in patients with a history substance use disorders [18].

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 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 [40]. 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 1980’s, MDMA was made illegal and many studies, mainstream news articles and government campaigns have highlighted the potential harms of chronic, high-dose recreational use, whilst studies on the safety and efficacy of therapeutic MDMA were halted [35]. 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, whilst 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 mental health 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 alphanumerical 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 [18]. 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 [6], 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 [1]. However, for patients to access MDMA-AP, it must first be accepted by the mental health community.

Researchers have previously described experiencing resistance in setting up trials of MDMA-AP in Australia, which they hypothesised was due to stigmatising beliefs [24, 26]. 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.

Acknowledgements

Thank you to all the participants who freely gave their time. Thank you to the following organisations for disseminating our research project to their members: RANZCP, ACPA, ASMR, and the APS. Thank you to the PHNs around Australia who passed on our research to professionals within their catchments. DW would like to thank Professor Caroline Hunt and Professor Suncica Lah for their support through the challenges that arose during the completion of this study.
Ethics

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.

Data Availability

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 on request from the corresponding author.

Declaration of Conflicting Interests

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

Author Contributions

DW, NG and BC designed the study. DW and NG recruited participants. DW conducted statistical analyses and wrote the paper. NG and BC provided feedback on the paper and amendments to the paper.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
References


**Figure 1.** Recruitment Flow Chart

**Figure 2.** Comparing the attitudes of mental health professionals towards 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.

**Figure 3.** Comparing the attitudes of psychiatrists, psychologists, and mental health (MH) researchers towards MDMA-AP and control, 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 = 9-28; significant simple effects: *p*<.05.

**Figure 4.** The relationship between experience and attitudes toward each vignette trial, measured on a 10-point scale. **A)** Level of safety concerns & **B)** strength of objection. Differences between correlations assessed using Fisher r to z transformations and comparisons; n = 43-51.
Sent recruitment advertisement to the following **Peak Bodies and research bodies**: Society for Mental Health Research (SMHR); Royal Australian & New Zealand College of Psychiatrists (RANZCP); Australian Psychological Society (APS); Australian Clinical Psychology Association (ACPA); Australian Association of Psychologists Incorporated (AAPi)

Sent recruitment advertisement to all **Primary Health Networks** - 31 PHNs

Sent to the following **Facebook Groups**: AAPI facebook page; Australian Psychologists; Psychology Australia; GP, doctor, allied health job group

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**Recruitment advertisement passed on to the members of organisation/group/networks**

**Peak Bodies**: SMHR, RANZCP, APS and ACPA all advertised via a direct email communication, through a monthly newsletter email, or in an ad on the website. It is unclear if an advertisement was sent through AAPI.

**PHNs**: 13 PHNs (42%) passed on recruitment (Hunter New England, Northern Sydney, North Coast NSW, South Western Sydney, Central and Eastern Sydney, Nepean Blue Mountains, Tasmania, Adelaide, Northern Territory, Northern Queensland, Brisbane South, Perth North, North Western Melbourne); 10 PHNs (32%) denied the request; and 8 PHNs (26%) did not clarify if recruitment was sent.

**Facebook Groups**: Psychology Australia was the only group to post the advertisement

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**Number of participants who began the survey** $N = 141$

**Participants who gave informed consent & completed all the primary outcome attitudes** $N = 100$

**After removing GPs and those without a listed profession** $N = 94$

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**Figure 1.** Recruitment flow chart

158x149mm (150 x 150 DPI)
Figure 2. Comparing the attitudes of mental health professionals towards 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.
**Figure 3.** Comparing the attitudes of psychiatrists, psychologists, and mental health (MH) researchers towards MDMA-AP and control, 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; $n = 9-28$; significant simple effects: *$p < .05$. 

169x194mm (150 x 150 DPI)
Figure 4. The relationship between experience and attitudes toward each vignette trial, measured on a 10-point scale. A) Level of safety concerns & B) strength of objection. Differences between correlations assessed using Fisher r to z transformations and comparisons; n = 43-51.

117x218mm (150 x 150 DPI)
Email Template Used in Recruitment

**Title:** “Evaluation of attitudes towards novel mental health treatments at the University of Sydney.”

“To...

Researchers from The Brain and Mind Centre, University of Sydney are seeking to understand the attitudes of psychiatrists, general practitioners, psychologists and mental health researchers towards new mental health treatments, as part of a Clinical Masters research project.

The survey will take 5 minutes to complete.

