An evaluation of the therapeutic value, benefits and risks of methylenedioxymethamphetamine (MDMA) and psilocybin for the treatment of mental, behavioural or developmental disorders

A report to the Therapeutic Goods Administration

Steve Kisely, Metro South Health, Queensland

Mark Connor, Macquarie University, Faculty of Medicine Health and Human Sciences

Andrew Somogyi, University of Adelaide, Faculty of Health and Medical Sciences

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Summary

There has been increasing interest in the use of methylenedioxymethamphetamine (MDMA) and psilocybin in the treatment of mental, behavioural or developmental disorders. Although there have been several recent systematic reviews, studies and participants have been limited, and the field is rapidly evolving with the publication of more studies.

With the aid of a professional librarian, we therefore searched MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL for randomised controlled trials (RCTs) of MDMA and psilocybin with either inactive or active controls. Articles were independently assessed. Outcomes were psychiatric symptoms measured by standardised, validated and internationally recognised instruments at least two weeks following administration. Quality was assessed using the Cochrane risk of bias assessment tool.

There were eight studies included on MDMA and six on psilocybin. Diagnoses of interest included post-traumatic stress disorder (PTSD), treatment-resistant depression (TRD), obsessive-compulsive disorder, social anxiety in adults with autism, and anxiety or depression in life threatening disease (LTD).

Results

MDMA: Six of the eight studies were on post-traumatic stress disorder, one on anxiety due to a life-threatening disease and the other on social anxiety in adults with autism. Half of the studies used inactive placebo as the control while the remainder used low doses of MDMA. In all studies both the intervention group and controls received supplementary intense psychotherapy.

In general, between four and twelve weeks following administration, there were statistically significant differences for MDMA doses of greater than 100 mg in comparison with inactive or active controls. Most information was on MDMA symptom scores compared to active controls in post-traumatic stress disorder (Standardised Mean Difference=-0.86, 95%CI=-1.23 to -0.50; k=4). We consider a standardised mean difference of this magnitude to be a strong effect size.

MDMA also resulted in statistically significant improvements in social anxiety in adults with autism when compared to placebo. However, the results for anxiety in life threatening disease were non-significant although participant numbers were low. Effect sizes were large in all comparisons but with wide confidence intervals.

MDMA was well tolerated in all the studies. The main adverse effects were anxiety, restlessness, fatigue, jaw-clenching, headache and transient increases in blood pressure. Serious events such as suicidal ideation were rare and occurred almost entirely in the placebo arm or were otherwise unrelated to the therapy.

Psilocybin: Four of the six studies were for anxiety or depression for a life-threatening disease, two on treatment-resistant depression and one on obsessive-compulsive disorder. Two used low-dose psilocybin as the control and another two used the vasodilator niacin as it induces a mild physiological reaction (e.g. flushing) without any psychological effects.

One study reported statistically significant differences between psilocybin and placebo (niacin) in treatment-resistant depression while another reported statistically significant differences between high and low dose psilocybin for subjects with anxiety or depression in life threatening disease. Psilocybin was superior to remaining on a wait-list in a third study and equally effective as a registered antidepressant (escitalopram) in a fourth study. In a fifth study there were no statistically significant differences between psilocybin and controls at the two-week follow-up, although both groups showed longer-term improvements following cross-over.

In the final study there was no significant effect of dose on obsessive-compulsive symptoms possibly because of low numbers and unexpectedly high response to the very low dose placebo. Three studies also assessed whether participants had shown a clinically significant response or were in remission as regards depression or anxiety. There were statistically significant differences between psilocybin and active placebo (niacin or low dose psilocybin) and psilocybin remained as effective as the antidepressant escitalopram.

Psilocybin was also well tolerated in all the studies. The main effects were anxiety, headache and transient increases in blood pressure.

Conclusion

By combining the effects of small and possibly underpowered studies, meta-analyses can help to establish the relative efficacy of interventions such as MDMA and psilocybin where large studies may be impractical. Although we were only able to combine results from 9 studies for either beneficial or adverse effects, we did demonstrate statistically significant differences of the two psychedelic agents between both inactive and active treatments for either continuous scores or dichotomous responses. However, it is important to note that this was in highly supportive and structured environments including intense psychotherapy sessions in many cases.

Both agents were well-tolerated in supervised trials with or without additional use of psychotherapy. However, trial quality including blinding and follow-up was variable and only a small proportion of potential participants were included in the randomised phase.

We conclude that MDMA and psilocybin may show promise in highly selected populations but only where these medicines are administered in closely clinically supervised settings and with intensive professional support.

Introduction

There has been increasing interest in the use of psychedelics in the treatment of mental, behavioural or developmental disorders (1-6), including methylenedioxymethamphetamine (MDMA) and psilocybin. This is reflected in the breakthrough designation by the US Food & Drug Administration (FDA) of MDMA and psilocybin for the treatment of posttraumatic stress disorder (PTSD) and treatment-resistant depression, respectively. Other work suggests that psilocybin may also be effective for treating anxiety disorders, substance use disorders, and end-of-life distress (4-7). Benefits appear to occur in both stand-alone therapy and when combined with psychotherapy. Although there have been several recent systematic reviews published (2-5, 7-10), the number of studies and participants have been limited, and the field is rapidly evolving with the availability of more studies and data. Ongoing reviews that are currently registered with PROSPERO are restricted to individual drugs or particular diagnoses and/or include non-RCTs (randomised clinical trials), which are subject to considerable biases. Furthermore, for drugs with a rapid onset of action it is important to consider studies with inactive and active controls in separate comparisons. In this report we have sought to compile data from randomized, double-blind, placebo-controlled trials of psilocybin and MDMA for mental health conditions.

Classical psychedelics are drugs with direct agonist actions at 5-HT2 receptors and include lysergic acid diethylamide (LSD), psilocybin/psilocin, mescaline and dimethyltryptamine (11). The development of our understanding of 5-HT function in the central nervous system was closely linked with early studies of the psychedelics including psilocybin, and classical psychedelics were used as adjuncts to psychological therapy in thousands of patients in the 1950s and 1960s, prior to the severe restrictions of their availability 50 years ago (reviewed in (12)). Psilocybin is a prodrug of the more active psilocin, which is produced by dephosphorylation (13) although it does have some biological activity of its own (14). Psilocin and psilocybin are agonists of 5-HT2 receptors (14, 15), and studies in humans suggest that 5HT2A receptor occupancy may be critical for the psychedelic experience produced by psilocybin (16, 17) although actions at other receptors could also be involved. Psilocin has a half-life of about 3 hours and its kinetics appear to be dose-linear(18).

MDMA has a complex pharmacology, with prominent actions at transporters for 5-HT (SERT), norepinephrine (NET) and dopamine (DAT), as well the vesicular monoamine transporter (VMAT). MDMA produces an increase in extracellular levels of each of these neurotransmitters (19), and while it may have some direct actions at neurotransmitter receptors, elevations of 5-HT and norepinephrine are thought to be the most important proximal cause of the conscious effects of MDMA in humans (20, 21).

Global changes in monoamine neurotransmitter levels will affect the activity of many neural circuits involving a plethora of neurotransmitters. MDMA is usually administered as a racemic mixture, but the pharmacological actions of the (+) and (-) enantiomers of MDMA are different, even at primary effectors such as SERT (22) in which R(-)-MDMA is more active. The clinical importance of MDMA enantiomers or the direct actions of MDMA at 5-HT and other monoamine receptors remains to be established. In addition, MDMA is O-demethylated to HHMA (3,4-dihydroxymethamphetamine) via the highly polymorphic CYP2D6 enzyme and a minor pathway involves N-demethylation (CYP2C19, CYP2B6) to the active MDA metabolite. CYP2D6 poor metabolisers have modest increases in MDMA and lower concentrations of HHMA. However, MDMA causes autoinhibition of CYP2D6, resulting in extensive and intermediate metabolisers being phenocopied to poor metabolisers, with the potential for drug interactions with many other drugs such as antidepressants. The half-life of MDMA is about 8 hours but increases with repeated dosing (23).

It is not known how activation of 5-HT2A receptors (or others) leads to changes in neuronal and circuit activity that produces a psychedelic experience. In a preclinical model, psilocybin was reported to produce a persistent increase in the size and density of dendritic spines – small, labile structures that are thought to be an anatomical substrate supporting neural plasticity (24). Intriguingly, similar changes in spine density have been associated with antidepressant actions (25). However, being able to definitively link changes in neuronal morphology or other properties to alterations in human consciousness remains one of the central unsolved problems of neuroscience. The neurochemical effects of MDMA have been studied much more extensively, but this has been almost exclusively from the perspective of MDMA-mediated neurotoxicity rather than any potential therapeutic benefit (19).

This systematic literature review and meta-analysis evaluates the current state of the evidence of therapeutic value benefits and risks of MDMA and psilocybin for the treatment of mental health conditions, including the size of effect and quality of evidence.

Method

The protocol was registered with the Open Science Framework (osf.io/hdt3s) on August 13th, 2021. In addition, we followed recommendations for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement including background, search strategy, methods, results, discussion and conclusions (26).

Health outcomes

The primary outcomes of interest were psychiatric symptoms as measured by standardised, validated and internationally recognised instruments at least two weeks following administration. These could include anxiety, depression and post-traumatic stress and substance use disorders. Secondary outcomes were psychiatric symptoms at other times and adverse effects either immediately following administration or up to seven days afterwards.

Inclusion and exclusion criteria

We included randomised controlled trials (RCTs) with inactive or active controls in the treatment of ICD-10 mental, behavioural or developmental disorders that were published in a peer-reviewed paper from any of the databases in the following paragraph. We only included studies on humans and excluded studies in healthy volunteers, and pre-prints that had not been peer-reviewed. Both crossover and parallel group trials were eligible for inclusion. However, we only used results of the first phase/arm of treatment in crossover trials. This was to minimize the bias of study designs where participants experience both active and control conditions, and, in the context of informed consent, know that what they are allocated to in the second phase/arm of a study will be the opposite of what they have already experienced in the first. Where data were available for two or more studies, they were combined in a meta-analysis.

Search strategy

With the aid of a professional librarian, we searched the following databases up till August 2021 with no language limitations: MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL. Appendix 1 gives details of the searches. We searched for further publications by scrutinizing the reference lists of initial studies identified and other relevant review papers. We made attempts to contact selected authors and experts. Pairs of reviewers (SK, MC and AS) independently assessed titles, abstracts and papers, as well as extracted and checked extracted data for accuracy. In the case of disagreements, consensus was reached on all occasions.

Study quality

We assessed the quality of included studies using the following criteria of the risk of bias assessment tool, developed by the Cochrane Collaboration to assess possible sources of bias in RCTs: 1. Adequate generation of allocation sequence; 2. Concealment of allocation to conditions; 3. Prevention of knowledge of the allocated intervention to participants and personnel; 4. Prevention of knowledge of the allocated intervention to assessors of outcome; 5. Dealing with incomplete outcome data; 6. Selective reporting of outcomes; and, 7. Other sources of bias (27).

Statistical analysis

We used Review Manager version 5.2 for Windows, a statistical software package for analysing Cochrane Collaboration systematic reviews. We calculated the standardised mean difference (SMD) for continuous data even where studies used the same scale, given findings that the SMD is more generalisable than the mean difference. We reported the risk ratio (RR) for any dichotomous outcome. Where possible, intention-to-treat analyses were used. We categorised the strength of effect size in terms of weak, moderate and strong (Table 1).

