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„Meta-Analysis on the Effects of Psychedelics- and MDMA-assisted Therapy in Clinical Settings“

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Abstract

In the past two decades, medical research on psychedelic and entactogen compounds has re-emerged. The so-called renaissance of psychedelic sciences continues to move forward after its abandonment in the 1970s. This meta-analysis focuses on the use of psychedelics and MDMA in clinical settings as a treatment for mental disorders. 17 studies with a total number of 347 participants were included and analysed at 6-month follow-up. The pre to post summary effect across studies was estimated as Hedge's *g* = -1.252 with an *SE* = 0.117, *p* = 0.0000 and 95% CIs of [-1.489, -1.024], and indicates large symptom reduction after treatment. The highest reductions were observed in ayahuasca (*g* = -2.288; *SE* = 0.292) and depression (*g* = -1,643; *SE* = 0.235) studies. However, high loss to follow-up rates of up to 50% and lack of blinding in some primary studies introduces risk of bias and limits the certainty of findings. Even though the nature of published studies does not allow for general conclusions on the broad application of these treatments, the symptom relief after psychedelic and entactogen therapy holds promise when risks and benefits are carefully weighted. Patients who fail to respond to currently available pharmacotherapy and psychotherapy could be the first to benefit from these novel treatment options.

Keywords: meta-analysis, mental health care, therapy, treatment, symptoms, psychedelics, entactogens, ayahuasca, ibogaine, psilocybin, LSD, MDMA, depression, anxiety, PTSD, substance use

Abstract

Die medizinische Erforschung von Psychedelica und Entactogenen lebt im 21. Jahrhundert wieder auf, nachdem Studien an diesen Substanzen in den 1970er Jahren großflächig zum Erliegen kamen. Diese Meta-Analyse befasst sich mit der Behandlung psychischer Störungen durch Psychedelica- und MDMA- unterstütze Therapie im klinisch-therapeutischen Kontext. Hierfür wurden 17 Studien mit insgesamt 347 PatientInnen ausgewertet. Die Prä-Post Effektstärke von Hedge's g = -1.252 mit SE = 0.117, p = 0.0000 und 95% Cis [-1.489, -1.024] weist auf signifikante Symptomreduktionen nach der Behandlung hin. Die größten Symptomreduktionen zeigten sich in Ayahuasca- (g = -2.288; SE = 0.292) und Depressions-Studien (g = -1,643; SE = 0.235). Hohe loss to follow-up Werte und mögliche Erwartungseffekte in manchen der eingeschlossenen Studien limitieren die Aussagekraft dieser Ergebnisse. Obwohl sich auf Basis der derzeit veröffentlichten Studien keine Aussage über die großflächige Anwendung dieser Substanzen im klinischen Kontext treffen lässt, ist die beobachtete Symptomreduktion vielversprechend, wenn Risiken und Chancen der Behandlung vorsichtig gegeneinander abgewogen werden. PatientInnen, die nicht auf derzeit angewendete Pharmakotherapien ansprechen, könnten als erstes von diesen Behandlungsmethoden profitieren.

Schlagworte: Meta-Analyse, Psychische Gesundheit, Therapie, Behandlung, Symptome, Psychedelica, Entactogene, Ayahuasca, Ibogain, Psilocybin, LSD, MDMA, Depression, Angststörung, PTBS, Abhängigkeit

Introduction

Psychedelics are a diverse group of substances that can alter cognition, emotion and perception of time and space. They are naturally occurring in various species of plants and fungi, and their use in medicinal and religious contexts goes back for centuries (Carhart-Harris & Goodwin, 2017; Martins et al., 2013; Rätsch, 2018). Carhart-Harris and Goodwin (2017) define them as “compounds with appreciable serotonin 2A receptor agonist properties that can alter consciousness in a marked and novel way“ (p. 1). Entactogens are substances that can evoke strong emotional reactions, euphoric states and physiological activation. They share some properties with psychedelics, however, they constitute a substance group of their own (Nutt, 2019). Recently, psychedelics and entactogens have been reviewed for their anti-depressive, anxiolytic, and anti-addictive effects (Begola & Dowben, 2018; dos Santos et al., 2018). Meanwhile, neuroimaging studies suggest that psychedelics “disrupt brain systems and circuits that encode […] repetitive thoughts and behaviours” (Nutt & Carhart-Harris, 2020, p. 122). The toxicity of psychedelics appears to be low in clinical settings, adverse reactions include “(a) dose-related transient headaches, (b) anxiety, (c) confusion, (d) nausea and vomiting” (Inserra, 2019, p.190). To better understand the status quo of research on psychedelic substances, their history in the 20st century is to be considered.

History of Psychedelic Science

The scientific interest in psychedelic substances sparked after the legendary discovery of lysergic acid diethylamide (LSD) by Albert Hofmann in the 1950s (Hofmann, 1979). In the following years, psychedelic substances were examined for their effects on animals, healthy humans, and patients affected by addiction, pain, existential distress, and

other conditions (Bogenschutz, et al., 2015). By the mid 1960s, more than 1000 clinical trials with over 40.000 subjects had been published for LSD alone (Vollenweider & Kometer, 2010). Meanwhile, the recreational use of psychedelic substances increased. They were associated with cultural rebellion and the movement against the Vietnam war, and therefore targeted by media and political campaigns and eventually categorized as Class A drugs by the convention on psychotropic substances in 1971 and as Schedule 1 drugs under the Misuse of Drugs Regulations in 2001 (Rucker et al., 2020). Consequently, human psychedelic research was abandoned until the 1990s (Strassman & Qualls, 1994; Vollenweider et al, 1997). In the 2010s, studies on psychedelics and psychiatric disorders re-emerged (Mash et al., 2001, Moreno et al. 2006).

Currently, many scientists believe the legal status of substances like psilocybin "is not evidence-based, but rather grounded in overstated historical assumptions of harm" (Rucker et al., 2020, p. 10). Psychedelic and entactogen compounds are once again examined for their effects, safety and efficacy in psychiatry, clinical psychology, and neurobiology. Rick Doblin, the founder of the Multidisciplinary Association of Psychedelic Studies states, "there is more psychedelic research happening today, both for neuroscience and therapeutic purposes than at any time in history" (Doblin et al., 2019, p. 49).

Mental health crisis

With globally rising rates of depression, anxiety, substance use and posttraumatic stress disorders (PTSD), we are finding ourselves in a mental health crisis (Krystal et al., 2017; Schenberg, 2018). Access to adequate treatment is limited, and the pharmacotherapies currently in use are frequently ineffective, often treating the symptoms rather than the cause of mental disorders (Rucker et al., 2020). The result is a staggering

need for effective and novel treatment options, especially for patients who do not respond to standard approaches (Doblin et al., 2019; Ot'alora et al., 2018). Within the scientific community, many argue that psychedelic and 3,4-Methylenedioxymethamphetamine (MDMA)-assisted therapy could potentially relief the suffering of various patient populations on a large scale (Schenberg, 2018). Since the 2000s, several studies have reported improvement in mental health outcomes after psychedelic- and MDMA-assisted psychotherapy (Bahji et al., 2020; Goldberg et al., 2020; Romeo et al., 2020). These studies involve treatment with ayahuasca, ibogaine, psilocybin, LSD and the entactogen MDMA for depression, anxiety, PTSD and addiction.

Treatment Setting

The treatment in these clinical trials is usually preceded by a washout period, during which concurrent pharmacotherapies like anti-depressive medication is stopped. Preparatory treatment sessions with healthcare professionals like psychiatrists, psychologists or psychotherapists trained in psychedelic or entactogen treatment are conducted. The medication session is taking place on-site, in a hospital or treatment centre. After drug intake, participants are encouraged to relax and focus inward. The therapists are present but non-directive during the whole session that can last up to several hours depending on drug and dosing (Carhart-Harris et al., 2018).

In some trials, initial doses were followed by a supplementary dose on the same day. Vitality signs like blood pressure and heart rate are monitored, and a medical practitioner is available upon request. Depending on the individual study, the patients are taking part in one or several drug sessions (Rucker et al., 2018). Scores of mental health instruments are assessed at baseline and various follow-up time points (Carhart-Harris et al., 2018; Gasser et

al., 2014; Griffiths et al., 2016; Mithoefer et al., 2018; Noller et al., 2018; 2013; Ot'alora et al., 2018; Palhano-Fontes et al., 2019). In the following paragraphs, the substances used in these trials are described with regard to their origins, effects and applications.

Ayahuasca

Ayahuasca is a potent psychoactive brew that contains the vine bark of banisteriopsis caapi and the leaves of psychotria viridis that belongs to the family of coffee plants, also called rubiaceae (Rätsch, 2018). It is traditionally used in ceremonial contexts in the Amazonian area and considered sacred by numerous indigenous communities in Latin America (Dos Santos et al., 2012). In recent years, ayahuasca has gained considerable attention worldwide and is often used in non-scientific contexts for spiritual and healing purposes (Rätsch, 2018). Sanches et al. (2016) explain, that "Banisteriopsis caapi contains β-carboline alkaloids (harmine, tetrahydroharmine, and harmaline) that act as reversible inhibitors of monoamine oxidase (MAO)-A, whereas P. viridis is rich in N,N-dimethyltryptamine (DMT), an hallucinogenic tryptamine that acts as a 5-HT1A/2A/2C agonist" (p.77). It has been reviewed for its anti-depressive effects with doses ranging from 1 to 2.2 ml/kg of body weight (Osorio et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016).