If you're interested in learning more about the study and taking part, please CLICK THIS LINK

Thank you for your attention.

Warm regards,

... 

(02) 9114 4343

email address

University of Sydney HREC project number [2019/872].”
Are you a GP, Psychiatrist, Psychologist or Mental Health Researcher?

Please complete this 5 minute online survey seeking to understand the Attitudes of Health Professionals Towards Novel Mental Health Medications

Research conducted by Brain and Mind Centre, University of Sydney - HREC [2019/872]

Supplementary Figure 1. The advertisement image used to recruit participants, alongside the written template.
Supplementary methods 1 - Vignettes

Vignette – Experimental condition

PLEASE READ THE ENTIRE STORY BEFORE MOVING ON TO ANSWER THE QUESTIONS.

Lisa is a 32-year-old primary school teacher. Three years ago, her ex-partner raped Lisa at knifepoint. A year later, Lisa was experiencing frequent vivid nightmares and would often have only a few hours sleep. Lisa noticed that she was “on edge” most of the day, withdrawing socially, and found it harder to focus on teaching her students. Lisa then began seeing you for treatment for post-traumatic stress disorder (PTSD). Lisa initially underwent exposure-based CBT for a period of 12 weeks. Lisa failed to see much improvement from this and started medication. Over the past 2 years, Lisa has tried two different types of antidepressant and had further CBT and EMDR therapy. Lisa continues to experience frequent nightmares, insomnia and high levels of daytime anxiety. Lisa has now ceased all psychiatric medications.

In her appointment today, Lisa has brought in a flyer for a clinical trial being conducted at a University. It states they are testing the effects of “Methylenedioxymethamphetamine (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’. The leaflet states that 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. Lisa is interested in participating in this trial and wants to know what you think.
Vignette – Control condition

PLEASE READ THE ENTIRE STORY BEFORE MOVING ON TO ANSWER THE QUESTIONS.

Lisa is a 32-year-old primary school teacher. Three years ago, her ex-partner raped Lisa at knifepoint. A year later, Lisa was experiencing frequent vivid nightmares and would often have only a few hours sleep. Lisa noticed that she was “on edge” most of the day, withdrawing socially, and found it harder to focus on teaching her students. Lisa then began seeing you for treatment for post-traumatic stress disorder (PTSD). Lisa initially underwent exposure-based CBT for a period of 12 weeks. Lisa failed to see much improvement from this and started medication. Over the past 2 years, Lisa has tried two different types of antidepressant and had further CBT and EMDR therapy. Lisa continues to experience frequent nightmares, insomnia and high levels of daytime anxiety. Lisa has now ceased all psychiatric medications.

In her appointment today, Lisa has brought in a flyer from a clinical trial being conducted at a University. “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. The leaflet states that preliminary studies have suggested this treatment has worked for a high proportion of people with PTSD and has very low chance for negative effects. Lisa wants to participate in this trial and wants to know what you think.
Supplementary methods 2 – Survey Questions

1. How likely are you to recommend that Lisa participates in this trial?
   Not at all 1---------2---------3---------4---------5---------6---------7---------8---------9---------10  Definitely

2. How strongly would you object to Lisa participating in this trial?
   Not at all 1---------2---------3---------4---------5---------6---------7---------8---------9---------10  Extremely

3. How likely do you think it is that MDMA-assisted psychotherapy will help Lisa?
   Not at all 1---------2---------3---------4---------5---------6---------7---------8---------9---------10  Extremely

4. How concerned are you about the safety of this treatment?
   Not at all 1---------2---------3---------4---------5---------6---------7---------8---------9---------10  Extremely

5. How concerned are you about people with mental health conditions taking part in ANY experimental drug trial?
   Not at all 1---------2---------3---------4---------5---------6---------7---------8---------9---------10  Extremely

6. How did you come to these opinions?

7. Would you recommend that Lisa try other therapies before considering this trial? [tick all that apply]
   a. Psychodynamic therapy
   b. Other talk therapies
   c. Augmentation with antipsychotics
   d. Transcranial magnetic stimulation
   e. Neurofeedback
   f. Other

8. Do you think recreational use of some drugs like ecstasy (MDMA) and magic mushrooms (psilocybin) should be decriminalised? YES/NO
   a. Why?
**Supplementary Table 1. Exploring qualitative responses that explain the rationale for mental health professionals’ attitudes**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Psychiatrist</th>
<th>Psychologist</th>
<th>MH Researcher</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>MDMA</td>
<td>Total</td>
<td>Control</td>
</tr>
<tr>
<td>Number of Participants</td>
<td>51</td>
<td>43</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>Number of Responses (%)</td>
<td>23</td>
<td>34</td>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>Neutral responses (%)</td>
<td>11</td>
<td>7</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: “Positive responses” are those which describe low concerns, low objections, high predicted efficacy or high recommendation, whilst “Negative responses” are the inverse. Neutral responses state: they have no personal opinion; they would seek more information; or would help the patient find her own answer.