Table 1: Effect size strength (28, 29)

Type of effect size	Small effect	Moderate effect	Strong effect
SMD	0.2	0.5	0.8
RR	2.0	3.0	4.0

Where studies compared different doses of active agent against the same controls, the number of controls was halved to avoid counting the same subjects twice. Where there were odd numbers that could not be halved, differences in comparisons were investigated using sensitivity analyses. Some studies measured the same outcome with several different scales such as the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale. In this situation we undertook sensitivity analysis of the effect of substituting one scale for another.

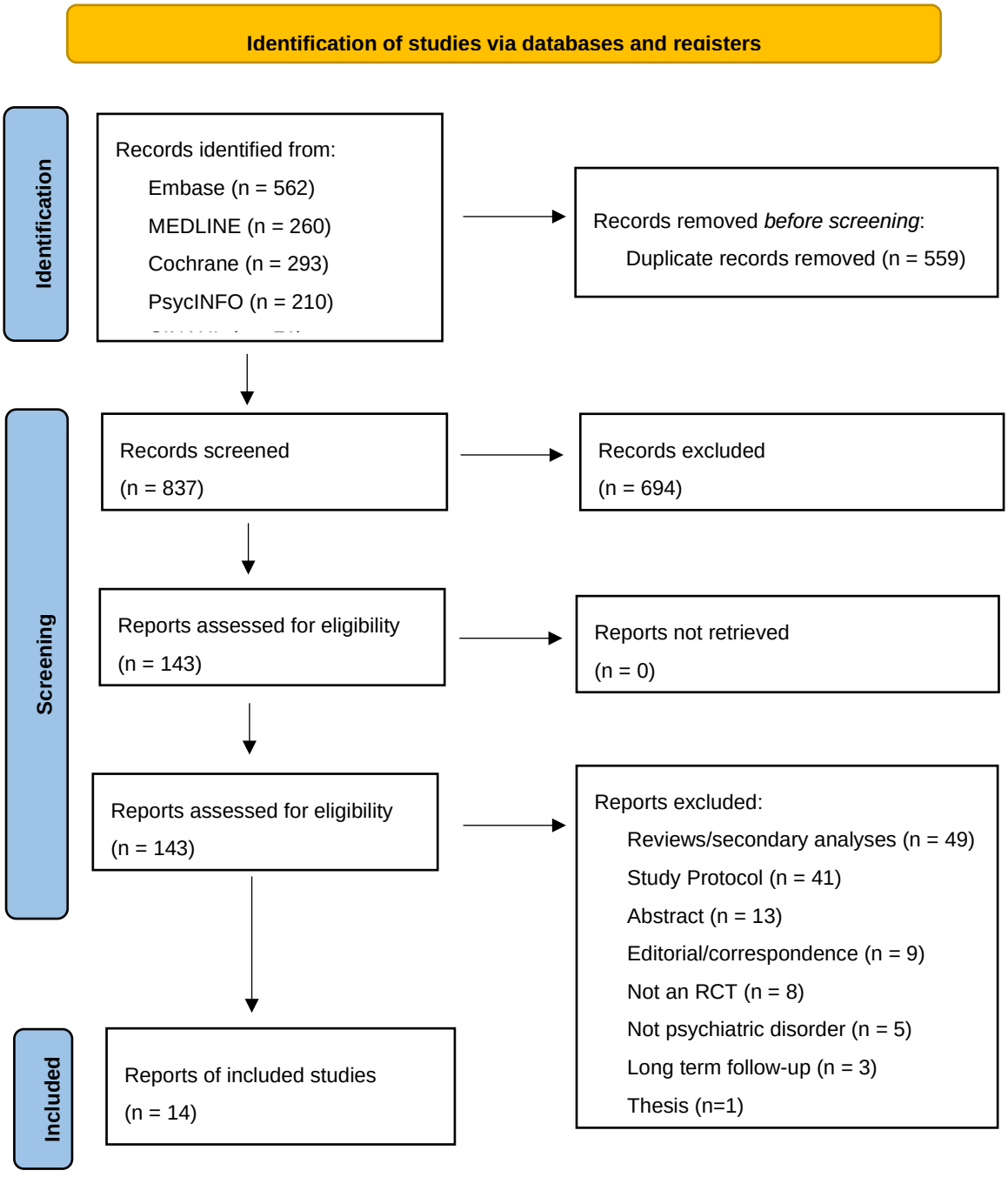
We assessed heterogeneity using the I2 statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small. It is calculated using the chi-squared statistic (Q) and its degrees of freedom [22]. An estimate of 50% or greater indicates possible heterogeneity, and scores of 75–100% indicate considerable heterogeneity.

We used the random effects model for all the analyses as we could not definitely exclude between-study variation even in the absence of statistical heterogeneity given the range of interventions under review. For any outcomes where there were at least 10 studies, we tested for publication bias using funnel plot asymmetry where low P-values suggest publication bias [22].

Results

We found 837 citations of interest after the elimination of duplicates, of which 143 full-text papers were potentially relevant and assessed for eligibility. Of these, 129 papers were excluded for reasons listed in Figure 1 and Supplementary Table 1. This left 14 papers (Figure 1).

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only[1]



[1] *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

Of these, nine had data that could be combined in a meta-analysis of either beneficial or adverse effects. There were eight studies on MDMA (30-37), and six on psilocybin (38-43). Conditions of interest included post-traumatic stress disorder (PTSD), treatment-resistant depression, obsessive-compulsive disorder, social anxiety in adults with autism and anxiety or depression in life threatening disease. There were no RCTs on other conditions such as substance use disorders and no studies were conducted in Australia.

Quality assessment

Study quality was not optimal on the risk of bias assessment tool (Supplementary Table 2). Generation of the random allocation sequence and risk of bias in allocation concealment were adequate in seven studies, while in the other seven it was unclear. Twelve of the studies were described as double-blinded (Table 2) while one used a wait-list control (41) and another made no mention of blinding (43). However, in three studies it was unclear whether blinding was successful as investigators were able to guess the correct allocation in a high proportion of cases (31, 37, 39).

Attrition bias was low in 13 out of the 14 studies because of high rates of follow–up, although only six explicitly used intention-to-treat (ITT) analyses, all but one of which were on MDMA (30, 32, 35-37, 42). All but two of the studies were rated as unclear for reporting bias largely because there was no protocol with which to make a comparison. In a further two studies, outcomes were largely presented as graphs. In the case of one study, where it was difficult to extract numbers from the relevant figures, the authors were contacted for clarification, but no reply was received. In terms of other sources of bias, all but two of the studies (41, 42) were either fully or partly funded and/or supported by the Heffter Research Institute or the Multidisciplinary Association of Psychedelic Studies (MAPS). Both are privately funded non-profit research and educational organisations that promote the therapeutic uses of psychedelics. The latter organisation includes MAPS Public Benefit Corporation (MAPS PBC), a wholly owned subsidiary that balances income from providing legal access to MDMA with the social benefits of MAPS' mission.

Another source of bias was that only a small proportion of potential participants were actually randomised. Where it was recorded, participants were overwhelmingly white/European. In addition, trials generally excluded people with a personal or family history of psychosis, personal history of mania, repeated violence towards others, and a recent personal history of a suicide attempt, as well as those with current drug or alcohol use disorders, which may limit generalisability. There was also an uneven distribution between the intervention and control arms with more participants allocated to the experimental group in all but three studies (39, 40, 42).

MDMA

Six of the eight studies on MDMA were on post-traumatic stress disorder, one was on anxiety due to a life-threatening disease and the other on social anxiety in adults with autism (Supplementary Table 3). All were parallel-arm RCTs often followed by open-label extensions. One half of the studies used inactive placebo as the control while the remainder used low doses of MDMA. In all studies both the intervention group and controls received supplementary intense psychotherapy.

There were statistically significant differences between intervention and controls groups in four out of seven studies, and non-significant differences in the remaining three (Supplementary Table 2). However, all the studies comprised a small number of participants. Five out of the six studies on PTSD used the Clinician Administered PTSD Scale (CAPS).

Figure 3: Continuous PTSD outcomes at four to twelve weeks

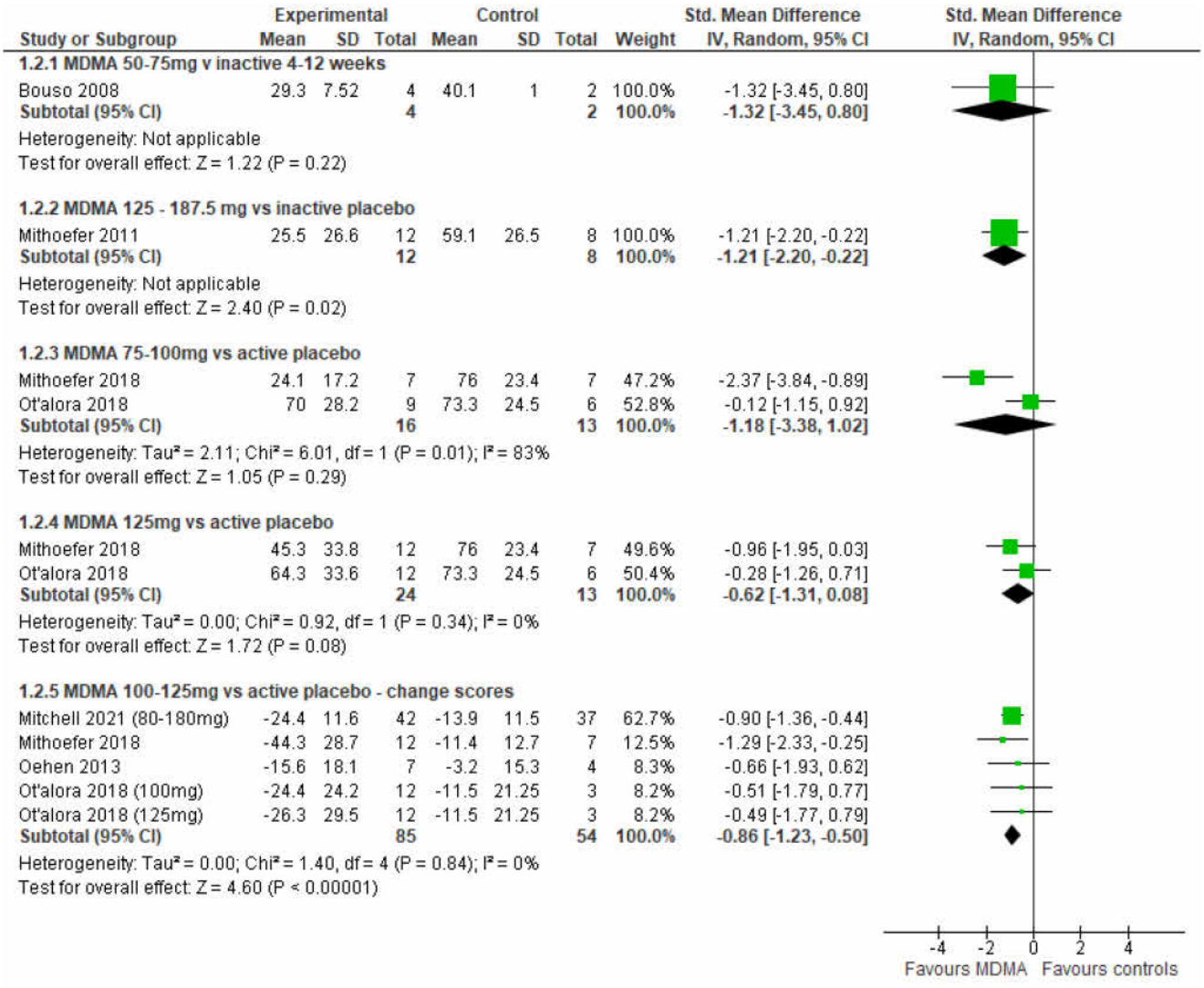
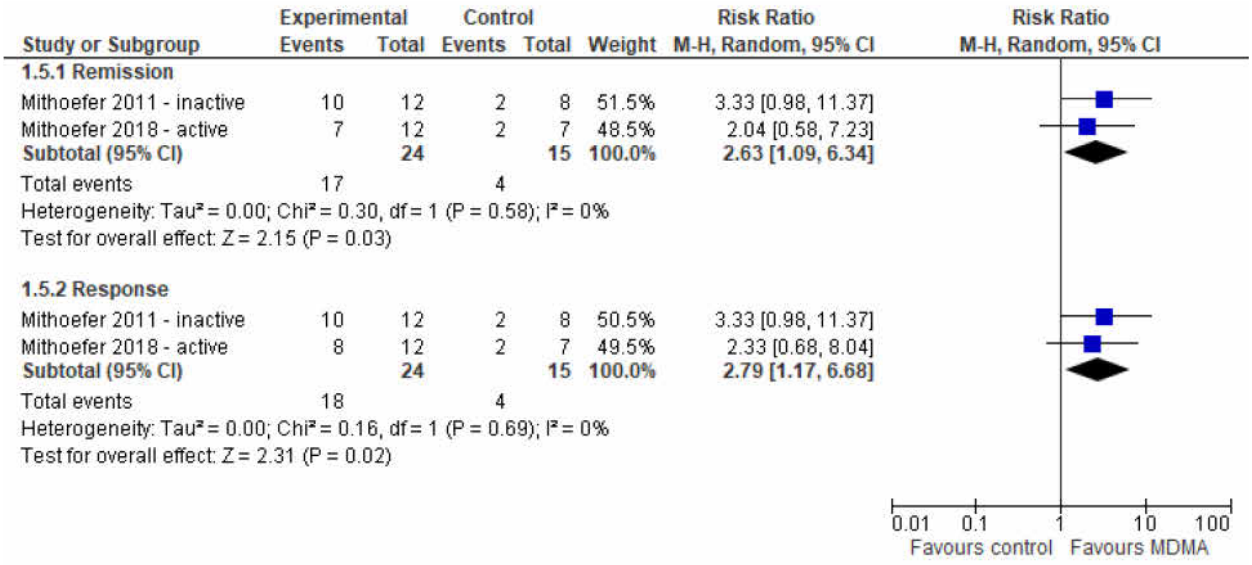


