A PHENOMENOLOGICAL EXPLORATION OF EXPERIENCES WITH SHORT-ACTING PSYCHEDELICS FOR LOW MOOD AND DEPRESSION

by

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THESIS OVERVIEW

This document contains two chapters that constitute the doctoral thesis for the degree of Clinical Psychology Doctorate (ClinPsyD).

Chapter 1 is a systematic literature review in the form of a meta-analysis of all clinical trials that have been conducted to date investigating the efficacy of classic psychedelic drugs in psychedelic assisted psychotherapy for the treatment of depression or anxiety symptoms in individuals with mental health diagnoses. Findings suggested positive outcomes for psychedelics in these clinical trials with moderate to large effect sizes. However, the studies to-date have been small, and with variable methodological quality and sources of bias, therefore larger and more robust trials would be needed for more certain results.

Chapter 2 is an empirical research paper exploring participant's experiences of using short-acting psychedelics, such as dimethyltryptamine, in an attempt to help with their low mood or depression. This study was conducted by interviewing nine participants and analysing the interviews using Interpretative Phenomenological Analysis (IPA) to generate themes. Four primary themes were generated: 1) Journey to Using DMT for Mental Health, 2) Psychological and Spiritual Insights, 3) Emotional Healing Through DMT, and 4) Personal Growth Following DMT.

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A META-ANALYSIS OF THE EFFICACY OF PSYCHEDELIC THERAPIES IN THE TREATMENT OF SYMPTOMS OF ANXIETY AND DEPRESSION FOR PEOPLE WITH MENTAL HEALTH CONDITIONS

ABSTRACT

Background: There has been a resurgence of research investigating the efficacy of psychedelic assisted psychotherapy for mental health conditions. Results from clinical trials have reported positive findings for conditions such as depression and anxiety. The aim of this meta-analysis is to systematically evaluate the totality of evidence thus far for the efficacy of these drugs for alleviating symptoms of anxiety and depression.

Methods: Web of Science, MEDLINE, PsychInfo, Cochrane and Embase databases were searched for all clinical trials of psychedelic assisted psychotherapy in the treatment of symptoms of anxiety or depression in individuals with mental health conditions. A total of 21 publications, comprised of 15 unique clinical trials, were found that could be included in this meta-analysis.

Results: The meta-analysis assessed anxiety and depression treatment outcomes for psychedelic assisted psychotherapy. Anxiety treatments showed significant and large overall effects (SMD -1.37), albeit with methodological variation influencing results, leading to adjusted effect sizes as low as SMD -0.43 when controlling for detection bias. Depression treatments also demonstrated substantial effects (SMD -1.27), with adjustments for detection bias reducing effect sizes to moderate (SMD -0.46). Likelihood of treatment superiority of psychedelic interventions ranged from 83% to 59% for anxiety and 82% to 62.8% for depression depending of methodological variation.

Conclusion: The meta-analysis highlights positive effects of psychedelic therapies on depression and anxiety symptoms. It is the largest meta-analysis to date on this topic, showing moderate to large treatment effects. However, methodological biases suggest the necessity for larger and more robust clinical trials going forward.

INTRODUCTION

Classic psychedelics refers to the classification of drugs, originally coined by Humfrey Osmond to mean “mind manifesting”, that are defined by their primary mechanism of action via the serotonin 2A (5HT-2A) receptors (Nichols et al., 2023). Within this classification are several categories such as tryptamines, phenethylamines, and ergolines, in which most classic psychedelics are found (Calvey & Howells, 2018). The most well-known of these drugs are mescaline, lysergic acid diethylamide (LSD), psilocybin mushrooms (magic mushrooms), N,N-DMT and 5-MeO-DMT. Furthermore, N,N-DMT is often consumed in a psychedelic brew, along with other compounds, that is often referred to as a separate drug called ayahuasca, which is also considered part of this classification (Calvey & Howells, 2018). Throughout this chapter the term “psychedelics” will refer, specifically, to “classic psychedelics”.