Ibogaine

Ibogaine is not considered a classical psychedelic substance. It is a psychoactive indole alkaloid with stimulatory and hallucinogenic effects that is derived from the root bark of the West African shrub tabernanthe iboga (Rätsch, 2018). It can be classified as an atypical hallucinogen or oneriogen and is an agonist of N-methyl-D-aspartate (NMDA) receptors (Shapiro, 2018). Observational studies have reported on the effects of ibogaine in

patients seeking opiate discontinuation in naturalistic settings (Brown & Alper, 2018; Noller et al., 2018). Animal studies have shown that ibogaine can reduce the self-administration of morphine, cocaine, amphetamine, methamphetamine, and nicotine (Shapiro, 2018). However, other than for classical psychedelics like psilocybin and LSD, the intake of Ibogaine was associated with fatalities by cardiac arrhythmia (Noller et al., 2018). Further, Knuijver et al. (2019) report hallucinogen persisting perception disorder (HPPD) in a patient seeking opiate discontinuation after ibogaine treatment.

Psilocybin

Psilocybin can be found in various species of fungi on all continents of the world (Rätsch 2018). Hofmann was among the first scientists to isolate and synthesize the psychoactive compounds psilocybin and psilocin from the mushroom psilocybe mexicana heim (Hofmann, Frey et al., 1958; Hofmann, Heim et al., 1958). After intake, psilocybin is metabolized to psilocyn, a 5-HT1A/2A/2C receptor agonist that is correlated to psychoactive effects in humans (Grob et al., 2011). Rucker et al. (2020) summarize:

> In humans, it induces temporary changes in mood, perception and cognition via activation of serotonin receptors in the brain. It is associated with a low potential for harm relative to other classes of psychoactive drugs: it has very low toxicity, its use is not associated with the development of physical dependence, nor with acquisitive or other crime, and deaths attributed to its abuse are extraordinarily rare. (p. 10)

Psilocybin has recently been reviewed for its effects on alcohol and tobacco use disorder, depression and anxiety in patients with life-threatening diseases as well as treatment-resistant depression and anxiety in autistic adults (Carhart-Harris et al., 2018;

Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Johnson et al., 2014; Ross et al., 2016).

LSD

The semisynthetic compound LSD is a potent psychedelic. It was first derived from an alkaloid found in the fungus ergot (Rätsch, 2018). In the human brain, it alters dynamic integration and segregation (Luppi et al., 2021). Only few therapists are currently licensed to legally work with LSD. Doses administered in these settings range from 100 – 200 µg and effects last for 6-9 hours or more. LSD sessions are usually preceded and followed by psychotherapy interventions. In 2014, the first randomized controlled trial with LSD was conducted for anxiety associated with a life-threatening disease by Dr. Gasser and his colleagues in Switzerland (Gasser et al., 2014; Gasser et al., 2015). After consumption, humans develop a strong tolerance towards LSD that cannot be overcome for several days even if the initial dose is quadrupled (Buchborn et al., 2016). Even though the use of LSD has been associated with the hallucinogen persisting perception disorder, it has shown to be non-addictive and relatively safe when administered in clinical trials (Lewis, 2020; Nichols, 2018).

MDMA

MDMA is a psychoactive amphetamine derivate that is classified as an entactogen due to its "properties that can promote empathy and compassion for self and others. MDMA stimulates release of serotonin, norepinephrine and dopamine, and may act directly on some adrenergic, cholinergic, and serotonergic receptors" (Feduccia et al., 2019, p. 2). In recreational context, MDMA is often referred to and sold under the name Ecstasy. However,

Ecstasy pills often contain other substances and are therefore considered less pure than the crystalline MDMA (European Monitoring Centre for Drugs and Drug Addiction, 2021).

In the treatment of traumatic experiences, MDMA has shown to allow for emotional engagement and to "induce an optimal state that complements the process of working through traumatic memories while reducing the fear response" (Ot'alora et al., 2018, p. 1296). Participants in these trials emphasized that not only the MDMA-sessions themselves but also the preparatory and integrative sessions as well as the therapeutic alliances had a strong impact (Doblin et al., 2019). Like psilocybin, MDMA was granted the status of a breakthrough therapy by the U.S. Food and Drug Administration (Feduccia et al., 2019). Currently large randomized controlled phase three trials are taking place in various sites worldwide to investigate the safety and efficacy of MDMA therapy for PTSD (Multidisciplinary Association for Psychedelic Studies, 2021b).

Trial Phases

Pharmacological studies are divided into several phases (Ruckert et al., 2020). Phase one trials are often open-label pilot studies that investigate the effects of a particular substance in a small number of healthy volunteers (Carhart-Harris et al., 2011). The effects of these substances can then be examined concerning particular symptoms or disorders in phase two trials. These trials may treat a modest number of patients in an open-label or randomized controlled design. The aim of phase two studies is usually to investigate the feasibility, safety and efficacy of a particular substance with regards to risks and benefits associated with their consumption (Bogenschutz et al., 2015; Johnson et al., 2014). Based on the outcomes of these trials, larger and usually randomized controlled phase three trials are designed. The outcomes of phase three trials are often considered as the foundation of

licensing decisions (Mitchell et al., 2021). If a substance has been approved as medicine, phase four trials further investigate effects and side effects for large numbers of patients (Ruckert et al., 2020). In a next step, meta-analyses are a useful tool to integrate results from one or more phases of trials and to make evidence-based decisions about the legal status of a substance (Liberati et. al 2009).

Meta-Analyses

Singular study results are subject to statistical and methodological biases, which results in the need for cumulative research (Döring & Bortz, 2016). When applied correctly, meta-analysis can systematically and comprehensively summarise existing research and provide a quantitative analysis of the variability of findings (Borenstein et al., 2009, Cooper et al., 2019). It can include both qualitative and quantitative research methods and is superior to the narrative review (Döring & Bortz, 2016). The aim of a meta-analysis is to integrate the results of studies that address the same fundamental question (Comprehensive Meta-Analysis, 2021). In order to make a statement on the efficacy of psychedelics and entactogens on the basis of the current primary studies in the context of a therapeutic application, a meta-analytic approach is expected to yield the best results (Liberati et. al 2009).

Several meta-analyses have been conducted on the effects of psychedelic and entactogens in clinical populations. Some of them have focused on the effects of single substances on certain disorders, like MDMA on PTSD (Bahji et al., 2020; Gorman et al., 2002), LSD on alcoholism (Krebs & Johansen, 2012), or psilocybin on depression and anxiety (Goldberg et al., 2020). Others like Romeo et al. (2020) evaluated the influence of a substance group like psychedelics on a particular disorder like depression. Even though

these studies used different methods and types of effect sizes, they all reported symptom relief after treatment or in comparison with control groups, with reductions ranging from small to large effects (Bahji et al., 2020; Goldberg et al., 2020; Gorman et al., 2002; Krebs & Johansen, 2012; Romeo et al. 2020). However, as of yet, no meta-analysis has been published that provides:

- An overall outcome for the use of psychedelic and entactogen compounds for the treatment of mental disorders in clinical settings
- Outcomes for a single substance on various disorders
- Outcomes for various substances on a single disorder

Therefore, in this study, the reader can expect an overview of clinical studies in the field of psychedelic therapy conducted in the first 20 years of this millennia. Effect sizes and characteristics are displayed not only for each study included, but also for subgroups within studies. Study results are combined for each substance (ayahuasca, ibogaine, LSD, psilocybin, MDMA) and for each patient group identified in the literature (anxiety, depression, PTSD, substance use). These groups of studies are then compared to each other. Lastly, additional analyses evaluate the relatedness of quality factors like study size, loss to follow-up and study design with individual outcomes. Through the objectives and methods described in the following paragraphs, this meta-analysis aims to close a gap in cumulative research and to provide an overall estimation for the effect of psychedelic- and MDMA-assisted therapy in mental healthcare.

Objectives

1. Objective – Symptom Change

The primary objective of this meta-analysis is to systematically document the changes in symptoms of mental disorders (depression, anxiety, PTSD, substance use) after psychedelic- (ayahuasca, ibogaine, psilocybin, LSD) and MDMA-assisted therapy. Therefore, the following hypotheses are formulated to test for statistical significance.

1. Do symptoms of mental disorders change after psychedelic and entactogen-assisted therapy?
    - Null hypothesis H0: The mean overall effect is zero, indicating that the symptoms of mental disorders do not change after psychedelic and entactogen-assisted therapy.

      H0: $g = 0.0$ or $p \geq .05$
    - Alternative hypothesis H1: The mean overall effect is not zero, indicating that the symptoms of mental disorders do change after psychedelic and entactogen-assisted therapy.

      H1: $g \neq 0.0$ or $p < .05$

2.-6. Objective – Substances

The secondary objective is to assess the changes in mental disorder symptoms separately for each substance.

2.-6. Do symptoms of mental disorders change after 2. ayahuasca-, 3. ibogaine-, 4. LSD-, 5. psilocybin-, and 6. MDMA-assisted therapy?

- H0: The mean overall effect is zero, indicating that the symptoms of mental disorders do not change after 2. ayahuasca-, 3. ibogaine-, 4. LSD-, 5. psilocybin-, and 6. MDMA-assisted therapy.

  H0: $g = 0.0$ or $p \geq .05$

- H1: The mean overall effect is not zero, indicating that the symptoms of mental disorders do change after 2. ayahuasca-, 3. ibogaine-, 4. LSD-, 5. psilocybin-, and 6. MDMA-assisted therapy.

  H1: $g \neq 0.0$ or $p < .05$

7.-10. Objective – Patient Groups

Likewise, the effects of psychedelic- and MDMA-assisted therapy were estimated for different patient groups.

7.-10. Do symptoms of mental disorders change after psychedelic- and MDMA-assisted therapy in 7. anxiety, 8. depression 9. PTSD, and 10. substance use patients?

- H0: The mean overall effect is zero, indicating that the symptoms of mental disorders do not change in 7. anxiety, 8. depression 9. PTSD, and 10. substance use patients.

  H0: $g = 0.0$ or $p \geq .05$

- H1: The mean overall effect is not zero, indicating that the symptoms of mental disorders do change in 7. anxiety, 8. depression- 9. PTSD, and 10. substance use patients.