Figure 3 summarises the outcomes and change in continuous scores at between four- and twelve-weeks following administration. In general, there were statistically significant differences in endpoint scores for MDMA doses of greater that 100 mg in comparison with inactive controls and change scores in comparison with active controls.

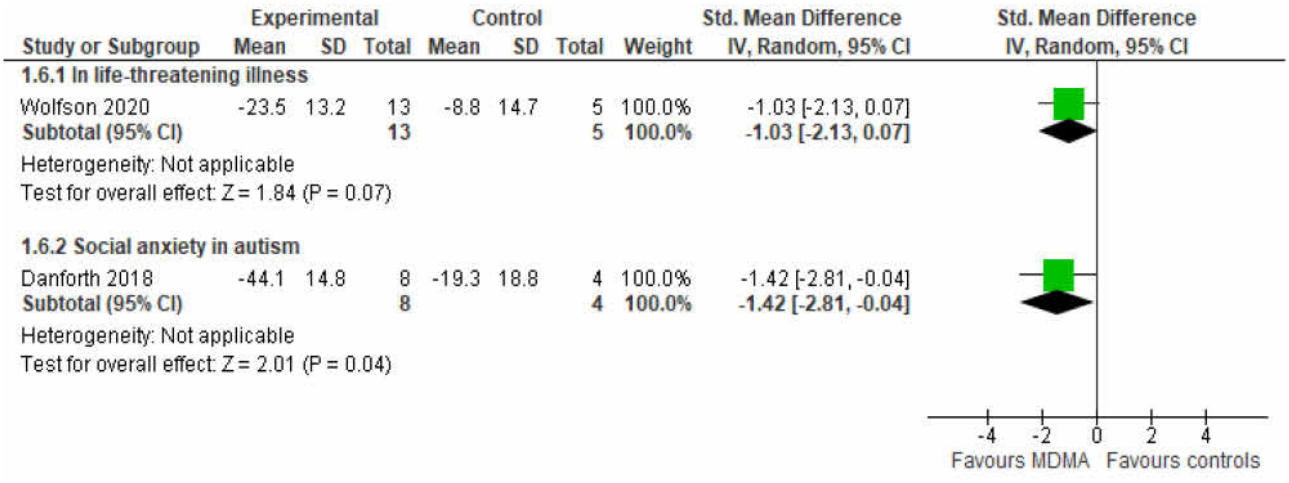
Two studies from the same group also assessed whether participants had shown a 30% reduction in CAPS scores (response) or no longer met criteria for a case (remission). For both outcomes, there were statistically significant differences, although the effect was greatest in comparisons against inactive controls (Figure 4).

Figure 4: Remission and response rates in PTSD scores at four weeks



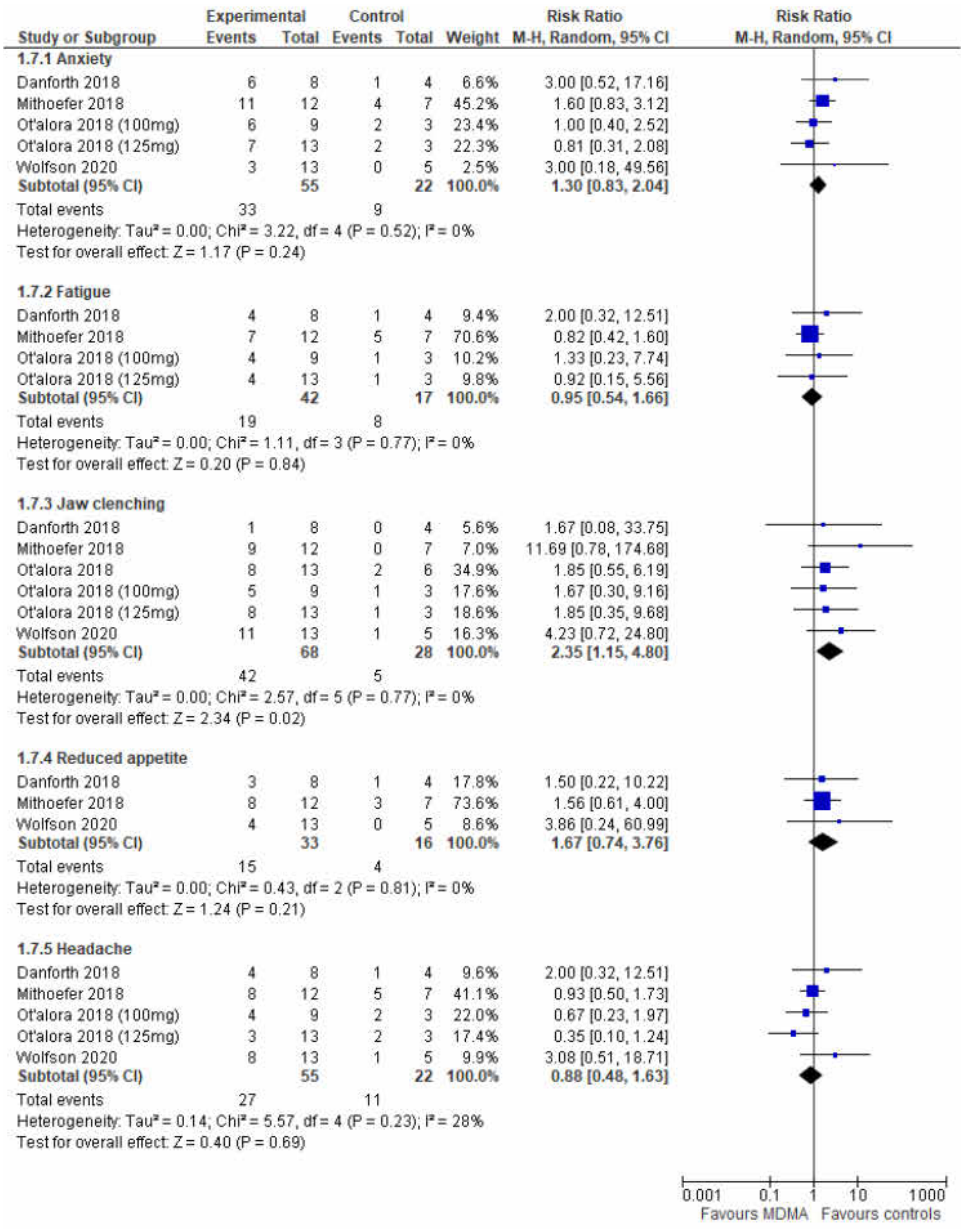
MDMA also resulted in statistically significant (P=0.04) improvements in social anxiety in adults with autism when compared to placebo (Figure 5). However, the results for life threatening disease were non-significant (P=0.07) although participant numbers were low (Figure 5). Effect sizes were large in all comparisons but with wide confidence intervals.

Figure 5: Continuous outcomes for anxiety in autism and life-threatening disease



MDMA was well tolerated in all the studies. The main adverse effects were anxiety, restlessness, fatigue, jaw-clenching, headache and transient increases in blood pressure. Serious events such as suicidal ideation were rare and occurred almost entirely in the placebo arm or were otherwise unrelated to the therapy. There were no attempts at assessing any biochemical or haematological changes. We were able to perform a meta-analysis from the results of five of the common adverse effects. Most information concerned the number of participants experiencing adverse events immediately after administration (Figure 6). The only statistically significant difference was that participants in the MDMA were more like to experience jaw clenching.

Figure 6: MDMA – adverse effects (immediate)



There were similar findings for adverse events up to seven days after drug administration except that participants who received MDMA were more likely to report a reduced appetite (Supplementary Figure 2). Two studies reported on events per session rather than patient. There were no significant differences between MDMA and control groups either immediately or up to seven days afterwards (Supplementary Figures 3 and 4).