The use of psychedelics has been around for millennia, with evidence of ancient civilisations using psychoactive drugs for ritualistic healing practices dating back as far as 1,000 years (George et al., 2022). Moreover, across the globe, many hunter-gatherer and traditional cultures have been found to use psychedelic substances as a form of medicine (Celidwen et al., 2023; George et al., 2022). Within Western medicine, research into classic psychedelics started in the 1940s and continued into the 1960s, by which time it had gained some recognition as an analgesic agent, with some growing sentiment that they could be used more broadly to enhance psychological and spiritual well-being among people (Doblin, 1991. Nichols & Walter, 2021; Kast & Collins, 1964). However, clinical trials investigating these substances at the time had been criticised due to poor methodology, such as lack of control groups, lack of blinding, unvalidated outcomes, and inconsistent application of treatments between groups (Rucker et al., 2018). By the 1970s research into psychedelics in humans had significantly slowed, in part because of the aforementioned criticisms but also increased regulatory controls for clinical trials

due to broader safety concerns in pharmaceutical research, as well as specific societal concerns around the potential harms of psychedelics (Bonson, 2018; Hall, 2022; Winship et al., 1992). Psychedelic drugs were placed in Schedule 1 of the 1967 United Nations Convention on Drugs, influencing regulatory and legal legislation around the world that made it significantly more difficult for researchers to gain the appropriate licenses to conduct clinical trials (Rucker et al., 2018; Bonson, 2018).

In the 1990s research into psychedelic drugs started again with a study by Strassman and Qualls (1994) of the (at the time lesser-known) drug N,N-DMT. This, in conjunction with a small number of similar studies, set the basis for early neuroimaging research into the classification of these substances, as well as a safety and tolerability profile on which to base subsequent clinical trials (Carhartt-Harris & Goodwin, 2017). Since, there have been notable strides in research into this area with a considerable number of clinical trials being conducted, investigating these substances for mental health conditions such as depression (Ko et al., 2023).

The Therapy of Psychedelics

While the exact mechanism through which psychedelic drugs provide therapeutic benefits for mental health conditions remains unclear, several have been proposed. Neurologically, they are believed to act through their interaction with the serotonin 2A receptor, hypothesised to enhance well-being by promoting neuroplasticity and adaptability to adversity (Carhart-Harris & Nutt, 2017). As a result, psychedelics may promote increased psychological flexibility, thereby loosening previously ridged thought patterns, which are suggested to play a role in various mental health conditions (Carhart-Harris & Nutt, 2017).

Moreover, it is important to note the psychological component of this line of research. While neuropsychological data may give some insight, it is crucial to keep in mind that the

pharmacological component of therapy, as indicated by its full name 'Psychedelic-Assisted Psychotherapy' (PAP), supports a broader therapeutic process. Bathje et al. (2022) emphasise the importance of the integration component of this type of therapy; that is, how participants make sense of their experiences, days, weeks and months after the acute effects have worn off. Within psychedelic-assisted psychotherapy, participants undergo some form of psychological support to help them process the content of their psychedelic experiences. Though there is no unified method for doing this, psychodynamic (Barrett, 2022) and cognitive-behavioural approaches, such as Acceptance and Commitment Therapy, have frequently been implicated (Wolff et al., 2020).

Previous Meta-Analyses

To date, there have been several meta-analyses looking at the effectiveness of PAP for mental health difficulties. Romero et al. (2020) conducted a meta-analysis of PAP on depressive symptoms. They identified eight studies to be included in the analysis, finding a large and statistically significant decrease in depressive symptoms at each time period measured, from the largest effect at day 21 (Cohen's d =-2.68, $p < 0.01$) to the smallest effect size at 6-8 weeks (Cohen's d = –0.72, $p = 0.002$), with two and four studies being included at each of these periods, respectively. It should be noted that this meta-analysis only included studies in which patients had a confirmed depression diagnosis. In a broader-ranging meta-analysis, Luoma et al. (2020) included nine studies that looked at the efficacy of all placebo-controlled trials for PAP. However, this meta-analysis also included 3,4-Methylenedioxymethamphetamine (MDMA) (a non-classic/atypical psychedelic) trials as part of their analysis, which constituted five of the nine studies. For their subgroup analysis, looking at just classic psychedelics, they

found a large effect size (*Hedges g* = 1.2) from the four remaining clinical trials. However, they did not report any meta-analytic effect for long-term follow-up for the classic psychedelics.

The two meta-analyses described above only considered data related to primary outcome measures within the trials, thus omitting any secondary measures that might have been administered to participants. This limited inclusion of data in their analyses suggests that the reported effect within these meta-analyses does not fully capture the totality of evidence from the studies included. Moreover, the generalisability of results from these meta-analyses is hindered by the small number of studies in both.