Chi-square statistics A: $\chi^2(1, N=94)=11.3$, $p<.001$; B: $\chi^2(1, N=49)=10.7$, $p=.001$; C: $\chi^2(1, N=14)=3.7$, $p=.05$
Supplementary Figure 2. Analysis of potential covariates with the strength of recommendation to participate in the vignette trials. There was no significant covariance of A) Age; B) Experience; C) Stance on decriminalisation; or D) Gender. After accounting for the covariance in each analysis, a significant interaction of profession and vignette condition on the strength of recommendation remained. Error bars represent mean ± SEM; n = 8-28; significant simple effects: *p<0.05.
Stance Towards Decriminalisation

The Effect of Decriminalisation Stance on Attitudes Towards MDMA-AP versus Control

Those in favour of decriminalisation of recreational use of drugs like MDMA and psilocybin, were less likely to be concerned about MDMA-AP ($M_{\text{DIFF}} = -2.3$, SE = .74, $p = .014$) and more likely to predict that MDMA-AP would be efficacious ($M_{\text{DIFF}} = 2.3$, SE = .57, $p < .001$), than those against decriminalisation (Supplementary Figure 3). Furthermore, participants against decriminalisation were less likely to recommend MDMA-AP than controls ($M_{\text{DIFF}} = 2.4$, SE = .72, $p = .008$), and those in favour of decriminalisation ($M_{\text{DIFF}} = 2.3$, SE = .72, $p = .011$). There are significant interactions of stance towards decriminalisation and vignette condition for: the likelihood of recommending the trial ($F(1, 82) = 8.12$, $p = .006$); the predicted efficacy ($F(1, 82) = 7.90$, $p = .006$); and the level of safety concerns ($F(1, 82) = 5.27$, $p = .024$).

Interpretation of the Effects of Stance Towards Decriminalisation of Recreational Use

Professionals against decriminalisation of the recreational use of drugs, like MDMA and psilocybin displayed bias towards MDMA-AP. They were less likely to recommend MDMA-AP than the control trial, whilst those in favour of decriminalisation recommended MDMA-AP and control equally. There was also bias in both political groups, with the predicted efficacy of, and concerns about MDMA-AP biased according to the political stance on recreational use. It is unclear if beliefs about the efficacy and safety of MDMA-AP are motivating participants political beliefs or if their political alignment may bias their view towards the therapeutic use of MDMA.
Stance Towards Decriminalisation

A) Concerns for Safety

\[ \rho_{\text{interaction}} = 0.024 \]
\[ \rho_{\text{MDA decrim}} = 0.029 \]

B) Strength of Objection

C) Predicted Efficacy

\[ \rho_{\text{interaction}} = 0.006 \]
\[ \rho_{\text{MDA decrim}} = 0.003 \]

D) Strength of Recommendation

Supplementary Figure 3. Comparing the attitudes of those for and against decriminalisation, towards MDMA-AP and control, measured on a 10-point Likert 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; \( n = 9-28 \); significant simple effects: \#p<0.05; \##p<0.01; \###p<0.001.
Supplementary Figure 4. Comparing the attitudes of males and females, towards MDMA-AP and control, 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 = 9-28; significant simple effects: *p<0.05; **p<0.01; ***p<0.001.
# CONSORT 2010 checklist of information to include when reporting a randomised trial*

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td>2</td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>4-5</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td>5</td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td>5, 7</td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>6</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>N/A</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>N/A</td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>6</td>
</tr>
<tr>
<td>Allocation concealment mechanism</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>6</td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>5</td>
</tr>
<tr>
<td>Title</td>
<td>Item</td>
<td>Description</td>
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<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
<td></td>
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<tr>
<td></td>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
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</tr>
<tr>
<td>Discussion</td>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
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<tr>
<td></td>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
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<tr>
<td></td>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
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<tr>
<td>Other information</td>
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<td>Registration number and name of trial registry</td>
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<tr>
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<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
<td></td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).*