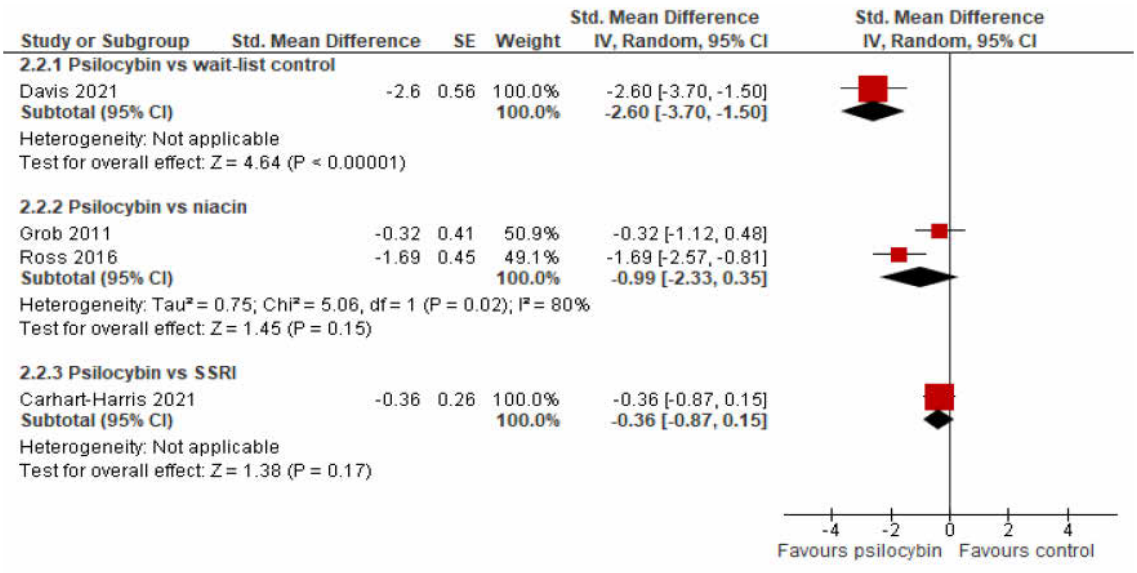
Psilocybin

Four of the six studies on psilocybin were for anxiety or depression due to a life-threatening disease, two on treatment-resistant depression and one on obsessive-compulsive disorder (Supplementary Table 4). Two used low-dose psilocybin as the control and two used the vasodilator niacin as the latter induces a mild physiological reaction (e.g. flushing) without any psychological effects (Supplementary Table 4). One study used escitalopram as the comparator and the final study used wait-list controls (Supplementary Table 4). Only one study was a parallel arm RCT (42). Primary outcomes such as those prior to cross-over were measured at between two and eight weeks.

One study reported statistically significant differences between psilocybin and niacin in treatment-resistant depression and another reported statistically significant differences between high and low dose psylocibin for subjects with anxiety or depression due to life threatening disease. Psilocybin was superior to remaining on a wait-list in a third study and equally effective as escitalopram in a fourth study although in the case of the latter, changes in secondary outcomes mostly favoured psilocybin. In a fifth study there were no statistically significant differences between psilocybin and controls at the two-week follow-up, although both groups showed longer-term improvements following cross-over. In the final study there was no significant effect of dose on obsessive-compulsive symptoms possibly because of low numbers and unexpectedly high response to the very low dose placebo.

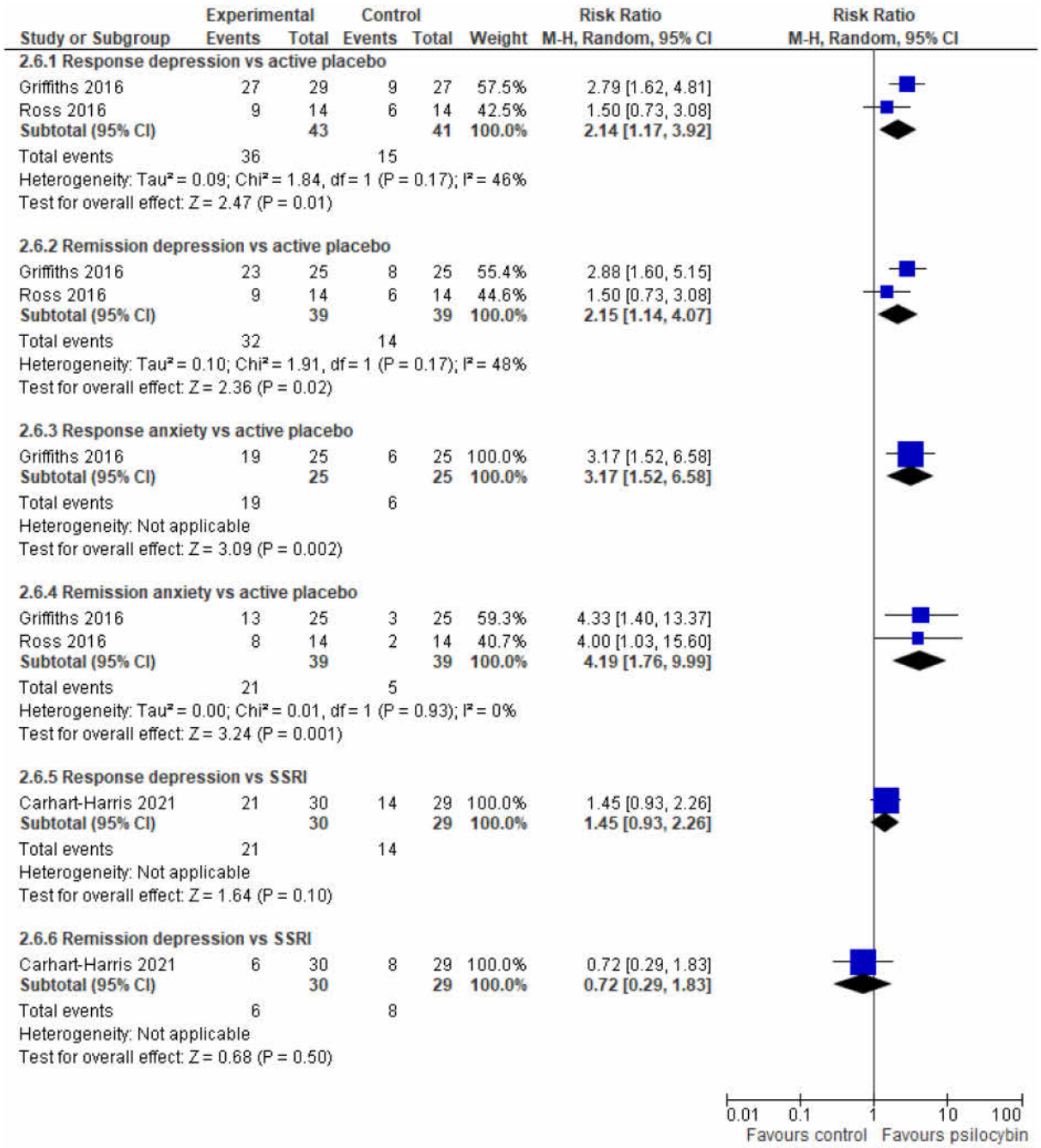
Figure 7 summarises the endpoint continuous scores for the primary outcomes of depression +/- anxiety at between four- and eight-weeks following administration. Psilocybin was significantly superior to wait-list control but not to niacin. It was equally as effective as escitalopram.

Figure 7: Psilocybin – benefits in primary outcomes



Three studies also assessed whether participants had shown a clinically significant response or were in remission as regards depression or anxiety (Figure 8). There were statistically significant differences between psilocybin and active placebo (niacin or low dose psilocybin) while psilocybin remained as effective as escitalopram (Figure 8). In comparison with active placebo, effect sizes were small to strong.

Figure 8: Remission and response rates in anxiety or depression scores



Adverse events were similar to those of MDMA and well tolerated in all the studies. The main effects were anxiety, headache and transient increases in blood pressure. None were coded as serious. It was not possible to combine the results quantitatively.

Sensitivity analyses

Sensitivity analyses of the effects of different doses of active agent or of substituting one scale for another made little difference to the outcomes.

Heterogeneity and publication bias

All but two of the results had an I^2 estimate of less than 50% suggesting that our results were not affected by heterogeneity. However, we were unable to test for publication bias as there were insufficient studies.

Discussion

The conditions that have been explored for potential therapeutic efficacy with MDMA and psilocybin are serious. For instance, a significant proportion of people living with PTSD or depression and anxiety in the face of a serious illness do not obtain adequate relief from existing therapeutic strategies. For instance, PTSD may affect 1-2% of Australians at any one time (44), and up to 12 % over their lifetime (45). PTSD prevalence is significantly increased in soldiers (46), emergency and health services personnel (47) and people living with entrenched disadvantage such indigenous Australians (48) and refugees (49). PTSD is also associated with depression and alcohol (and other) substance use disorders. Current treatments involve psychological therapies and medication; psychological therapies produce remission in up to 50% and symptom reduction in others, while anti-psychotic medications can provide symptomatic relief (50, 51). However, many people are not helped by any interventions and the social and economic costs are high for unresolved and lifelong PTSD (52). More effective treatments are needed. Similarly, anxiety and depression are common in people with life-threatening disease and can contribute to poor recovery from medical procedures and early mortality (53, 54). In addition, many patients with major depression do not achieve full or lasting recovery and so require switching, combination or augmentation of medication plus/ minus neurostimulation (e.g., electro-convulsive therapy), all of which increase side-effects (55).

By combining the effects of small and possibly underpowered studies, meta-analyses can help to establish the relative efficacy of interventions such as MDMA and psilocybin where large studies may be impractical. Although we were only able to combine results from 9 studies, we did demonstrate statistically significant ($P<0.05$) differences between the two psychedelic agents and both inactive and active treatments for either continuous scores or dichotomous responses. However, it is important to note that this was in highly supportive and structured environments including intense psychotherapy sessions in many cases. Effect sizes ranged from small to strong and 95% confidence intervals were wide. Evidence was strongest for MDMA, especially in doses of over 100 mg.

Both agents were well tolerated with limited evidence of acute serious adverse reactions in trial participants at the dosing regimens used. This is an important observation given concerns over the potential for neurotoxicity, diversion and psychosis in unregulated environments (56).

However, there are several limitations to these findings. The most obvious is that we were only able to find and combine data from nine eligible studies. Overall, study quality was not optimal, despite studies being described as double–blinded. In some cases, it appeared on questioning that observers and/or patients may still have been aware of their treatment allocation. There was relatively little loss to follow-up after randomisation in any of the studies. However, in several trials, only a small proportion of potential participants were included in the randomised phase. In addition, the exclusion criteria limit the findings to people with PTSD, depression, anxiety and obsessive-compulsive disorders, but not those with a family or past history of other psychiatric disorders (particularly schizophrenia and bipolar disorder). Furthermore, we were unable to find any RCTs on substance use disorders. In addition, there were relatively small samples, largely restricted to white/European populations and none were conducted in Australia. This is particularly relevant given the high rates of PTSD in Indigenous Australians (48). All these factors may limit the generalisability of the findings.

In most of the studies psilocybin and MDMA were combined with psychotherapy. A major unknown is the degree to which the psychedelic/psychotherapy interaction is dependent on the specific type of psychotherapy administered. This raises the question as to whether clinical practice would need to follow a specific protocol.

Many of the studies on psilocybin used a crossover design, which limits the interpretation after the crossover, such that only the outcomes prior to the crossover, open-label continuation can be reliably due to the drug. Finally, we had insufficient studies to test for publication bias and although the I-squared values were low, we cannot exclude the possibility of heterogeneity given the wide 95% confidence intervals.

In conclusion MDMA and psilocybin may show potential as therapeutic agents in highly selected populations when administered in closely supervised settings and with intensive support. Evidence appears strongest for MDMA. By contrast, randomised findings for psilocybin are largely limited to short follow-up data prior to cross-over.