A more recent, and larger, meta-analysis from Ko et al. (2023) reviewed the efficacy of PAP on any patient group with clinically elevated depressive symptoms. They identified 14 studies, comprised of 11 unique clinical trials, that matched the inclusion criteria for the analysis. They found large effect sizes for reductions in depressive symptoms at all time points: day 1 (Cohen's d = -01.36, p=0.02), week 1 (Cohen's d =- 1.37, p = .009), weeks 3-5 (Cohen's d =-3.12, p = .05), and weeks 6-8 (Cohen's d = -1.52, p = .14) all with statistical significance, except weeks 6-8. In another meta-analysis, Leger and Unterwald (2022) evaluated 9 studies looking at the effectiveness of PAP for people with confirmed anxiety or depression disorders. They found improvements in outcome measures for depression studies (n=9, Cohen's d = 1.38, <0.001) and anxiety studies (n=7, Cohen's d = 1.26, p<0.001). However, a limitation of both the above analyses is that they did not report on any long-term follow-up data; Ko et al. (2023) did not report on any effect past 8 weeks following PAP, while Leger and Unterwald (2022) did not report on any data past 1-week post-PAP. Leger and Unterwald (2022) is limited by the small number of studies included in their analysis, and while Ko et al. (2023) had a larger

sample, based on the searches from the current study, there has been significant progress in the field since the publication of their findings.

It is also noteworthy that several of these meta-analyses exhibit Conflicts of Interest (COI). For instance, Ko et al. (2023) include authors affiliated with the Psychoactive Trials at King's College London, which receives funding from COMPASS Pathways and Beckley PsyTech, both pharmaceutical companies that manufacture psychedelic drugs. Romero et al. (2020) also include authors who receive consulting fees from pharmaceutical companies and hold positions on pharmaceutical company boards. Additionally, Luoma et al. (2020) have authors involved in leading psychedelic trials (e.g., Davis et al., 2021).

The Present Study

The present study aims to build upon prior research, specifically addressing recent developments in the literature. After the most recent meta-analyses, a considerable number of newer and larger studies have emerged, necessitating their inclusion in our analysis. While the largest of the previous meta-analyses (Ko et al., 2023) incorporated data from 14 articles and 11 distinct clinical trials, the search for the current study identified a total of 21 studies and 15 unique clinical trials eligible for analysis (refer to Figure 1 for comprehensive details).

Furthermore, the current study seeks to expand upon previous methodologies by encompassing all clinical trials (both open-label and closed-label) that evaluate symptoms of anxiety or depression in any client group with a diagnosable mental health condition. Notably, the current study will utilise psychometric data for anxiety and depressive symptomology from these studies, including both primary and secondary data. Through this broad inclusion criteria, this meta-analysis aims to comprehensively assess the overall body of evidence regarding the efficacy of psychedelic therapies for alleviating anxiety and depressive symptoms among

individuals with mental health conditions. Additionally, this study will conduct subgroup analyses to control for potential sources of bias within the included studies, thereby evaluating any fluctuations in effect sizes within the meta-analytic data based on disparities in study methodology quality. Notably, this subgroup analysis was not conducted in any of the previously mentioned meta-analyses.

METHOD

Registration

The study protocol is registered at PROSPERO (CRD42023448263).

Identifying Primary Studies

Search of Electronic Databases

A systematic literature search was conducted on 5th May 2023 using the databases Web of Science Core Collection, MEDLINE, PsychInfo, Cochrane Database of Controlled Trials, and Embase to identify clinical trials of psychedelic-assisted psychotherapy for the treatment of symptoms of depression and anxiety in people with mental health conditions. This choice of databases was based on a previous meta-analysis (Ko et al., 2023) of psychedelic therapy for depressive symptoms. Full details of the search terms, method of search, limits and Boolean variables can be seen in Table 1.

Table 1

Search Criteria

Construct	Free Text Search Terms	Method of Search	Limits
Psychedelic Drugs	Psychedelic psilocybin" LSD Lysergic acid diethylamide Ayahuasca DMT Dimethyltryptamine hallucinogen* mescaline" peyote" 3, 4, 5-trimethoxyphenethylamine	All intra-construct search terms combined with *OR* then inter-construct search terms with *AND*	English Language Any Date

Mental Health	depress* anxi* distress” traum* post-traumatic PTSD obsessive OCD alcohol* substance addict*		
Clinical Trials	trial" randomi* placebo *blind		

Example of Full Search Term:

(“psychedelic*” OR “psilocybin” OR “LSD” OR “Lysergic acid diethylamide” OR “ayahuasca” OR “*DMT” OR "*dimethyltryptamine" OR “hallucinogen*” OR “mescaline” OR “peyote” OR “3, 4, 5-trimethoxyphenethylamine”) AND (“depress*” OR “anxi*” OR “distress” OR “traum*” OR “post-traumatic” OR "PTSD" OR “obsessive" OR “OCD”, “alcohol*” OR "substance" OR "addict*") AND ("trial" OR "randomi*" OR "placebo" OR "*blind")

Inclusion/Exclusion Criteria

The inclusion criteria consisted of adults diagnosed with mental health conditions according to DSM-IV, DSM-V, ICD-10, or ICD-11, emphasising clinical trials (randomised and non-randomised) published in peer-reviewed journals that investigated the effects of classical psychedelics and utilised clinically relevant outcome measures (i.e. psychometric measures of depression or anxiety symptomology). Healthy participants were excluded, as well as studies involving non-classic psychedelics or those not using clinically relevant outcome measures.