  H1: $g \neq 0.0$ or $p < .05$

11. Objective – Comparison of Substance Groups

To test for differences in outcomes, the different groups of substances will be compared to each other.

11. Are the overall mean effects in MDMA-assisted therapy and psychedelic-assisted therapy different from each other?

- H0: The overall mean effects are not different between MDMA- and psychedelic-assisted therapy.

  H0: $p(Q) \geq .05$

- H1: The overall mean effects are different between MDMA- and psychedelic-assisted therapy.

  H1: $p(Q) < .05$

12. Objective – Comparison of Patient Groups

The effects will be compared between different groups of patients.

12. Are the overall mean effects different in depression, anxiety, PTSD, and substance use disorder patients?

- H0: The overall mean effects are not different between depression, anxiety, PTSD, substance use disorder patients.

  H0: $p(Q) \geq .05$

- H1: The overall mean effects are different between depression, anxiety, PTSD, substance use disorder patients.

  H1: $p(Q) < .05$

Methods

In the following paragraphs, the methods of searching and selecting studies, collecting data, evaluating risks of bias, integrating study outcomes and interpreting results are outlined and described. Guidelines used for the content of this meta-analysis were the reporting standards of the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) group, the 7th edition Manual of the American Psychological Association, and the Cochrane Handbook for Systematic Reviews of Intervention (American Psychological Association, 2020; Higgins et al. 2019; Liberati et. al 2009).

Eligibility Criteria

According to Higgins et al. (2019), "The starting point for developing a search strategy is to consider the main concepts being examined in a review. This is often referred to as PICO – that is Patient (or Participant or Population or Problem), Intervention, Comparison and Outcomes" (p. 80).

For this meta-analysis, PICO was defined as:

- Participants: Any Participants who meet criteria of a mental disorder
- Interventions: Psychedelic- or MDMA-assisted therapy
- Comparisons: Change between pre and post scores
- Outcomes: Scores of instruments assessing symptoms of mental health

Finally, the following characteristics of studies were used as criteria for eligibility, including PICO:

- Publication status and language: Published and unpublished trials in English language[1]
- Years considered: post-millennial studies from 2000-2020
- Study design: Randomized controlled trials (including crossover designs) and open label trials. If reported, crossover arms that received placebo first, followed by a medication session were included as well.
- Participants: diagnosis of any mental or behavioural disorder
- Interventions: psychedelic- or MDMA-assisted therapy
- Outcomes and comparisons: changes in scores of instruments assessing symptoms of mental health before and after (pre to post) psychedelic- or MDMA- therapy

Further, it is recommended to specify an independent and dependent variable along with the eligibility criteria (Cooper et al. 2019). For the primary objective, the independent variable is defined as the intervention and the dependent variable is defined as the change in symptoms.

Information Sources

The database selection was guided by the objectives and the eligibility criteria. To identify relevant studies, a comprehensive literature search was performed in the electronic databases PsycINFO, SCOPUS and PUBMED (American Psychological Association, 2020;

[1] Morrison et al. (2012) and Dechartres et al. (2018) couldn't find significant differences between meta-analyses that included multiple languages, and meta-analysis restricted to English language articles.

Elsevier, 2021; U.S. National Library of Medicine 2020a). To search for grey literature and unpublished studies, the trial registry platform Clinicaltrials.gov was consulted (U.S. National Library of Medicine, 2020b). In some cases, original investigators were located, contacted, and asked to clarify whether similar studies were referring to the same set of participants. Details like the last dates searched are reported in Table 1 of the search section.

Search

Search strings are combinations of search terms and operators entered into a search engine in order to find the desired results. To construct these search strings, keywords were systematically deduced from the eligibility criteria for primary studies. These terms were first combined with the Boolean operator OR to achieve sensitivity within concepts and then combined with the Boolean AND operator, to ensure each concept is represented in the final search (Higgins et al., 2019). The final search strings can be seen in Table 1. According to the Cochrane Handbook for Systematic Reviews of Interventions:

> Searches for systematic reviews aim to be as extensive as possible in order to ensure that as many of the relevant studies as possible are included in the review. It is, however, necessary to strike a balance between striving for comprehensiveness and maintaining relevance when developing a search strategy. (Higgins et al., 2019, p. 82)

The search string was slightly adapted for each database to receive comparable numbers of results.

Table 1

Information on databases used for the literature search

Database	Search string	Filters	Last date searched	No of results
PsycINFO[a]	psychedelic OR psychedelics OR hallucinogen OR entactogen AND (treatment OR therapy OR patients OR symptoms OR disorder)	2000 – current	27.03.20	606
SCOPUS[b]	psychedelic OR hallucinogen OR entactogen AND (treatment OR therapy OR patients OR symptoms OR disorder)	PUBYEAR > 1999 AND NOT (mice)	06.04.20	740
PUBMED[c]	psychedelic OR hallucinogen OR entactogen OR psilocybin OR lsd OR mdma OR peyote OR mescaline OR dimethyltryptamine OR ayahuasca OR ibogaine AND (treatment OR therapy OR patients OR symptoms OR disorder)	Clinical trials, humans, 2000-dato	09.04.20	767

Note. [a]American Psychological Association, 2020; [b]Elsevier, 2021; [c]U.S. National Library of Medicine 2020a

Study Selection

The search results from each database were merged using the reference management software Mendeley (Elsevier, 2020). Duplicate records reporting the same journal title, volume and pages were individually checked and then removed. Next, titles and abstracts were screened to remove reports that didn't meet the eligibility criteria. The remaining studies were categorised and tagged. Relevant full-text reports were retrieved and closely examined for compliance with the eligibility criteria.

Before making final decisions on study selection, the records were again carefully screened for overlapping populations, even if the title and authors weren‘t the same as “duplicate publication can introduce substantial biases if studies are inadvertently included more than once in a meta-analysis” (Higgins et al., 2019, p.92). To document and display the process of selecting studies, a PRISMA flow chart was used (see Figure 1).

Data Collection Process

Items of interest were identified in line with the research questions and methods. A coding protocol was designed, and studies were systematically screened for relevant information. Cooper et al. (2019) state that “capturing variations in settings, participants, methodology, experimental manipulations and measured variables is an important goal of the coding protocol not only for careful description but also for use in the analysis to explain variation in study findings” (p. 154). Data items were entered into the coding file, and then, re-examined by the coder to reduce the risk of coding mistakes.

Obtaining Data from Investigators

A common source of bias in the process of data collection are reporting deficiencies in primary studies (Cooper et al., 2019). According to the Cochrane Handbook for Systematic Reviews of Interventions, “studies should not be omitted from a review solely on the basis of measured outcome data not being reported” (Higgins et al., 2019, p. 94). To reduce the error of reporting deficiencies, three strategies were applied. Firstly, original investigators were located, contacted and kindly asked to provide missing data. Secondly, Anees Bahji and Simon Goldberg, the corresponding authors of meta-analyses on the effects of MDMA and psilocybin, were located and contacted (Bahji et al., 2020; Goldberg et al., 2020). They agreed to share their coding files which include primary data not reported in original

publications. Thirdly, data that was not reported in publications or supplementary files but visually displayed was extracted using the WebPlotDigitizer, a semi-automated opensource tool to extract data from plots and graphs (Rohatgi, 2020). The method of extraction for primary studies is reported in the section Results of individual studies.

Data Items

The choice of relevant data items was based on the research questions and statistical methods. The following data items were extracted:

(1) author name, (2) year of publication, (3) substance, (4) study design, (5) population, (6) subgroups within study, (7) number of sessions, (8) dosing at each session, (9) number of participants within subgroup pre, (10) number of participants within subgroup post, (11) loss to follow-up in %, (12) assessment points, (13) assessment points used in synthesis, (14) assessment tools, (15) assessment tools used in synthesis[2], (16) effect sizes and measure of precision[3], (17) means of pre and post scores and measure of precision, (18) mean differences and measure of precision, (19) t-values, (20) p-values of paired t-test, (21) information on correspondence with original authors.

The 6-month follow-up time point was chosen as the unit of analysis. If no values were assessed at 6-month follow-up, the follow-up point closest to the 6-month follow-up were included.

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[2] To improve the comparability of different studies, data was sought for the assessment tools used most frequently for each population across primary studies. The individual tools used in the synthesis can be seen in Table 2.

[3] Measures of precision: Variances, Standard Deviations or Standard Errors

Risk of Bias in Individual Studies

The Cochrane Handbook for Systematic Reviews of Interventions defines bias as a "systematic error, or deviation from the truth, in results. Biases can lead to under-estimation or over-estimation of the true intervention effect and can vary in magnitude" (Higgins et al., 2019, p.177). Bias can occur on individual study outcome level as well as on meta-analysis outcome level. Higgins et al. suggest that "review author[s] should strive to assess risk of bias in the results of outcomes that are most important to patients" (Higgins et al., 2019, p.188). Important risks of bias factors were identified as: study design, non-reporting and selective under-reporting of results, and loss to follow-up. The results for each study and subgroup are reported in Table 3, as well as under Results of Individual Studies.

Study Design

The covariate study design is referring to the first active medication session participants received. Study design was included as a categorical covariate into a regression model to estimate if it is related to changes in symptoms following treatment. Subgroups were chosen as the unit of analysis. *Q*-values, *df* and *p(Q)* values were estimated, and *p* values of < .05 were interpreted as support of the alternative hypothesis H1.

Objective – Study design. The corresponding hypotheses are:

- H0: The covariate study design is not related to the symptom change of mental disorders after psychedelic and entactogen-assisted therapy.

  H0: $p(Q) > .05$
- H1: The covariate study design is related to the symptom change of mental disorders after psychedelic and entactogen-assisted therapy.