Conflicts of interest

Dr Kisely is a member of both the Advisory Committee on Medicines of the Therapeutic Goods Administration and one of the committees that provided comments on the clinical memorandum on the therapeutic use of psychedelic substances from the Royal Australian and New Zealand College of Psychiatrists.

Dr Somogyi is a co-investigator on two National Health and Medical Research Council funded clinical trials on ketamine treatment for depression and an associate investigator on an application to the Medical Research Future Fund for a clinical trial using ketamine or psilocybin in mood and stress disorders. He is also a member of the Controlled Substances Advisory Council of South Australia.

None known for Dr Connor.

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Supplementary tables

Supplementary Table 1: Excluded studies

Study		Year	Reason excluded
1.	Aday *et al*.	2021	Reviews/ secondary data analyses
2.	Agin-Liebes	2021	Thesis
3.	Agin-Liebes *et al*.	2020	Longer-term follow-up of included study
4.	Amoroso *et al*.	2016	Reviews/ secondary data analyses
5.	Amoroso	2015	Reviews/ secondary data analyses
6.	Andersen *et al*.	2021	Reviews/ secondary data analyses
7.	Australian & New Zealand Clinical Trials Register	2012	Study protocol
8.	Australian & New Zealand Clinical Trials Register	2019	Study protocol
9.	Australian & New Zealand Clinical Trials Register	2019	Study protocol
10.	Baggott *et al*.	2010	Abstract
11.	Baggott *et al*.	2016	Not on psychiatric disorders
12.	Baggott *et al*.	2016	Not on psychiatric disorders
13.	Bahji *et al*.	2019	Abstract
14.	Bahji *et al*.	2020	Reviews/ secondary data analyses
15.	Barone *et al*.	2019	Not an RCT
16.	Barrett	2019	Abstract
17.	Belser	2010	Abstract
18.	Benville *et al*.	2021	Abstract
19.	Berkovitch *et al*.	2021	Reviews/ secondary data analyses
20.	Blinderman	2016	Editorial/ correspondence
21.	Bogenschutz	2012	Abstract
22.	Bogenschutz	2015	Not an RCT

23.	Bogenschutz	2016	Editorial correspondence
24.	Bogenschutz	2013	Reviews/secondary data analyses
25.	Bogenschutz *et al*.	2018	Not RCT
26.	Borissova *et al*.	2020	Not on psychiatric disorders
27.	Breeksema	2021	Reviews/ secondary data analyses
28.	Cao *et al*.	2019	Reviews/ secondary data analyses
29.	Carhart-Harris	2015	Abstract
30.	Carhart-Harris & Nutt	2016	Editorial/ correspondence
31.	Carhart-Harris *et al*.	2018	Not an RCT
32.	Castro Santos & Gama Marques	2021	Reviews/ secondary data analyses
33.	Chabrol	2013	Editorial/ correspondence
34.	Clinical Trials Register	2004	Study protocol
35.	Clinical Trials Register	2006	Study protocol
36.	Clinical Trials Register	2006	Study protocol
37.	Clinical Trials Register	2006	Study protocol
38.	Clinical Trials Register	2009	Study protocol
39.	Clinical Trials Register	2009	Study protocol
40.	Clinical Trials Register	2010	Study protocol
41.	Clinical Trials Register	2012	Study protocol
42.	Clinical Trials Register	2013	Study protocol
43.	Clinical Trials Register	2013	Study protocol
44.	Clinical Trials Register	2013	Study protocol
45.	Clinical Trials Register	2014	Study protocol
46.	Clinical Trials Register	2015	Study protocol

47.	Clinical Trials Register	2017	Study protocol
48.	Clinical Trials Register	2018	Study protocol
49.	Clinical Trials Register	2018	Study protocol
50.	Clinical Trials Register	2019	Study protocol
51.	Clinical Trials Register	2019	Study protocol
52.	Clinical Trials Register	2019	Study protocol
53.	Clinical Trials Register	2020	Study protocol
54.	Clinical Trials Register	2020	Study protocol
55.	Clinical Trials Register	2020	Study protocol
56.	Clinical Trials Register	2020	Study protocol
57.	Clinical Trials Register	2021	Study protocol
58.	Clinical Trials Register	2020	Study protocol
59.	Clinical Trials Register	2017	Study protocol
60.	Clinical Trials Register	2018	Study protocol
61.	Clinical Trials Register	2018	Study protocol
62.	Cohen	2016	Abstract
63.	Commentary	2018	Reviews/ secondary data analyses
64.	Corey *et al*.	2016	Not an RCT
65.	Curran *et al*.	2016	Abstract
66.	Danforth	2014	Abstract
67.	Danforth *et al*.	2016	Reviews/ secondary data analyses
68.	Davey	2021	Editorial/ correspondence
69.	Davis and Griffiths	2012	Editorial/correspondence
70.	de Veen *et al*.	2017	Reviews/ secondary data analyses

71.	dos Santos *et al*.	2016	Reviews/ secondary data analyses
72.	dos Santos et al.	2019	Reviews/ secondary data analyses
73.	dos Santos *et al*.	2018	Reviews/ secondary data analyses
74.	d'Otalora, and Doblin.	2013	Study protocol
75.	European Union Clinical Trial register	2020	Study protocol
76.	European Union Clinical Trial Register	2018	Study protocol
77.	European Union Clinical Trial Register	2020	Study protocol
78.	European Union Clinical Trial register	2018	Study protocol
79.	European Union Clinical Trial Register	2020	Study protocol
80.	European Union Clinical Trial Register	2014	Study protocol
81.	Feduccia *et al*.	2021	Not an RCT
82.	Feduccia *et al*.	2019	Reviews/ secondary data analyses
83.	Franz et al.	2013	Reviews/ secondary data analyses
84.	Galvao-Coelho *et al*.	2021	Reviews/ secondary data analyses
85.	Garakani *et al*.	2020	Reviews/ secondary data analyses
86.	Gill *et al.*	2020	Reviews/ secondary data analyses
87.	Goldberg *et al*.	2020a	Reviews/ secondary data analyses
88.	Goldberg *et al*.	2020b	Reviews/ secondary data analyses
89.	Goldberg *et al*.	2020	Reviews/ secondary data analyses
90.	Goldberg *et al*.	2020	Reviews/ secondary data analyses
91.	Gorman *et al*.	2020	Reviews/ secondary data analyses
92.	Grassi *et al*.	2018	Reviews/ secondary data analyses
93.	Griffiths	2015	Abstract
94.	Griffiths, R. *et al*.	2019	Abstract

95.	Grob	2012	Abstract
96.	Grob	2014	Study protocol
97.	Grob *et al*.	1995	Not on psychiatric disorders
98.	Grossman *et al*.	2018	Not on psychiatric disorders
99.	Hendrie &. Pickles	2016	Editorial/ correspondence
100.	Heuschkel &. Kuypers	2020	Reviews/ secondary data analyses
101.	Hoskins *et al*.	2021	Reviews/ secondary data analyses
102.	Illingworth *et al*.	2021	Reviews/ secondary data analyses
103.	Jacobs	2020	Reviews/ secondary data analyses
104.	Jerome *et al*.	2020	Reviews/ secondary data analyses
105.	Kerbage & Richa	2015	Reviews/ secondary data analyses
106.	Kishi	2013	Reviews/ secondary data analyses
107.	Kotler	2013	Study protocol
108.	Kuypers	2020	Reviews/ secondary data analyses
109.	Luoma	2020	Reviews/ secondary data analyses
110.	Malone	2018	Reviews/ secondary data analyses
111.	Mithoefer *et al*.	2013	Longer-term follow-up of included study
112.	Mithoefer *et al*.	2019	Reviews/ secondary data analyses
113.	Muthukumaraswamy *et al*.	2021	Reviews/ secondary data analyses
114.	Pacey	2013	Study Protocol
115.	Ponte	2021	Reviews/ secondary data analyses
116.	Reiche	2018	Reviews/ secondary data analyses
117.	Reiff	2020	Reviews/ secondary data analyses
118.	Reynolds	2021	Editorial/ correspondence

119. Romeo	2020	Reviews/ secondary data analyses
120. Ross	2021	Reviews/ secondary data analyses
121. Schindler *et al*.	2020	Not on psychiatric disorders
122. Sessa	2019	Not an RCT
123. Stroud	2018	Not an RCT
124. Trope	2019	Reviews/ secondary data analyses
125. Varker	2021	Reviews/ secondary data analyses
126. Wagner	2017	Reviews/ secondary data analyses
127. White	2014	Reviews/ secondary data analyses
128. Yazar-Klosinski	2021	Editorial/correspondence
129. Yazar-Klosinski & Mitchell	2021	Longer-term follow-up of included study

Supplementary Table 2: Risk of bias table

	Random sequence generation (selection bias) (high, low or unclear)	Allocation concealment (selection bias) (high, low or unclear)	Blinding of participants, personnel (performance bias) (high, low or unclear)	Blinding of outcome assessment (detection bias) (high, low or unclear)	Incomplete outcome data (attrition bias) (high, low or unclear)	Selective outcome reporting (reporting bias) (high, low or unclear)	Other sources of bias (high, low or unclear)
1. Grob 2011	Unclear	Low	Low	Unclear	Low	Unclear	High
2. Ross 2016	Low	Low	Unclear	Unclear	Low	Unclear	High
3. Griffiths 2016	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
4. Moreno 2006	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
5. Davis 2021	Low	Unclear	Low	High (wait-list controls)	Low	Unclear	High
6. Carhart-Harris 2021	Low	Low	Low	Low	Low	Low	High
7. Danforth *et al*. 2018	Unclear	Unclear	Low	Low	Low	Unclear	High
8. Mithoefer 2011	Low	Low	Unclear	Low	Low	Unclear	High
9. Oehen 2013	Unclear	Unclear	Low	Low	Low	Unclear	High
10. Bouso 2008	Unclear	Unclear	Low	Low	High	Unclear	High

11. Mithoefer 2018	Low	Low	Low	Low	Low	Unclear	High
12. Ot'alora 2018	Low	Low	Low	Low	Low	Unclear	High
13. Wolfson *et al*. 2020	Low	Low	Unclear	Low	Low	Unclear	High
14. Mitchell *et al*. 2020	Unclear	Unclear	Low	Low	Low	Low	High