Table 2

Inclusion Criteria

Inclusion criteria	Justification
Individuals diagnosed with a mental health condition based on DSM-IV, DSM-V, ICD-10, or ICD-11 criteria.	Excluding healthy participants helps to maintain a focus on individuals with established mental health conditions, aligning with the study's goal of assessing the effectiveness of psychedelics in treating anxiety and depressive symptoms. Having a broad scope for any mental health diagnosis accommodates a wider range of psychiatric illnesses, providing a more comprehensive understanding of the potential applications of psychedelics in mental health treatment.
Adult population.	The inclusion criterion specifying an "adult population" is implemented to ensure that the participants in the selected studies are of a consistent age group. There may be significant differences in the effects of psychedelic-assisted psychotherapy based on a person's level of development, both in terms of therapeutic effect and potential risk of side effects.
Clinical trials, both randomised and non-randomised	The inclusion of both randomised and non-randomised clinical trials ensures a comprehensive evaluation of classical psychedelics' impact on symptoms of anxiety and depression in people with psychiatric conditions. Including multiple study designs allows for a more comprehensive account of the literature.
Published in peer-reviewed journals	As a baseline standard for quality, credibility, and transparency of the evidence to be included in the meta-analysis
Investigating the effects of classical psychedelics	The decision to exclusively include "classic" psychedelics in the meta-analysis is grounded in a desire for methodological precision and scientific focus. Classic psychedelics share a defined pharmacological class and established psychedelic properties (Nichols et al., 2023), allowing for a more homogenous evaluation of their therapeutic potential in mental health treatment. This approach enhances comparative analysis, mitigates safety concerns, and aligns with the current state of research on the effects of classic psychedelics on mental health conditions
Use of clinically relevant outcome measures	This criterion ensures that the chosen studies measure outcomes that have direct implications for clinical practice, promoting the relevance and applicability of the findings.