  H1: $p(Q) \leqslant .05$

Loss to Follow-up

A major concern in clinical studies are patients that drop out of studies (Cooper et al., 2019). To assess the risk of bias that may arise from loss to follow-up, the percentage of dropouts between baseline and included follow-up for each study subgroup was extracted and displayed in Table 3. It was then considered as a continuous covariate in a meta-regression.

Objective – Loss to Follow-up. The corresponding hypotheses are:

- H0: The covariate loss to follow-up is not related to the symptom change of mental disorders after psychedelic and entactogen-assisted therapy.
- H0: $p(Q) > .05$
- H1: The covariate loss to follow-up is related to the symptom change of mental disorders after psychedelic and entactogen-assisted therapy.
- H1: $p(Q) \leqslant .05$

Selective non-reporting and under-reporting of results

A major concern in scientific publications is the selective non-reporting and selective under-reporting of results. Often results are reported without measures of dispersion, only partially or not at all (Higgins et al., 2019). Excluding such studies from meta-analysis increases the risk of bias. Aiming to reduce it, due to reporting deficiencies in primary studies, primary authors were contacted and data was extracted from plots and graphs as described in the section Data collection process.

Summary Measures

Before synthesising and analysing the outcomes of primary studies, an effect size reflecting the treatment effect has to be calculated for each study (Cooper et al., 2019). A significance level of $p \leqslant .05$ was chosen for all tests of statistical significance. Calculations were carried out with the statistical software Comprehensive Meta Analysis (Borenstein et al., 2013). The calculation of the summary measure Hedge‘s *g* for this meta-analysis can be divided into

- Calculation of Hedge‘s *g* for selected instruments
- Integration of selected instruments to study level Hedge‘s *g*
- Integration of study level Hedge‘s *g* into overall summary effects

Hedge‘s g – The Principal Summary Measure

Hedge‘s *g* reflects the standardized mean difference between two groups or time points (Hedges & Olkin, 1985). The commonly used effect size Cohens *d* tends to overestimate the true population value, while Hedges *g* includes the correction factor *J* and is therefore especially useful for smaller sample sizes. Therefore, Hedge‘s *g* for pre to post designs was used as the principal summary measure to quantify changes in clinical symptoms following treatment. Hedge‘s *g* was computed with the program Comprehensive Meta Analysis (Borenstein et al., 2013).

Hedge‘s g for selected instruments

Cooper et al. (2019) explain that:

> When researchers have access to a full set of summary data such as mean, standard deviations, and sample size for each group, the computation of the effect size and its

variance is relatively straightforward. In practice, however, researchers will often find themselves working with only partial data (p.209).

Depending on the availability of data, Hedge's *g* for selected instruments was calculated using either: means of pre and post scores and measures of dispersion, mean differences and their measures of dispersion, effect sizes and their measures of dispersion, *t*-values or *p*-values of paired *t*-test and sample sizes at assessment points used in synthesis. As the correlation of pre and post scores was not stated in primary studies, a correlation of $r = .5$ was imputed between time points as suggested by Hoyt et al. (2018).

Study level Hedges g

In clinical studies, it is common practice to use more than one instrument. When combining multiple outcome effect sizes, a more precise result is expected (Moeyaert et al., 2017). As recommended by Borenstein, Hedges, Higgins, and Rothstein (2009), a mean effect size was used to combine the multiple instruments for each study. In this case, it is essential to address that multiple outcomes in each study are not independent of each other. In order not to over- or underestimate the variance, and therefore the precision of the study level Hedge's *g*, the correlation among the different outcomes has to be considered. Unfortunately, the correlation was not reported in most of the studies, and so, a correlation of $r = .5$ was imputed. The effect sizes for each outcome were then aggregated to study level Hedge's *g* following the recommended procedure of combining multiple outcomes by Borenstein et al. (2009).

Methods of Analysis

After calculating Hedge's *g* for each study as described above, the following steps were taken to answer the objectives presented in the introduction:

- Study level Hedge‘s *g* were weighted and integrated using a random effects model
- Heterogeneity was assessed with *Q*-Statistics
- Hypotheses were tested using *Z*-Values, *Q*-Values and *p*-values

Random Effects Model

In meta-analysis, it is critical to choose an adequate statistical framework (Döring & Bortz, 2016). The choice between a random effects model and a fixed effect model affects assumptions about the population studies are drawn from, the weights assigned to individual studies and the interpretation of results (Cooper et al., 2019). The choice of the model can be tested via Q-Statistics. Due to the methodological differences between studies, a random effects model was chosen to integrate study-level Hedge‘s *g* with the inverse variance weight method (Borenstein et al., 2009). In the following, methods of analysis are given for the objectives.

Objective 1

To answer the primary objective, the pre to post Hedge’s *g* across all primary studies was tested for significance with a *Z*-Test and an according *p*-value. 95% confidence intervals and standard errors (SEs) were calculated for this summary effect. Heterogeneity across studies was estimated with a *Q*-value, *df* and *p*-value. A *p*-value of < .05 was interpreted as a significant indicator of heterogeneity and confirmation of the random effects model. I^2 was calculated as the percentage of variation across studies due to real heterogeneity, rather than error (Cooper et al., 2019).

Objectives 2-10

To assess the changes in mental disorder symptoms separately for substances and patient populations, studies were grouped as displayed in Table 4 in the Synthesis of Results

section. A meta-analysis was conducted for each group of primary studies. Hedge's *g,* 95% confidence intervals and SEs were estimated. The summary effects for each group were tested for significance with a *Z*-Test and responding *p*-values. Heterogeneity in each meta-analysis was estimated with *Q*-values, *df, I^2* and *p*-values. *Tau*, *Tau^2*, and its SE and variance were calculated for each group of studies. When a significant level of heterogeneity was reached ($p(Q) < .05$), a random effects model was chosen.

Objectives 11 & 12

Objectives 11 & 12 were meant to estimate the influence of different variables on psychedelic- and MDMA-assisted therapy outcomes. Subgroup analyses were applied to compare effect sizes in subgroups of studies. Regarding substances, MDMA and psychedelics studies were compared to each other. For different patient groups; depression, anxiety, PTSD and substance use disorder studies were compared. Q-values, df and p-values were estimated within and between subgroups. Between subgroup p-values of $p < .05$ were interpreted as support of the alternative hypotheses H1: The overall mean effects are different between subgroups.

Risk of Bias Across Studies

Risk of bias should be considered not only on individual study level, but also across studies. According to Higgins et al. (2019):

> There is convincing evidence that results that are statistically non-significant and unfavourable to the experimental intervention are less likely to be published than statistically significant results, and hence are less easily identified by systematic reviews […]. This leads to results being missing systematically from syntheses, which can lead to syntheses over-estimating or under-estimating the effects of an intervention (p.178).

To visually display the distribution of effect sizes and standard errors, a funnel plot was conducted (Figure 3, Results). Without publication bias, the effect sizes of individual studies would typically distribute symmetrically around the summary mean effect. Missing studies on one side of the mean effect can be an indicator of publication bias. However, visual interpretation of the funnel plot is limited due to its subjectivity (Comprehensive Meta-Analysis, 2021). To quantify bias seen in the funnel plot, Egger's linear regression method was applied. One-tailed *p*-values < .05 were interpreted as an indicator of publication bias. Begg and Mazumdars (1994) rank correlation test was computed to assess if effect size is correlated to study size. A significant inverse correlation between study size and effect size ($p < .05$) could be interpreted as an indicator for publication bias. To account for publication bias, Duval and Tweedie's (2000) Trim and Fill was applied. "The Trim and Fill procedure imputes […] missing studies, adds them to the analysis, and then re-computes the summary effect size" (Borenstein et al., 2013).

The results of meta regressions on the impact of study design and loss to follow-up are reported under Additional Analyses.