Supplementary Table 3: Included MDMA studies

Source	N	Mean Age (SD) & Sex	Dose	Control	Mental Illness	Tool	Study Design	Results	Side-effects	Comments
1. Danforth *et al*. 2018	12	31.3 (8.8) 83% M	MDMA 75 +100 mg (n=4), 100 + 125 mg (n=4) one month apart + therapy'	Placebo	Social anxiety in adults with autism	LSAS	Double-blind parallel RCT	Improvement in LSAS scores from baseline to the primary efficacy variable endpoint was statistically significantly greater for combined MDMA groups compared to the placebo group in ITT analysis.	Most commonly reported reactions were anxiety (75.0% MDMA versus 25.0% placebo) and difficulty concentrating (62.5% MDMA versus 25.0% placebo). No drug-related serious adverse events. BP increases by MDMA not clin sig. No clinically significant AEs were reported based on elevations in blood pressure, pulse rate, or temperature.	Only 24% pf potential participants randomised. After preliminary evidence of safety and efficacy had been established, a protocol amendment was approved allowing the last nine subjects to receive a supplemental dose of MDMA or placebo in all experimental sessions. The purpose of this supplemental dose, half the initial dose administered 2 h afterwards, was to prolong the therapeutic window of MDMA effects and gather pilot data about dose for design of future clinical trials. The optional supplemental dose of 62.5 mg MDMA or placebo was administered 2–2.5 h after the initial dose if the investigators judged it to be safe and advisable and the subject agreed to it. The supplemental dose was administered in 22 of the 23 sessions in which it was an option.
2. Mithoefer *et al*. 2011	20	41.01 >80%F	125 mg MDMA + therapy; n=12	Placebo N=8	PTSD	CAPS IESR	Double-blind parallel RCT followed by open label crossover phase	Rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group. Open-label benefits maintained at between 17 to 74 months.	There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases.	Only 17% pf potential participants randomised. Fifteen of the 20 subjects had previously undergone multiple medication trials (mean 4.2 different psychiatric drugs) and 15 had completed more than one course of psychotherapy. After preliminary evidence of safety and efficacy had been established, a protocol amendment was approved allowing the last nine subjects to receive a supplemental dose of MDMA or placebo in all experimental sessions. The purpose of this supplemental dose, half the initial dose administered 2 h afterwards, was to prolong the therapeutic window of MDMA.

										effects and gather pilot data about dose for design of future clinical trials. The optional supplemental dose of 62.5 mg MDMA or placebo was administered 2–2.5 h after the initial dose if the investigators judged it to be safe and advisable and the subject agreed to it. The supplemental dose was administered in 22 of the 23 sessions in which it was an option. Only one additional psychotherapy session was conducted following placebo sessions, whereas 20 such sessions were provided to seven of 13 subjects following MDMA-assisted sessions.
3. Oehen et *et al*. 2013	12	41.4 (11.2) 10F/ 2M	MDMA 125 mg, + 62.5 mg supplement & therapy (n=8)	MDMA 25 mg, + 12.5 mg supplemental dose & therapy (n=4)	TR PTSD	CAPS PDS	Double-blind parallel RCT	No statistical difference between active & placebo groups on CAPS but there was on the PDS.	Moderate insomnia (125 mg: 43%; 150 mg: 50%), loss of appetite and restlessness in subjects receiving 125 mg MDMA, and headache, moderate insomnia (31%) & loss of appetite in those receiving 25 mg MDMA. Restlessness, tight jaw, thirst and feeling cold commonly reported in the full-dose group. No drug-related serious adverse events. Two dropouts after 1st session.	There was an amendment to the protocol allowing for two additional sessions of MDMA-assisted psychotherapy for any subjects deemed to show insufficient response, which was referred to as "Stage 3" and employed a dose of 150 mg MDMA and a supplemental dose of 75mg MDMA.
4. Bouso *et al*. 2008	6	29-49 6F	MDMA 50 (n=3), 75mg (n=1) + therapy	Placebo + therapy (n=2)	TR PTSD	SSSPTSD STAl; BDI; HAM-D;	Double-blind parallel RCT	No statistical difference between active & placebo groups.	Only 2 subjects reported mild side effects. No abnormalities in blood pressure or heart rate.	Low rates of follow-up. Possibly underpowered to statistically differences between active & placebo groups.
5. Ot'alora et al., 2018	28	42 68%F	MDMA 100 (n=9) to 125 (n=13) mg + therapy 2 sessions 1 month apart	MDMA 40 mg (n=6) + therapy 2 sessions 1 month apart	PTSD	CAPS	Double-blind	No statistical difference between active & placebo groups in ITT analysis but only in the per protocol set.	No drug-related serious adverse events. TEAEs 42% 100 mg, 53% 125 mg, 5% 40 mg. Heart rate and SBP increased as dose ascended.	Only 37% pf potential participants randomised. A supplemental dose half the quantity of the initial dose (62.5, 50 or 20 mg) was available approximately 90 min after the first dose, if not contraindicated. Study extended over 4 years.
6. Mithoefer *et al*. 2018	26	37.2 (10.3) 73%M	MDMA 75 (n=7), 125 mg	MDMA 30 mg (n=12,	PTSD	CAPS-IV BDI, PSQI	Randomized, double-blind, dose	75 mg and 125 mg groups had statistically	85 adverse events were reported by 20 participants. Of these, four (5%) were serious: three were	4 years to recruit 26 subjects. Six (23%) of 26 participants had previously taken ecstasy 2–5 times before study. Not

			(n=7) + therapy	active control) + therapy		GAF PTGI, NEO-PI-R) DES-II	response trial with open-label crossover	significantly greater decreases in PTSD symptoms no difference between these doses. Open-label benefits maintained at 12 months. Significantly better outcomes on other measures.	deemed unrelated and one possibly related to study drug treatment. Common effects were anxiety, headache, fatigue, and muscle tension and insomnia. Significant dose effect on BP.	powered to detect statistical significance. ITT Analyses used.
7. *Wolfson et al*. 2020	18	54.9 (7.9) 80%F	MDMA 125 mg + therapy (n=13)	Placebo + therapy (n=5)	Anxiety LTD	STAI PTGI FFMQ	Double-blind, parallel placebo controlled RCT (2 sessions 2-4 wk intervals) plus open label follow-up.	Both groups improved but there was no statistical difference in STAI between active & placebo groups. MDMA group significantly better on PTGI & FFMQ. Benefits maintained at 6- & 12-month follow-up.	Well -tolerated. Most commonly thirst, jaw clenching/tight jaw, dry mouth, headache, and perspiration, fatigue, insomnia, low mood and anxiety.	Only 16% pf potential participants randomised. An optional supplementary dose of 62.5 mg of MDMA or placebo was offered 1.5 to 2.5 h after the initial dose. The optional supplemental dose was taken in all but one session. Analysed as intention-to-treat. Investigators guessed correctly 89%, participants 86%. This was a feasibility study and therefore was not powered to detect statistical significance. Problems with 1 outlier in placebo group.

8. Mitchell *et al*., Yazar-Klosinski *et al*. 2021	90	41(12) 66%F	MDMA 80-180 mg (3 sessions) + therapy	Placebo (3 sessions) + therapy	Severe PTSD	CAPS-5, SDS BDI	Double-blind, parallel placebo-controlled, multi-site Phase 3 trial	MDMA group significantly better on all three outcomes 9 weeks after last dose.	Transient increase in systolic and diastolic blood pressure and heart rate in the MDMA group. Two in the MDMA group has transient increase in temperature. Five participants in the placebo group and three in the MDMA group had suicidal ideation, suicidal behaviour or self-harm. Two subjects in placebo group had suicidal behaviour & 1 in MDMA group dropped out due to depression. Serious suicidal ideation (a score of 4 or 5 on the C-SSRS) was minimal during the study and occurred almost entirely in the placebo arm. Used intention-to-treat (ITT) analyses.	Only per protocol results presented. Only 0.7% pf potential participants randomised. No details of placebo. Substantial FDA involvement in trial design leading to amendments.

Abbreviations: M=male, F=female, SD=standard deviation, TRD=treatment resistant depression, TR=treatment resistant, RCT=randomized control trial, CAPS=clinically administered-PTSD scale, QIDS-SR16=quick inventory of depressive symptomatology (self-report) (16-item), BDI=Beck depression inventory HADS=hospital anxiety and depression scale, LTD= Life threatening disease; MADRS= Montgomery–Åsberg Depression Rating Scale, HAM-D=Hamilton depression rating scale, SDS=Sheehan Disability Scale, PTGI=Posttraumatic Growth Inventory; STAI=State-Trait Anxiety Inventory, YBOCS = The Yale-Brown Obsessive Compulsive Scale, PDS=Posttraumatic Diagnostic Scale, LASA=Leibowitz Social Anxiety Scale, FFMQ= Five Factor Mindfulness Questionnaire, ITT=intention-to-treat.

Supplementary Table 4: Included psilocybin studies

Source	N	Mean Age (SD) & Sex	Psilocybin or MDMA	Control	Mental Illness	Outcomes	Study Design	Results	Side-effects	Comments
1.Grob *et al.*, 2011	12	40.2 11F/1M	Psilocybin 0.2 mg/kg	Niacin, 250 mg	Depression and Anxiety LTD (Advanced Stage Cancer)	BDI, STAI POMS BPRS	Randomized, double-blind, placebo-controlled crossover trial (spaced several weeks apart).	At 2-week follow-up, no significant differences between Psilocybin and controls on BDI, POMS, ATAI, BPRS. Significant improvements on BDI lasted six months.	Non-clinically significant elevations in BP and HR that were greater in intervention group. Systolic increase in bp from 118 to 138 mmHg in active group while niacin decreased bp. Temperature not reported.	Subjects did not appear to have been questioned as to treatment allocation and only 4 had no prior hallucinogen experience. Main outcomes solely presented as graphs.
2.Ross *et al.*, 2016	29	56.28 18F/11M	Psilocybin 0.3 mg/kg + psychotherapy	Niacin, 250 mg + therapy	Anxiety, Depression LTD (life threatening cancer)	HADS, BDI STAI	Randomized, double-blind, placebo-controlled crossover trial (7 weeks apart).	At 6-week follow-up prior to cross-over, decreases anxiety, depression, cancer-related demoralisation and hopelessness. Effect size at 6 weeks for HADS was 1.69 Improved spiritual wellbeing, and increased quality of life. Improvements sustained at six-month follow-up.	Non-clinically significant elevations in BP and HR (76%), headaches/ migraines (28%), and nausea (14%); the most common psychiatric AEs were transient anxiety (17%) and transient psychotic- like symptoms (7%: one case of transient paranoid ideation and one case of transient thought disorder. None were serious.	Less than 1 third of potential subjects entered study. It seems they picked the psilocybin session. Main outcomes solely presented as graphs or bar charts. Staff members guessed allocation correctly in 28/29 participants (97%). However, the participants were not asked to record their guesses as to which drug they received on dosing session days.
3.Griffiths *et al.*, 2016	51	56.3 49% F	Psilocybin 22 or 30 mg/70 kg	Psilocybin 1 or 3 mg/70 kg (intended as placebo)	Anxiety, Depression LTD (cancer)	GRID-HAMD BDI, STAI-Trait POMS	Randomized, double-blind, placebo-controlled crossover trial (5 weeks between sessions).	At 5-week follow-up, high-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. Improvements sustained at six-month	An episode of elevated systolic blood pressure (>160 mm Hg at one or more time-point) occurred in 34% of participants in the high-dose session and 17% of participants in the low-dose session. Nausea or vomiting occurred in up to 15% of high dose sessions. Physical discomfort (any type) in up to 21% Psychological discomfort (any type) in up to 32%. No	Only 10% pf potential participants randomized. All study monitors correctly believed that psilocybin had been administered. This may have biased results as monitors played a major role during sessions, monitors in encouraging participants to "trust, let go and be open" to the experience".

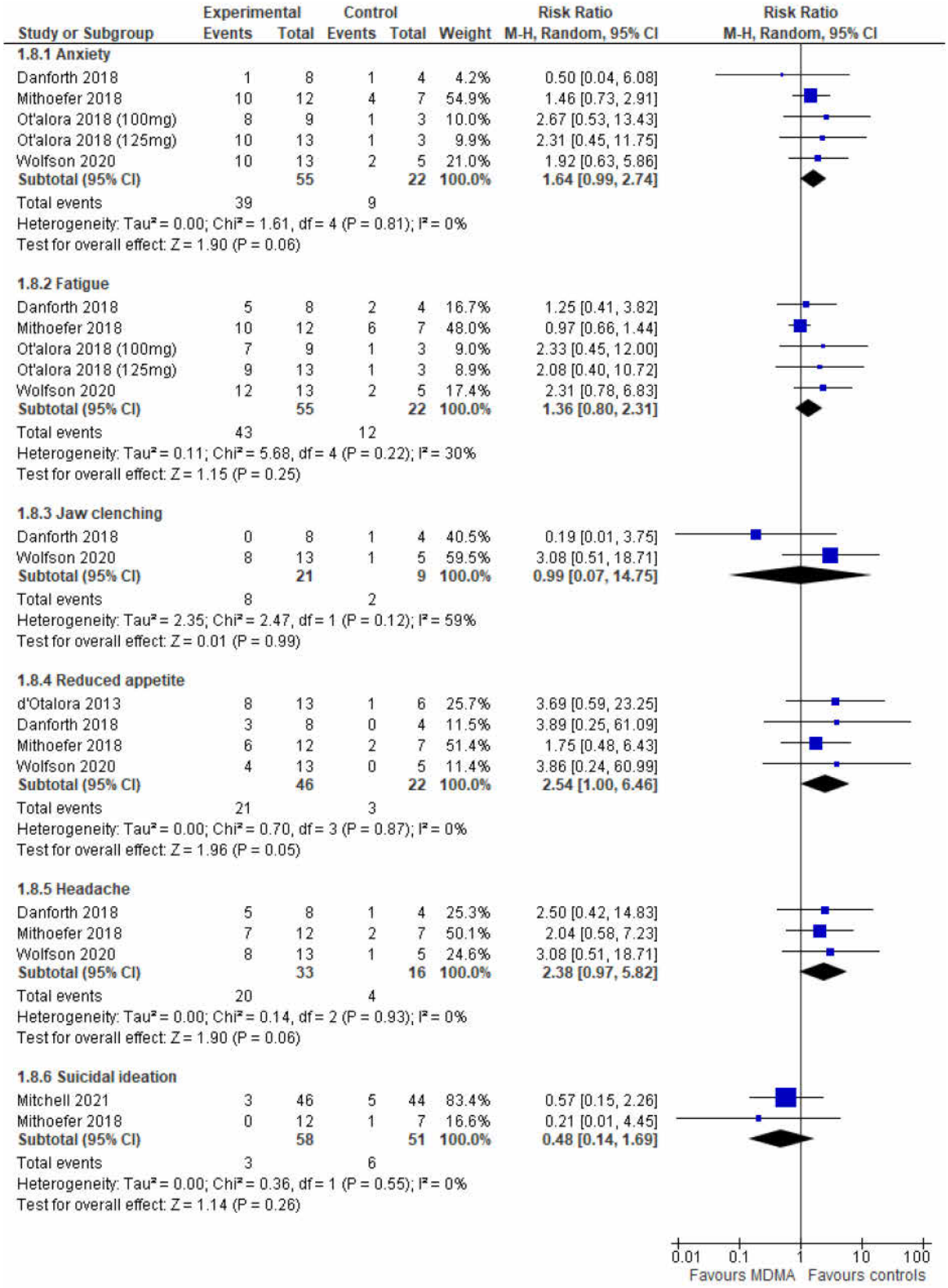
								follow-up.	cases of hallucinogen persisting perception disorder or prolonged psychosis.	
4.Davis *et al*., 2020	27	39.8 67%F	Psilocybin 20 mg/70 mg + 30 mg/70 kg (mean 1.6 weeks apart)	Wait-list control	TRD	GRID-HAMD, QIDS-SR	Randomized, waiting list-controlled clinical trial.	The mean HAMD scores were statistically significantly lower in the immediate treatment group at weeks 1 and 4 than comparable times in the delayed treatment controls. Rapid decrease in QIDS-SR score maintained at 4 weeks. 17 participants (71%) at week1 and17 (71%) at week 4 had a clinically significant response.	Challenging emotional (e.g., fear and sadness) and physical (e.g., feeling body shake or tremble) experiences in ½ of sessions. Mild to moderate transient headache in one-third of sessions. A transient increase in blood pressure in 1 session. There were no serious adverse events.	Only 10% of potential participants randomised & only 8% non- white Not blinded. Need to consider the erratum. Concurrent use of other antidepressants was unclear and could be a bias.
5.Carhart-Harris *et al*., 2021	59	41 66% M	X2 Psilocybin 25 mg 3 weeks apart 6 weeks placebo + psychological support	X2 Psilocybin 1 mg 3 weeks apart 6 weeks daily escitalopram + psychological support	TRD	QIDS-SR BDI HAMD MADRS	Double-blind, placebo-controlled RCT.	No significant difference in antidepressant effects between psilocybin and escitalopram in QIDS-SR-16 at week 6 Changes from baseline to week 6 on the BDI-1A, HAM-D-17, and MADRS mostly favoured psilocybin. Used intention-to-treat (ITT) analyses.	Adverse events were similar in the two groups & none were serious.	Only 0.06% of potential participants randomised & only 12% non- white. Difference in onset of action & may have disadvantaged escitalopram given short study duration & compromised blinding ~40% had discontinued psychiatry medicines. Unclear escitalopram dosing and brief duration of dosing. Confidence intervals for the between-group differences were not adjusted for multiple comparisons.
6.Moreno *et al*., 2006	9	40.9 7M/ 2F	Psilocybin 100 µg/kg Psilocybin 200 µg/kg Psilocybin 300 µg/kg	Psilocybin 25 µg/kg x1 inserted randomly after first dose	Obsessive-compulsive disorder	YBOCS	Modified dose escalation blinded trial.	There was no significant effect of dose or dose-time on YBOCS. Overall Improvement generally lasted beyond 24 hours with and two-thirds maintaining a 50% decrease in YBOCS scores with at least 1 of	One subject experienced transient hypertension without relation to anxiety or somatic symptoms. Two declined further treatment after 1st dose due to discomfort of an inpatient stay as required by the protocol.	Proof of concept study. Modified blind may have influenced expectations in both subjects and raters. No attempt at safety assessment. Only 6 completed all 4 doses. Unexpectedly high response to the very low dose

		the testing doses.	placebo raising concerns re conducting bias-free RCTs in this area.

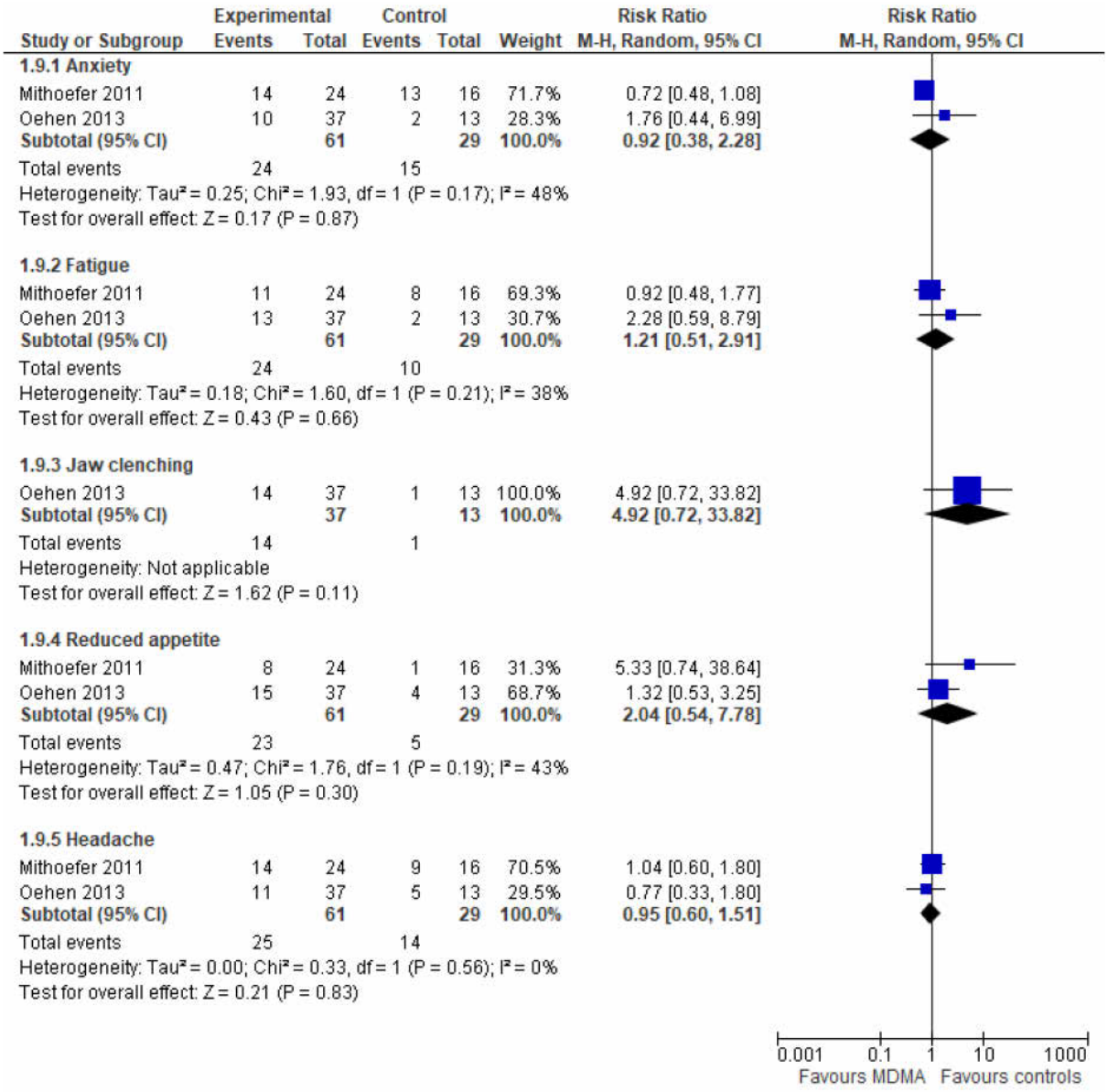
Abbreviations: M=male, F=female, SD=standard deviation, TRD=treatment resistant depression, RCT=randomized control trial, CAPS=clinically administered-PTSD scale, QIDS-SR16=quick inventory of depressive symptomatology (self-report) (16-item), BDI=Beck depression inventory HADS=hospital anxiety and depression scale, LTD= Life threatening disease; MADRS= Montgomery–Åsberg Depression Rating Scale, HAM-D=Hamilton depression rating scale, SDS=Sheehan Disability Scale, PTGI=Posttraumatic Growth Inventory; STAI=State-Trait Anxiety Inventory, YBOCS = The Yale-Brown Obsessive Compulsive Scale.