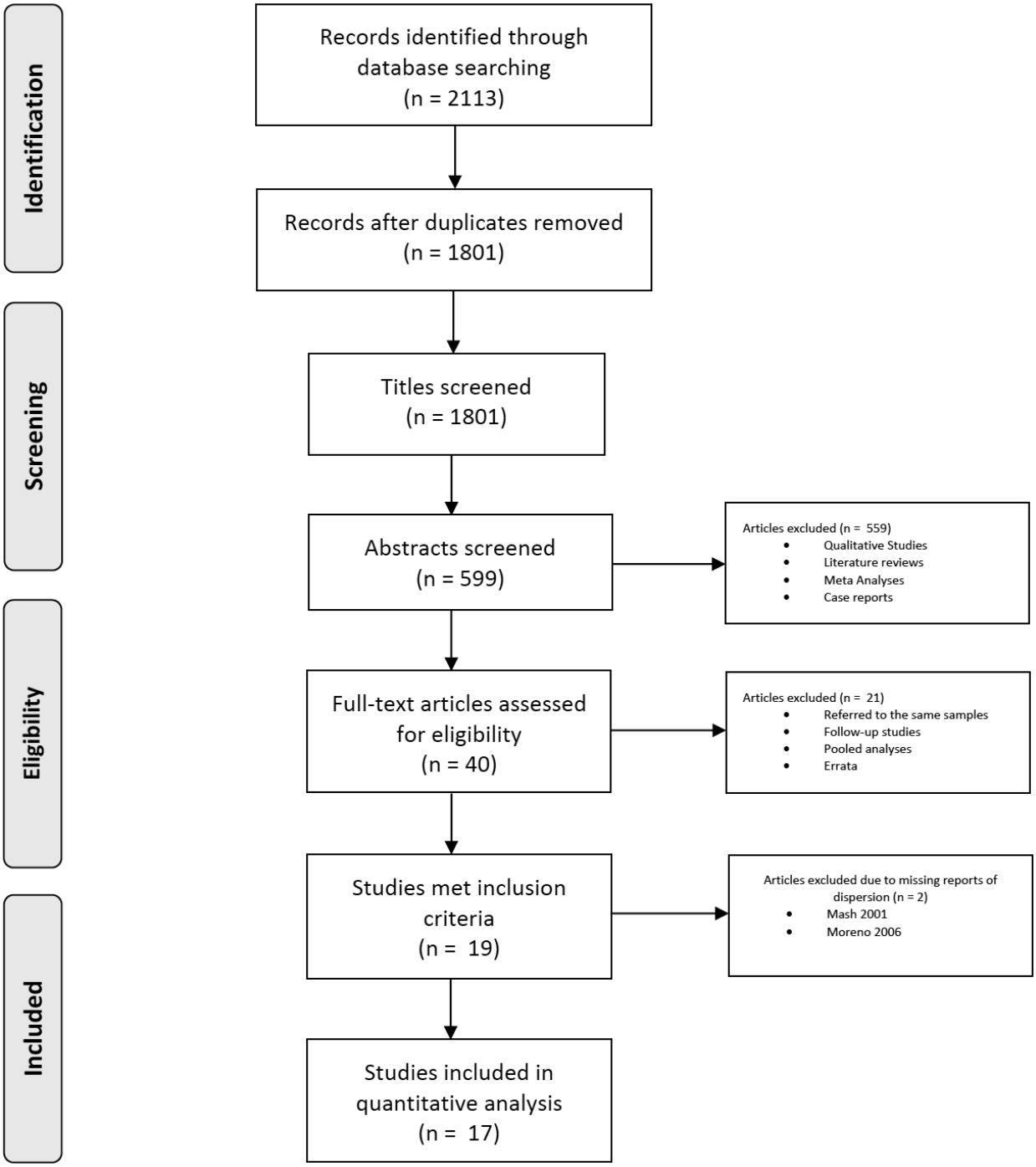
Results

Study Selection

Numbers of studies identified, screened for eligibility, and included in the analysis are displayed in Figure 1, with reasons for exclusion. The template was retrieved from Liberati et al. (2009). At baseline, primary studies included a total number of 347 participants.

Figure 1

PRISMA Flow Chart of the meta-analysis



Note: Articles excluded due to missing reports of dispersion are referring to Mash et al. (2001) and Moreno et al. (2006).

Study Characteristics

Characteristics of the 17 included studies and their references are displayed in Table 2.

Table 2

Characteristics of Studies Included in the Meta-Analysis

Author, Year	Substance	Population, Sample size	Design	Included instruments
Sanches et al., 2016	Ayahuasca	Recurrent MDD, *n* = 17	Open-label	HAM-D MADRS
Palhano-Fontes et al., 2019	Ayahuasca	Resistant MDD, *n* = 29	RCT, Placebo (water, yeast, citric acid, zinc and colorant)	HAM-D MADRS
Glue et al., 2016	Ibogaine	Opioid addiction, *n* = 27	RCT, Placebo	OOWS COWS
Brown et al., 2018	Ibogaine	Opioid addiction, *n* = 30	Open-label	SOWS
Noller et al., 2018	Ibogaine	Opioid addiction, *n* = 14	Open-label	ASI Drug Use ASI Psychiatric Status
Gasser et al., 2014	LSD	Anxiety in patients with life-threatening disease *n* = 12	RCT, Control (20µg LSD)	STAI-S STAI-T HADS-A
Grob et al., 2011	Psilocybin	Anxiety and depression in patients with advanced-stage cancer *n* = 12	RCT, Placebo (Niacin)	STAI-S STAI-T BDI
Johnson et al., 2014	Psilocybin	Tobacco addiction, *n* = 15	Open-label	TLFB Breath carbon monoxide Urine cotinine
Bogenschutz et al., 2015	Psilocybin	Alcohol addiction *n* = 10	Open-label	TLFB drinking days TLFB heavy drinking days PACS

Author, Year	Substance	Population, Sample size	Design	Included instruments
Griffiths et al., 2016	Psilocybin	Depressive symptoms in patients with life-threatening cancer *n* = 51	RCT, Control (1-3 mg Psilocybin/70 kg)	STAI-S STAI-T BDI
Ross et al., 2016	Psilocybin	Anxiety and depression in patients with life-threatening cancer *n* = 29	RCT, Placebo (Niacin)	STAI-S STAI-T BDI
Carhart-Harris et al., 2018	Psilocybin	Resistant MDD *n* = 20	Open-label	STAI-S STAI-T BDI
Mithoefer et al., 2011	MDMA	Chronic resistant PTSD *n* = 20	RCT, Placebo (lactose)	CAPS IES-R
Oehen et al., 2013	MDMA	Chronic resistant PTSD *n* = 12	RCT, Control (25 mg MDMA + 12.5 mg supplemental dose)	CAPS PDS
Danforth et al., 2018	MDMA	Social Anxiety in autistic adults *n* = 12	RCT, Placebo (lactose)	LSAS BDI-II
Mithoefer et al., 2018	MDMA	Chronic resistant PTSD *n* = 26	RCT, Control (30 mg MDMA)	CAPS-IV BDI-II
Ot'alora et al., 2018	MDMA	Chronic resistant PTSD *n* = 28	RCT, Control (40mg MDMA)	CAPS-IV BDI-II

Note. RCT = randomised controlled trial; MDD = major depressive disorder; PTSD = posttraumatic stress disorder. HAM-D = hamilton depression rating scale; MADRS = montgomery-asberg depression rating scale; OOWS = objective opiate withdrawal scale; COWS = clinical opiate withdrawal scale; SOWS = subjective opiate withdrawal scale; ASI = addiction severity index; STAI-S = spielberger state anxiety inventory; STAI-T = spielberger trait-anxiety inventory; HADS-A = hospital anxiety and depression scale - anxiety subscale; BDI = beck depression inventory, PACS = penn alcohol craving scale; CAPS = clinician-administered ptsd scale; IES-R = impact of events scale-revised; PDS =

posttraumatic diagnostic scale, LSAS = liebowitz social anxiety scale (Bogenschutz et al., 2015; Thomas Kingsley Brown et al., 2018; Carhart-Harris et al., 2018; Danforth et al., 2018; Gasser et al., 2014; Glue et al., 2016; Griffiths et al., 2016; Grob et al., 2011; Johnson et al., 2014; Mithoefer et al., 2011; Mithoefer et al., 2018; Noller et al., 2018; Oehen et al., 2013; Ot'alora et al., 2018; Palhano-Fontes et al., 2019; Ross et al., 2016; Sanches et al., 2016).

Risk of Bias Within Studies

The methodological risk of bias features extracted from each subgroup like study size, design, number and dosing of sessions and loss to follow-up are reported in Table 3. Three of the 27 subgroups have lost more than 20% of participants to the follow-up and were therefore judged to be at a high risk of bias (National Heart, Lung and Blood Institute, 2020). Design and Loss to Follow-up were included into a meta regression to estimate whether they are related to the effect size. The results of these are reported under additional analyses.

Table 3

Risk of Bias Features Within Studies and Subgroups

Author, Year	Substance	Dosing	No. of sessions	Population	Subgroup	N pre	N post	% Lost to FU	Hedges *g*	SE
Sanches et al., 2016	Ayahuasca	2.2 ml per kg	1	Depression	Open Label	17	17	0,00	-2,267	0,391
Palhano-Fontes et al., 2019	Ayahuasca	1 ml per kg	1	Depression	Randomised Controlled	17	14	17,64	-2,314	0,438
Glue et al., 2016	Ibogaine	60 mg	1	Substance use	Randomised Controlled	6	6	0,00	-0,534	0,329
	Ibogaine	180 mg	1	Substance use	Randomised Controlled	6	5	16,66	-0,177	0,333
	Ibogaine	120 mg	1	Substance use	Randomised Controlled	6	6	0,00	-0,656	0,341
Brown et al., 2018	Ibogaine	1540 ± 920 mg total dose	1 (Multiple doses)	Substance use	Open Label	30	14	53,33	-1,421	0,335
Noller et al., 2018	Ibogaine	25–55 (ø 31,4) mg/kg total dose	1 (Multiple doses)	Substance use	Open Label	15	12	20	-0,879	0,298
Gasser et al., 2014	LSD	200 µg	2	Anxiety	Open Label	4	3	25	-0,851	0,392
	LSD	200 µg	2	Anxiety	Randomised Controlled	8	8	0,00	-1,737	0,447

Author, Year	Substance	Dosing	No .of sessions	Population	Subgroup	N pre	N post	% Lost to FU	Hedges *g*	SE
Grob et al., 2011	Psilocybin	0.2 mg per kg	1	Anxiety	Randomised Controlled	12	8	33,33	-0,356	0,276
Johnson et al., 2014	Psilocybin	2x 0.29 mg per kg 1x 0.29-0.43 mg per kg	2-3	Substance use	Open Label	15	15	0,00	-1,4	0,308
Bogenschutz et al., 2015	Psilocybin	1x 0.3 1x 0.4 mg/kg optional	1-2	Substance use	Open Label	10	9	10	-1,059	0,319
Griffiths et al., 2016	Psilocybin	0.31 mg/kg	1	Depression	Randomised Controlled	27	22	18,5	-1,212	0,226
	Psilocybin	0.31-0.43 mg/kg	1	Depression	Randomised Controlled	29	24	17,24	-1,433	0,235
Ross et al., 2016	Psilocybin	0.3 mg/kg	1	Anxiety	Randomised Controlled	15	12	20	-1,163	0,293
	Psilocybin	0.3 mg/kg	1	Anxiety	Randomised Controlled	16	11	31,25	-1,612	0,365
Carhart-Harris et al., 2018	Psilocybin	1x 10 mg 1x 25 mg	2	Depression	Open Label	20	19	5	-1,211	0,255
Mithoefer et al., 2011	MDMA	2-3x 125 mg + optional supplemental dose of 62.5 mg	2-3	PTSD	Open Label	8	7	12,5	-1,229	0,402
	MDMA	2-3x 125 mg + optional supplemental dose of 62.5 mg	2-3	PTSD	Randomised Controlled	15	12	20	-1,856	0,402