Supplementary figures

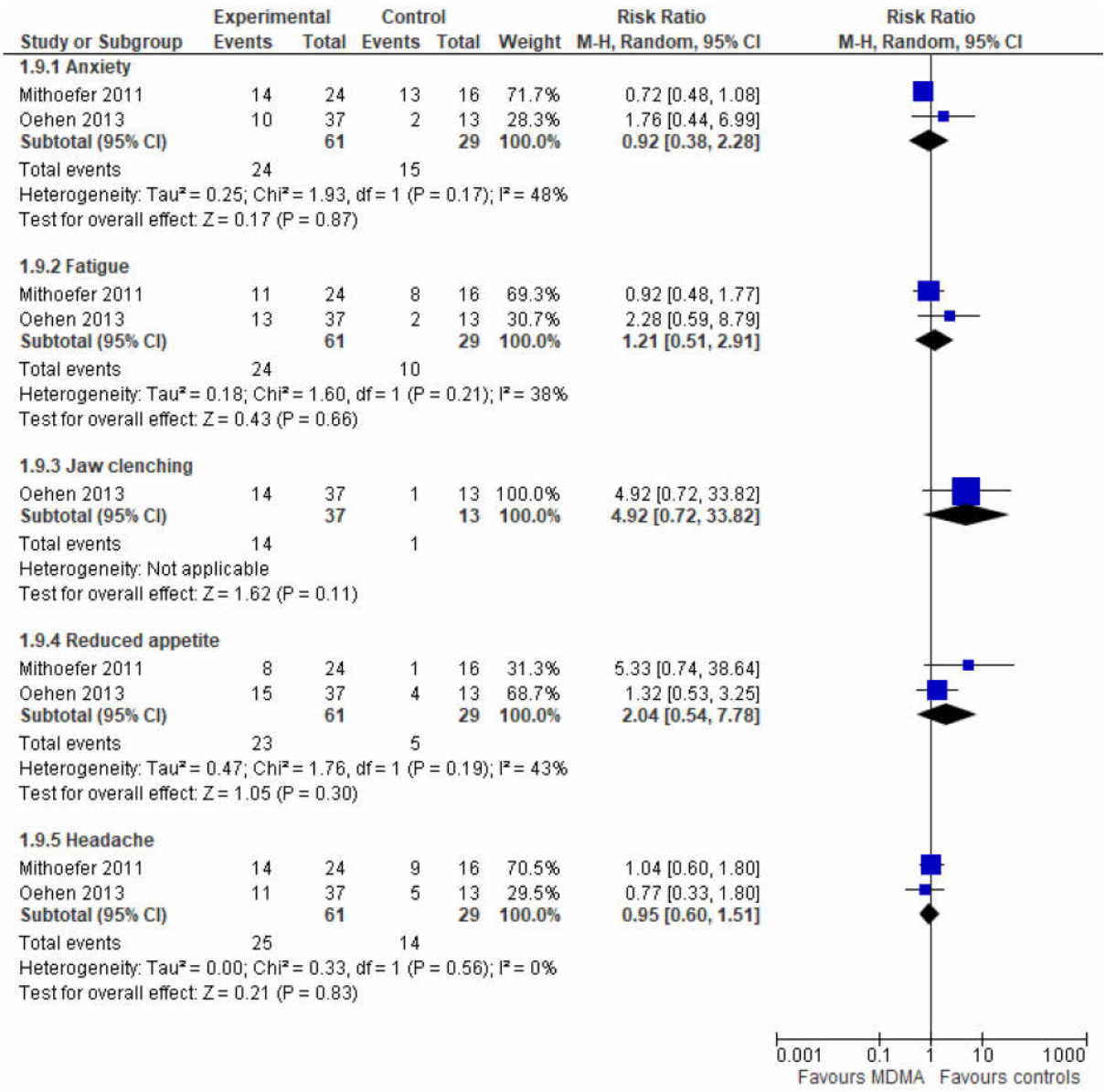
Supplementary Figure 2: MDMA – adverse effects per subject (up to seven days)



Supplementary Figure 3: MDMA – adverse events / session (immediate)



Supplementary Figure 4: MDMA – adverse effects per session (up to seven days)



Appendix 1: MDMA and Psilocybin searches

The searches were performed on the 16th August 2021.

Databases used

Embase (Platform: Ovid) (562 articles retrieved)

MEDLINE (Platform: Ovid) (260 articles retrieved)

PsycInfo (Platform: Ovid) (210 articles retrieved)

Cochrane Central Register of Controlled Trials (Platform: Cochrane Library) (293 articles retrieved)

CINAHL (Platform: EBSCOHost) (71 articles retrieved)

Ovid Embase <1974 to 2021 August 13>		
#	**Search Statement**	**Results**
1	exp mental disease/	2323415
2	(mental* or depress* or anxi* or mood or "affective disorder*" or stress* or trauma* or "end of life" or palliative or terminal* or EOL or PTSD or PTSS or addicti* or "substance use" or "substance abuse").mp.	4312421
3	1 or 2	5339198
4	exp Psilocybine/	1636
5	("magic mushroom*" or psilocibin or psilocibine or psilocybin or psilocybine or "cy 39" or cy39 or indocybin).mp.	1837
6	(2rv7212bp0 or 520-52-5).af.	1502
7	4 or 5 or 6	1837
8	exp midomafetamine/	1787
9	(MDMA or midomafetamine or ecstasy or "methamphetamine,3,4 methylenedioxy" or "n-methyl-3,4-methylenedioxyamphetamine").mp.	8524
10	42542-10-9.af.	7904

11	8 or 9 or 10	10708
12	exp randomized controlled trial/	671641
13	(randomi#ed adj3 trial*).mp.	1062312
14	exp placebo/	369455
15	placebo*.mp.	478557
16	exp single blind procedure/ or exp double blind procedure/	227765
17	((single or double or triple) adj2 blind*).mp.	325242
18	12 or 13 or 14 or 15 or 16 or 17	1377404
19	3 and 7 and 18	243
20	3 and 11 and 18	351
21	19 or 20	562

Ovid MEDLINE(R) ALL <1946 to August 13, 2021>		
#	**Search Statement**	**Results**
1	exp mental disorders/	1309392
2	(mental* or depress* or anxi* or mood or "affective disorder*" or stress* or trauma* or "end of life" or palliative or terminal* or EOL or PTSD or PTSS or addicti* or "substance use" or "substance abuse").mp.	3222585
3	1 or 2	3887974
4	exp Psilocybin/	787
5	("magic mushroom*" or psilocibin or psilocibine or psilocybin or psilocybine or "cy 39" or cy39 or indocybin).mp.	1204
6	(2rv7212bp0 or 520-52-5).af.	787

7	4 or 5 or 6	1204
8	exp Methylenedioxymethamphetamine/	4005
9	(MDMA or midomafetamine or ecstasy or "methamphetamine,3,4 methylenedioxy" or "n-methyl-3,4-methylenedioxyamphetamine").mp.	6478
10	42542-10-9.af.	1
11	8 or 9 or 10	6478
12	exp randomized controlled trials/	150743
13	(randomi#ed adj3 trial*).mp.	844590
14	exp placebos/	38485
15	placebo*.mp.	242054
16	exp Single-Blind Method/ or exp Double-Blind Method/	196079
17	((single or double or triple) adj2 blind*).mp.	249347
18	12 or 13 or 14 or 15 or 16 or 17	969316
19	3 and 7 and 18	94
20	3 and 11 and 18	173
21	19 or 20	260

Ovid APA PsycInfo <1806 to August Week 2 2021>		
#	**Search Statement**	**Results**
1	exp Mental Disorders/	899900
2	(mental* or depress* or anxi* or mood or "affective disorder*" or stress* or trauma* or "end of life" or palliative or terminal* or EOL or PTSD or PTSS or addicti* or "substance use" or "substance abuse").mp.	1415060

3	1 or 2	1752856
4	exp Psilocybin/	285
5	("magic mushroom*" or psilocibin or psilocibine or psilocybin or psilocybine or "cy 39" or cy39 or indocybin).mp.	642
6	(2rv7212bp0 or 520-52-5).af.	0
7	4 or 5 or 6	642
8	exp Methylenedioxymethamphetamine/	2148
9	(MDMA or midomafetamine or ecstasy or "methamphetamine,3,4 methylenedioxy" or "n-methyl-3,4-methylenedioxyamphetamine").mp.	3743
10	42542-10-9.af.	0
11	8 or 9 or 10	3805
12	exp Randomized Controlled Trials/ or exp Randomized Clinical Trials/	991
13	(randomi#ed adj3 trial*).mp.	57994
14	exp Placebo/	6059
15	placebo*.mp.	43279
16	((single or double or triple) adj2 blind*).mp.	27262
17	12 or 13 or 14 or 15 or 16	100602
18	3 and 7 and 17	82
19	3 and 11 and 17	132
20	18 or 19	210

Cochrane Library (Date Run: 16/08/2021 06:26:19)		
#	**Search Statement**	**Results**
1	MeSH descriptor: [Mental Disorders] explode all trees	76529
2	(mental* or depress* or anxi* or mood or "affective disorder*" or stress* or trauma* or "end of life" or palliative or terminal* or EOL or PTSD or PTSS or "obsessive compulsive" or OCD or addict* or "substance use" or "substance abuse"):ti,ab,kw (Word variations have been searched)	259609
3	MeSH descriptor: [Psilocybin] explode all trees	80
4	("magic mushroom*" or psilocibin or psilocibine or psilocybin or psilocybine or "cy 39" or cy39 or indocybin):ti,ab,kw (Word variations have been searched)	188
5	MeSH descriptor: [N-Methyl-3,4-methylenedioxyamphetamine] explode all trees	198
6	(MDMA or midomafetamine or ecstasy or "methamphetamine,3,4 methylenedioxy" or "n-methyl-3,4-methylenedioxyamphetamine"):ti,ab,kw (Word variations have been searched)	410
7	MeSH descriptor: [Randomized Controlled Trial] explode all trees	119
8	((randomised or randomized) and trial*):ti,ab,kw (Word variations have been searched)	797025
9	MeSH descriptor: [Placebos] explode all trees	24376
10	(placebo*):ti,ab,kw (Word variations have been searched)	330704
11	(((single or double or triple) and blind*)):ti,ab,kw (Word variations have been searched)	364362
12	1 or 2	291159
13	3 or 4	188
14	5 or 6	410
15	7 or 8 or 9 or 10 or 11	1016621

16	12 and 13 and 15	102
17	12 and 14 and 15	197
18	16 or 17	295 (2 Cochrane reviews and 293 trials)

CINAHL (EBSCOhost)		
#	**Search Statement**	**Results**
1	(MH "Mental Disorders+")	594,662
2	mental* or depress* or anxi* or mood or "affective disorder*" or stress* or trauma* or "end of life" or palliative or terminal* or EOL or PTSD or PTSS or "obsessive compulsive" or OCD or addict* or "substance use" or "substance abuse"	982,455
3	"magic mushroom*" or psilocibin or psilocibine or psilocybin or psilocybine or "cy 39" or cy39 or indocybin	226
4	(MH "Methylenedioxymethamphetamine")	1,117
5	MDMA or midomafetamine or ecstasy or "methamphetamine,3,4 methylenedioxy" or "n-methyl-3,4-methylenedioxyamphetamine"	1,670
6	(MH "Randomized Controlled Trials+")	118,332
7	((randomised or randomized) N3 trial*)	245,512
8	(MH "Placebos")	12,965
9	placebo*	70,507
10	(MH "Single-Blind Studies")	15,036
11	(MH "Double-Blind Studies")	51,061
12	(MH "Triple-Blind Studies")	189

13	((single or double or triple) N3 blind*)	84,240
14	1 OR 2	1,227,480
15	4 OR 5	1,878
16	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	301,756
17	14 AND 15 AND 16	45
18	3 AND 14 AND 16	28
19	17 OR 18	71