Author, Year	Substance	Dosing	No. of sessions	Population	Subgroup	N pre	N post	% Lost to FU	Hedges *g*	SE
Oehen et al., 2013	MDMA	3-5x 125 mg + optional supplemental dose of 62.5	3-5	PTSD	Randomised Controlled	9	8	11,11	-0,768	0,319
Danforth et al., 2018	MDMA	1x 75-100 mg 1x 100-125 mg	2	Anxiety	Randomised Controlled	8	7	12,5	-1,565	0,455
Mithoefer et al., 2018	MDMA	1x 40 mg+ optional supplemental dose of 20 mg 3x 100-125 mg+ optional supplemental dose	3	PTSD	Open Label	7	6	14,25	-0,917	0,378
	MDMA	1x 75 mg+ optional supplemental dose of 37.5 mg 3x 100-125 mg+ optional supplemental dose	4	PTSD	Randomised Controlled	7	7	0,00	-2,082	0,578
	MDMA	3x 125 mg+ optional supplemental dose of 62.5	3	PTSD	Randomised Controlled	12	12	0,00	-1,869	0,409
Ot'alora et al., 2018	MDMA	1x 40 mg+ optional 20 mg supplemental dose 3x 100-125 mg	4	PTSD	Open Label	6	5	16,66	-1,421	0,498
	MDMA	1x 100 mg+ optional 50 mg supplemental dose 1x 100-125 mg	2	PTSD	Randomised Controlled	9	9	0,00	-1,858	0,467
	MDMA	1x 125 mg+ optional 62.5 mg supplemental dose 1x 100-125 mg	2	PTSD	Randomised Controlled	13	12	7,69	-1,287	0,326

Note. Design is referring to the design of the first active medication session.

Results of Individual Studies

The forest plot in Figure 2, shows pre-post Hedge's *g* for primary studies, their standard errors, as well as lower and upper limits of 95% confidence intervals (Comprehensive Meta-Analysis, 2021). The *p*-values for each study correspond to *Z*-tests conducted for the objective: Do symptoms of mental disorders change after psychedelic- and MDMA-assisted therapy? Any *p*-values lower than .05 indicate that symptoms of mental disorders significantly changed after psychedelic and entactogen-assisted therapy in that study. Remarkably, all effect sizes were negative, and therefore, indicated symptom relief after the therapy.

In some cases, original researchers were located, contacted, and asked to provide results that were not reported, as described in the section *data collection process*. Sanches et al. (2016), Glue et al. (2016), Brown et al. (2018) and Noller et al. (2018) kindly provided missing data. For the studies from Grob et al. (2011), Bogenschutz et al. (2015) and Ross et al. (2016), data had to be retrieved with the "WebPlotDigitizer" (Rohatgi, 2020). For all other studies, data could be retrieved from original publications, supplementary files or other meta analyses (Bahji et al., 2020; Goldberg et al., 2020).

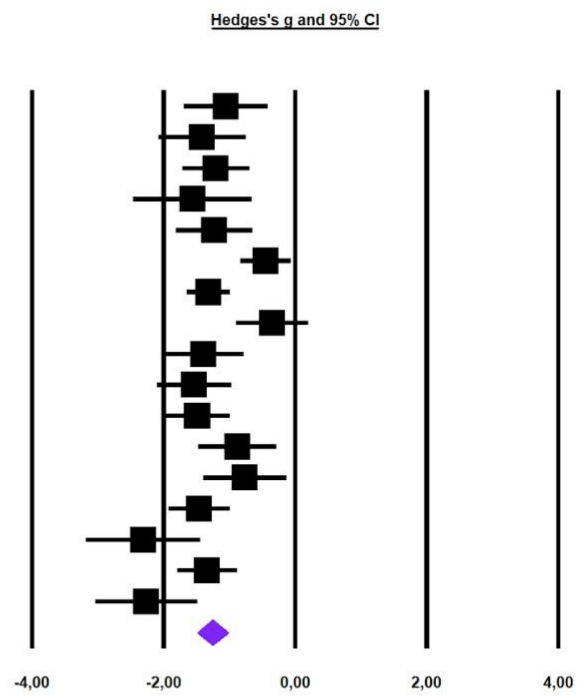
Synthesis of Results

To assess the changes in mental disorder symptoms separately for groups of substances, individual substances and patient groups, primary studies were grouped. The summary effects for each meta-analysis, *SE*s, confidence intervals and *p*-values of the pre to post *Z*-Test are displayed in Table 4. *Q*-values, *df(Q)* and *p(Q)* values, I^2, *Tau*, Tau^2, its *SE* and Variances are displayed in the Supplementary Figures 1-3. To compare groups of studies, between study *Q*-values, *df(Q)* and *p(Q)* values refer to Supplementary Figures 3 and 4.

Figure 2

Forest plot with Results for Primary Studies

Study name	Subgroup within study	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bogenschutz 2015	OL	-1,059	0,319	0,102	-1,685	-0,433	-3,316	0,001
Brown 2018	OL	-1,421	0,335	0,112	-2,077	-0,765	-4,246	0,000
Carhart-Harris 2018	OL	-1,211	0,255	0,065	-1,711	-0,711	-4,750	0,000
Danforth 2018	RCT	-1,565	0,455	0,207	-2,457	-0,673	-3,440	0,001
Gasser 2014	Combined	-1,236	0,295	0,087	-1,815	-0,658	-4,192	0,000
Glue 2016	Combined	-0,454	0,193	0,037	-0,831	-0,076	-2,352	0,019
Griffiths 2016	Combined	-1,318	0,163	0,026	-1,637	-0,999	-8,104	0,000
Grob 2011	RCT	-0,356	0,276	0,076	-0,896	0,184	-1,291	0,197
Johnson 2014	OL	-1,400	0,308	0,095	-2,004	-0,796	-4,542	0,000
Mithoefer 2011	Combined	-1,543	0,285	0,081	-2,100	-0,985	-5,420	0,000
Mithoefer 2018	Combined	-1,492	0,250	0,063	-1,983	-1,002	-5,964	0,000
Noller 2018	OL	-0,879	0,298	0,089	-1,464	-0,294	-2,946	0,003
Oehen 2013	RCT	-0,768	0,319	0,102	-1,394	-0,142	-2,405	0,016
Ot'alora 2018	Combined	-1,462	0,235	0,055	-1,923	-1,001	-6,212	0,000
Palhano-Fontes 2019	RCT	-2,314	0,438	0,192	-3,173	-1,455	-5,281	0,000
Ross 2016	Combined	-1,339	0,229	0,052	-1,787	-0,891	-5,860	0,000
Sanches 2016	OL	-2,267	0,391	0,153	-3,034	-1,500	-5,796	0,000
		-1,252	0,117	0,014	-1,481	-1,024	-10,734	0,000



Note. The effect across studies is displayed in the bottom row. Line width: 95% confidence intervals.

Table 4

Results of Meta-Analyses

Group of studies	Number of included studies	Model	Hedges *g* (SE)	95 % Confidence Interval	Z-value	p-value
Overall	17	REM	-1.252 (0.117)	[-1.489, -1.024]	-10.734	0.0000
Psychedelica	9	REM	-1.320 (0.149)	[-1.611, -1.028]	-8.867	0.0000
MDMA	5	FEM	-1.389 (0.128)	[-1.634, -1.132]	-10.801	0.0000
Ibogaine	3	REM	-0.853 (0.251)	[-1.345, -0.361]	-3.400	0.0007
Ayahuasca	2	FEM	-2.288 (0,292)	[-2.860, -1.716]	-7.840	0.0000
Psilocybin	6	FEM	-1.171 (0,097)	[-1.361, -0.980]	-12.045	0.0000
LSD	1	FEM	-1.236 (0,295)	[-1.815, -0.658]	-4.192	0.0000
Substance use	5	REM	-0.998 (0,206)	[-1.402, -0.593]	-4.834	0.0000
Anxiety	4	REM	-1.084 (0,236)	[-1.547, -0.621]	-4.591	0.0000
Depression	4	REM	-1,643 (0,235)	[-2,102, -1,183]	-7,005	0.0000
PTSD	5	FEM	-1.367 (0,226)	[-1.629, -1.106]	-10,247	0.0000

Note. Q-values, p(Q)-values, i2, tau, tau2, SEs, and variances are presented in the CMA outputs (see Supplemental Material), REM = Random effects model; FEM = fixed effects model.

Objective 1

Do symptoms of mental disorders change after psychedelic and entactogen-assisted therapy? To assess the primary objective, a total number of 290 participants (at follow-up) from 17 studies were included into this meta-analysis. The overall pre to post summary effect across studies was estimated as Hedge's *g* = -1.252 with a of *SE* = 0.117, *p* = 0.0000, 95% *CIs* of [-1.489, -1.024], and indicates significant reduction in symptoms. The summary effect is presented in

the bottom line of the forest plot (Figure 2). The *Q*-value, a measure of heterogeneity between studies was $Q = 47.913$ with $df(Q) = 16$ and $p(Q) = 0.000$. This p-value indicates that the true effect size probably does vary from study to study, as it is unlikely that all of the observed variance is due to sampling error, and therefore, confirms the choice of the random effects model (Comprehensive Meta-Analysis, 2021; Cooper et al., 2019). I^2, the percentage of variation across studies due to real heterogeneity rather than error, was calculated as $I^2 = 66.606$. The *p*-value of the *Z*-test supports the alternative hypothesis H1:

- ➔ H1: The mean overall effect is not zero, indicating that the symptoms of mental disorders do change after psychedelic and entactogen-assisted therapy.

  H1: $g \neq 0.0$ or $p < .05$

Objectives 2-6

Do symptoms of mental disorders change after 2. ayahuasca-, 3. ibogaine-, 4. LSD-, 5. psilocybin- and 6. MDMA-assisted therapy? The negative Hedge's *g* shows a reduction in symptoms after therapy. All *p*-values of the *Z*-test were significant, indicating that:

- ➔ H1: The symptoms of mental disorders do change after 2. ayahuasca-, 3. ibogaine-, 4. LSD-, 5. psilocybin-, and 6. MDMA-assisted therapy.

  H1: $g \neq 0.0$ or $p < .05$

Objectives 7-10

Do symptoms of mental disorders change after psychedelic and MDMA therapy in 7. anxiety, 8. depression, 9. PTSD, and 10. substance use populations? As symptoms were reduced after the therapy, and all *p*-values of the *Z*-Test were significant, the findings indicate that:

- ➔ H1: The symptoms of mental disorders do change in 7. anxiety, 8. depression, 9. PTSD, and 10. substance use populations.

  H1: $g \neq 0.0$ or $p < .05$

Objective 11: Comparing substance groups

To test for differences between outcomes, the MDMA and psychedelics studies were compared to each other in a mixed effects analysis. The between study *Q*-value of 0.0423 and *p*-value of 0.8371 indicated that

- ➔ H0: The overall mean effects were not different between MDMA- and psychedelics-studies.

  H0: $p(Q) \geqslant .05$

Objective 12: Comparing patient groups

Lastly, the outcomes for studies with different patient groups were compared in a mixed effects analysis. Again, no significant differences between populations could be seen based on the between study Q-value of 4.942 and *p*-value of 0.176.

- ➔ H0: The overall mean effects were not different between anxiety, depression, PTSD and substance use studies.

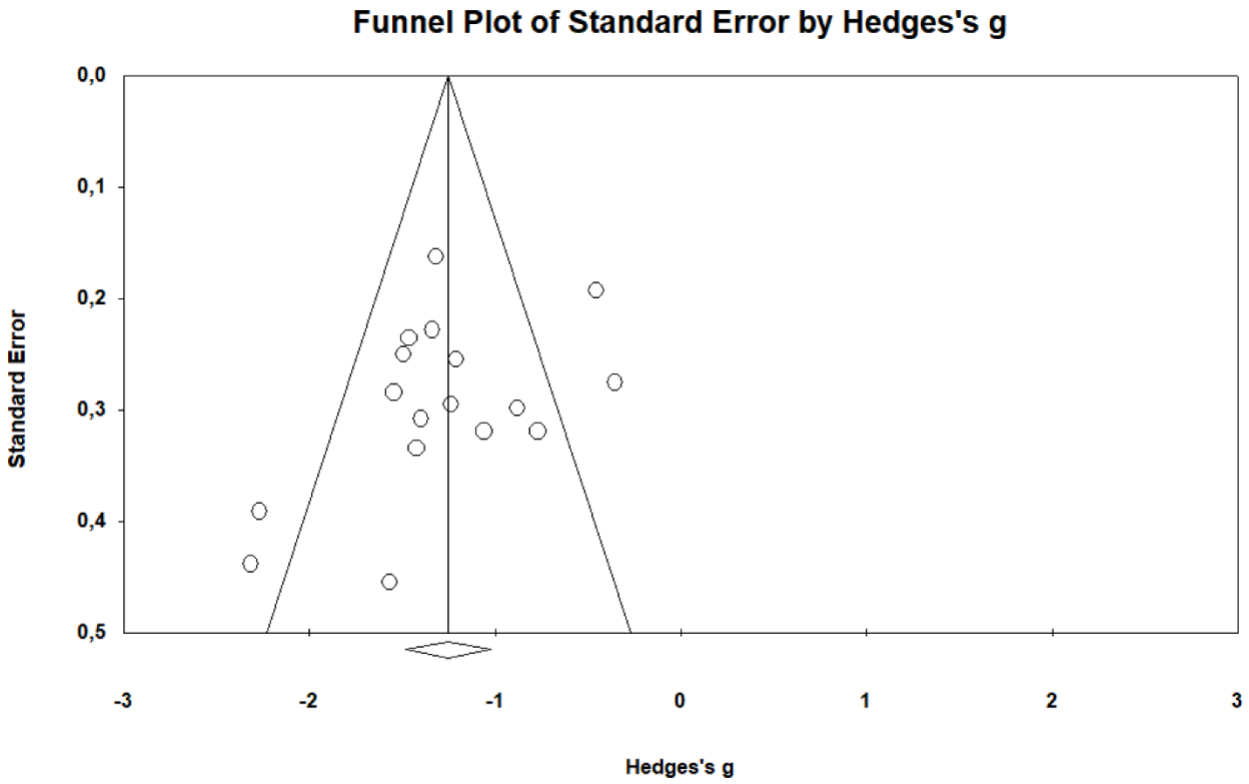
  H0: $p(Q) \geqslant .05$

Risk of Bias Across Studies

The funnel plot for all included studies is displayed in Figure 3.

Figure 3

Funnel Plot



Note. The circles represent included studies, the middle line indicates the overall mean effect with 95% confidence intervals to the left and right.

Visual interpretation of the funnel plot suggested the presence of publication bias, as the bottom of the plot showed a higher concentration of studies on the left side. In presence of publication bias, “small studies are disproportionately associated with larger effect sizes” (Comprehensive Meta-Analysis, 2021). However, this visual interpretation was not confirmed statistically: Egger’s linear regression intercept was estimated as -2.316, 95% confidence

interval [-5.621;0.989], with *t* = 1,494, *df* = 15. The one-tailed *p*-value of 0.078 was not significant, and did therefore, not confirm publication bias. In Begg and Mazumdars (1994) rank correlation test, Kendall's tau *b* was computed as -0,19118, with a 1-tailed non-significant *p*-value of 0,14208. Therefore, there seems to be no correlation between study size and effect size. However, a "[…] non-significant correlation may be due to low statistical power, and cannot be taken as evidence that bias is absent" (Comprehensive Meta-Analysis, 2021).

To account for the possibility of publication bias, Duval and Tweedie's (2000) trim and fill method imputed three studies on the right of the funnel plot. The corrected summary effect across studies was Hedge's *g* = -1,137 [-1,375; -0.900].

Additional Analysis

Study design

To estimate whether study design is related to effect size, study design was included as a categorical covariate into a regression model. The Q value of 0.00 and *p*(*Q*) value of 0.9647 were interpreted as support of the null hypothesis.

➔ H0: The covariate study design is not related to the symptom change of mental disorders after psychedelic- and MDMA-assisted therapy.

H0: $p \geqslant .05$

Loss to Follow-up

Another objective was to assess the influence of the percent of participants lost to follow-up on the overall mean effect. A meta-regression was conducted, and the test of the model *Q* value of 0.80 and *p*(*Q*) value of 0.3697 were interpreted as support of the null hypothesis:

➔ H0: The covariate loss to follow-up is not related to the symptom change of mental disorders after psychedelic and MDMA-assisted therapy.

H0: $p \geqslant .05$

Discussion

In the following section, main findings are summarized and limitations are discussed at study and outcome level. In the conclusion, outcomes are discussed in the context of other evidence with implications for future research.

Summary of Evidence

In this meta-analysis, 17 studies were integrated with the objective to evaluate if the symptoms of various mental disorders could be reduced after psychedelic- and MDMA-assisted therapy. The overall summary effect was estimated as Hedge's *g* = -1.252 with a of *SE* = 0.117. The publication bias corrected overall summary effect was estimated as *g* = -1,137. This value indicates a significant reduction of symptoms following psychedelic- and MDMA-assisted therapy. However, the high loss-to follow-up rates and design features of some studies limit the certainty of findings. The lowest symptom reductions were observed for opioid use after ibogaine treatment (*g* = -0.826, SE = 0.210). For ayahuasca-assisted treatment of depression, the reduction of symptoms was very large with an effect size of *g* = -2.288 and *SE* = 0,292. In none of the studies did symptoms worsen after therapy.

As expected, the heterogeneity across studies was marked (I^2 = 66.606), likely due to the various substances, instruments, designs, and populations included. More homogenous results could be seen in studies of MDMA-assisted therapy (I^2 = 10.821). Crossover designs, where participants received blinded and open-label medication, add complexity to the data structure.

The two quality-related moderators' loss-to follow-up and design of the first session couldn't explain any of the observed variance between studies in meta regressions (R^2 = .00). The tests for publication bias did not gain statistical significance, but might have been underpowered. Dosing could have been an interesting moderator, however the data was not suitable for such an analysis. In some studies multiple sessions with varying dosed took place and the reporting thereof was not always consistent.

Adverse Reactions

Currently, applied pharmacotherapy for psychiatric symptoms is often associated with slow onsets, low response rates and high relapse rates (Carhart Harris et al. 2017, Romeo et al. 2020; Rucker et al. 2020). In the included studies, there were several adverse reactions, but few of them lasted beyond the sessions. Research "[…] indicates that adverse reactions associated with psychedelics are primarily a consequence of inappropriate use" (Velder et al., 2017). However, a careful evaluation of risk factors before treatment is mandatory, as well as further investigation of side effects especially in the case of ibogaine (Brown et al., 2018; Knuijver et al., 2018).

Effect Size in Context

Are the presented findings comparable to those of other meta-analyses in the field? In a meta-analysis of psilocybin treatment for anxiety and depression, Goldberg et al. (2020) used a

similar methodology and observed pre-post values[4] of *g* = 1.17 for anxiety and *g* = 1.16 for depression at 6-month follow-up. These effect sizes are very similar to the *g* = -1.17 (see Table 4) for psilocybin therapy in the present study. However, Goldberg et al. (2020) included only four studies and concluded that "high risk of bias was present for most studies (performance bias and detection bias due to lack of blinding, attrition bias)" (Goldberg et al., 2020, p.284).

Another meta-analysis by Romeo et al. (2020) estimated a pre to post standardized mean difference of *SEM* = -1.07 for psychedelics in the treatment of depression at 6-month follow-up. In comparison, the Hedges *g* = -1.320 value for nine psychedelics studies displayed in Table 4 is slightly higher, possibly because Romeo analysed only four studies at the 6-month follow-up.

Bahji et al. (2020) included five studies to evaluate the efficacy of MDMA treatment for PTSD. Rate ratios (*RR*'s) showed significantly higher response to (RR = 3.47) and remission after treatment (RR = 2,63) in groups that received active MDMA than in the control groups. The mean difference of *SEM* = -1.39 following MDMA treatment was almost the same as in this meta-analysis (Hedge's *g* = -1.389), even though Bahji et al (2020) did not include the study by Danforth et al. (2018). Again, the quality of primary studies assessed with the Cochrane Risk of

[4] Even though Goldberg et al. (2020) used a different direction of effects, they are also referring to reductions in anxiety and depression symptoms.

Bias Tool for Randomized Controlled Trials was only moderate (Bahji et al., 2020). Remission rates could have been a useful effect size measure for this meta-analysis as well, however, they can only be applied in studies with control groups.

To conclude, the mentioned studies were published in peer-reviewed journals, and several authors allowed for multiple coders and multiple reviewers of study quality. Even though results were similar, the risk of coding mistakes and flaws in statistical processing prevails in this meta-analysis.

Limitations

The studies included into this meta-analysis were methodologically diverse in various respects. The complexity of the data structure that included different substances, disorders and designs allows for cautious interpretations. Even though significant effects could be seen for all substances and all disorders, these effects might be limited in their generalizability to broader populations. A multi-level meta-analysis could be a useful tool to discriminate effects, especially with respect to the dependent nature of pre-post effect sizes (Moeyaert et al., 2017).

Risk of bias in primary studies was only evaluated for a few domains, and the methodological quality of primary studies needs further exploration. Existing risk of bias assessment tools are limited to either open-label pre-post designs or comparisons between control and active groups. Future risk of bias tools should take the risk that arises from patient selection, confounding interventions, study power and other areas into account and provide options for multiple study designs.

The loss to follow-up reached levels of more than 20% in the studies of Brown et al. (2018) Grob et al. (2011) and Ross et al. (2016). Whether these participants were missing at

random, missing completely at random or not missing at random needs further investigation.

In general, pre to post effect sizes are limited in their generalizability, because without comparison to a control group, no causal relationship can be attributed (Cuijpers et al. 2017). However, the effects of psychedelics and MDMA are highly salient. This makes it hard to establish an effective placebo, and participants in controlled studies frequently guessed correctly their group assignment (Labate & Cavnar, 2018).

One limitation of the search strategy is, that the last time databases were searched for primary studies was in 2020. Since then, other studies have been published that fall into the inclusion criteria (Mitchell et al., 2021). Recency and efficacy of the meta-analytic process could be facilitated with open access solutions, that allow for constantly updated meta-analytic and scientific data.

Several of the included studies were funded by the Multidisciplinary Association of Psychedelic Studies (MAPS). One of MAPS' aims is "developing psychedelics and marijuana into prescription medicines" (Multidisciplinary Association for Psychedelic Studies, 2021a). Therefore, a conflict of interest in primary studies is possible, and independent research of psychedelics and MDMA is encouraged.

Conclusions

The field of psychedelic research is moving forward. As we begin to understand the complexity of these compounds, new perspectives and areas of applications emerge. Diverse populations of patients could potentially benefit from psychedelic- and MDMA-assisted therapy, especially patients that fail to respond to currently available pharmacotherapy and psychotherapy. Currently, the nature of published studies does not allow for general

conclusions on the broad application of these treatments. Large phase two and phase three studies are underway, and some have already been published after completion of the literature search for this meta-analysis (Mitchell et al., 2021; Multidisciplinary Association for Psychedelic Studies, 2021b).

Future studies should apply strategies to prevent loss to follow-up and improve study quality in line with reporting standards (Higgins et al., 2019; Page et al., 2021). If more raw data was made available, scientists and meta-analysts, policy makers and patients could benefit, as the accuracy and efficacy of further research could significantly improve (Ferreira & Patino, 2019). Therefore, the provision of supplemental material and the concept of open science is to be supported.

Several psychedelic substances have not yet been examined for their medical indications in an experimental design. To give an example, the mescaline-containing and psychoactive peyote and San Pedro cacti have a history of medical application in America's indigenous communities (Krebs, 2015).

Psychedelic- and MDMA-assisted therapy seem to challenge our currently prevailing concepts of psychiatry, clinical psychology and pharmacology. It will be up to policy makers, politicians and care providing institutions to base their decisions on scientific evidence rather than public opinion (Rucker et al., 2020).

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Supplemental Material

Supplementary Figure 1

Objective 1 Overall Output

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	17	-1,198	0,065	0,004	-1,325	-1,071	-18,450	0,000	47,913	16	0,000	66,606	0,146	0,082	0,007	0,382
Random	17	-1,252	0,117	0,014	-1,481	-1,024	-10,734	0,000								

Supplementary Figure 2

Objective 2-6 Substance Output

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Ayahuasca	2	-2,288	0,292	0,085	-2,860	-1,716	-7,840	0,000	0,006	1	0,936	0,000	0,000	0,244	0,060	0,000
Ibogaine	3	-0,739	0,146	0,021	-1,024	-0,453	-5,067	0,000	6,565	2	0,038	69,534	0,167	0,245	0,060	0,409
LSD	1	-1,236	0,295	0,087	-1,815	-0,658	-4,192	0,000	0,000	0	1,000	0,000	0,000	0,000	0,000	0,000
MDMA	5	-1,383	0,128	0,016	-1,634	-1,132	-10,801	0,000	4,485	4	0,344	10,821	0,010	0,067	0,005	0,102
Psilocybin	6	-1,171	0,097	0,009	-1,361	-0,980	-12,045	0,000	10,802	5	0,055	53,713	0,070	0,084	0,007	0,264
Total within									21,859	12	0,039					
Total between									26,054	4	0,000					
Overall	17	-1,198	0,065	0,004	-1,325	-1,071	-18,450	0,000	47,913	16	0,000	66,606	0,146	0,082	0,007	0,382
Mixed effects analysis																
Ayahuasca	2	-2,289	0,340	0,116	-2,955	-1,622	-6,730	0,000								
Ibogaine	3	-0,826	0,210	0,044	-1,237	-0,414	-3,936	0,000								
LSD	1	-1,236	0,384	0,147	-1,989	-0,484	-3,220	0,001								
MDMA	5	-1,371	0,172	0,030	-1,708	-1,033	-7,962	0,000								
Psilocybin	6	-1,136	0,144	0,021	-1,418	-0,854	-7,895	0,000								
Total between									14,503	4	0,006					
Overall	17	-1,232	0,091	0,008	-1,411	-1,053	-13,504	0,000								

Supplementary Figure 3

Objective 7-10 & 12 Population Output

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
Anxiety & Depr.	4	-1,071	0,143	0,021	-1,352	-0,790	-7,471	0,000	9,599	3	0,022	68,745	0,192	0,236	0,056	0,438
Depression	4	-1,468	0,124	0,015	-1,712	-1,225	-11,830	0,000	9,763	3	0,021	69,271	0,177	0,226	0,051	0,421
PTSD	4	-1,367	0,133	0,018	-1,629	-1,106	-10,247	0,000	4,311	3	0,230	30,414	0,032	0,085	0,007	0,178
Substance use	5	-0,889	0,122	0,015	-1,127	-0,650	-7,294	0,000	10,660	4	0,031	62,476	0,132	0,153	0,023	0,363
Total within									34,333	13	0,001					
Total between									13,581	3	0,004					
Overall	17	-1,198	0,065	0,004	-1,325	-1,071	-18,450	0,000	47,913	16	0,000	66,606	0,146	0,082	0,007	0,382
Mixed effects analysis																
Anxiety & Depr.	4	-1,084	0,236	0,056	-1,547	-0,621	-4,591	0,000								
Depression	4	-1,643	0,235	0,055	-2,102	-1,183	-7,005	0,000								
PTSD	4	-1,337	0,226	0,051	-1,779	-0,895	-5,929	0,000								
Substance use	5	-0,998	0,206	0,043	-1,402	-0,593	-4,834	0,000								
Total between									4,942	3	0,176					
Overall	17	-1,249	0,112	0,013	-1,470	-1,029	-11,123	0,000								

Supplementary Figure 4

Objective 11 Substance Type Output

Groups		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Group	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed effect analysis																
MDMA	5	-1,3828	0,1280	0,0164	-1,6338	-1,1319	-10,8010	0,0000	4,4853	4,0000	0,3443	10,8206	0,0103	0,0675	0,0046	0,1016
Psychedelic	9	-1,2784	0,0880	0,0077	-1,4510	-1,1059	-14,5228	0,0000	24,0176	8,0000	0,0023	66,6911	0,1472	0,1175	0,0138	0,3837
Total within									28,5029	12,0000	0,0047					
Total between									0,4515	1,0000	0,5016					
Overall	14	-1,3119	0,0725	0,0053	-1,4541	-1,1698	-18,0865	0,0000	28,9545	13,0000	0,0066	55,1019	0,0929	0,0689	0,0047	0,3047
Mixed effects analysis																
MDMA	5	-1,3679	0,1981	0,0392	-1,7561	-0,9797	-6,9061	0,0000								
Psychedelic	9	-1,3174	0,1452	0,0211	-1,6020	-1,0328	-9,0715	0,0000								
Total between									0,0423	1,0000	0,8371					
Overall	14	-1,3350	0,1171	0,0137	-1,5646	-1,1055	-11,3993	0,0000								