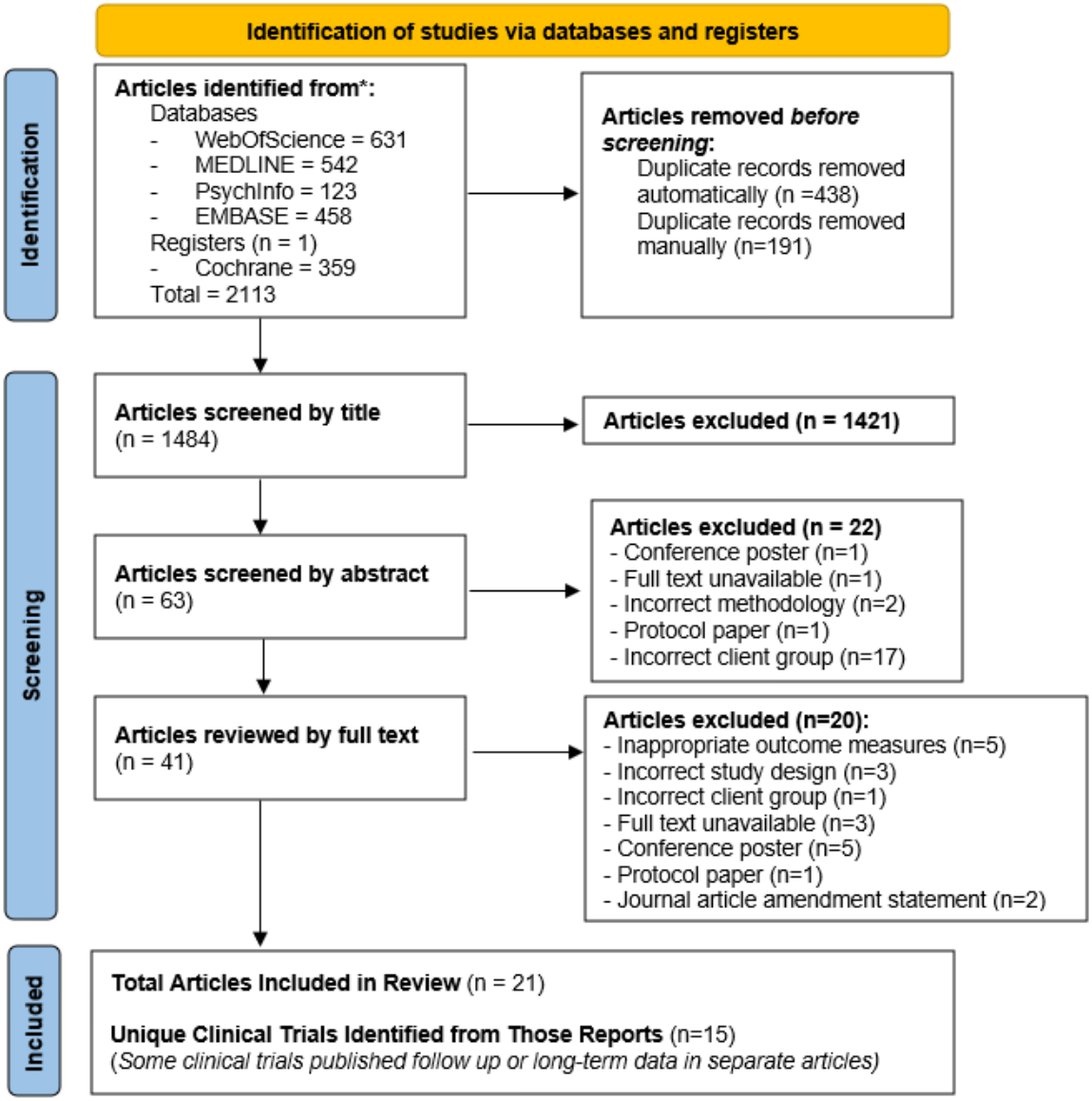
The results of the database search are depicted in Figure 1. Initially, 2113 articles were identified, which was reduced to 1484 after the removal of duplicates after importing into a reference manager. The title review led to the exclusion of 1421 articles. The abstracts of the remaining 63 articles were reviewed, and 22 were subsequently excluded. The full text of 41 articles were scrutinised, resulting in the exclusion of 20 studies. Ultimately, 21 full publications met the inclusion criteria, from which a total of 15 unique clinical trials were

identified for inclusion within this meta-analysis (see Figure 1 for details of the selection and exclusion processes).

Data extraction

Figure 1

Flowchart of Study Selection



Treatment outcomes were primarily based on standardised mean differences (SMD) in the form of Cohen's D between treatment and control groups (alongside standard deviations and sample sizes). Where individual standard deviations for each group were omitted from papers, a pooled standard deviation served as a substitute. In instances where means, standard deviations, and n-sizes were not reported, transformations of Student t or F statistics into Cohen's d estimates were used. In the absence of summary statistics or t and F statistics, effect sizes calculated within the primary studies were used. It is noteworthy that effect sizes reported in primary studies are frequently derived from data adjusted for associations with one or more covariates. Such adjustments underscore the idiosyncratic nature of reported effects and may introduce divergence from effects reported in other primary studies.

Where possible, attempts were made to amalgamate multiple outcomes into a singular quantitative outcome using the methodologies outlined by Borenstein et al. (2009). This occurred when studies reported multiple measures of the same outcome or reported the same outcome measure across different subgroups. In cases where merging multiple effects into a single quantitative effect proved impractical, these repeated measures were included in the meta-analysis. The inclusion of repeated measures from the same primary study reduced the confidence intervals for the weighted average effect, due to the replication of the study's sample size with the inclusion of each repeated measure.

Clinical trials included in this meta-analysis were categorised into different time points based on the duration between drug administration and the recording of outcome measures. These timepoints were defined as Short-term (up to 2 months), Medium-term (2-6 months), and Long-term (6-12 months) follow-up post-administration. Each time point was treated as a distinct data point in the analysis. For instance, when a trial reported multiple outcome data at

different time points, each time point was considered an independent data point in the analysis, rather than combining multiple effect sizes within a study to generate a single outcome per trial. As a result, the 15 trials included in the analysis were made up of 656 unique participants and yielded 39 outcome data points: 16 for anxiety and 23 for depression. See Table 1.3 for a full list of trials included, with the publications from which the outcome data was extracted. For the remainder of this report analysis, the data will be referred to by the name of the parent clinical trial form on which each study was based.

Table 3

Trials and Publications for Sources of Data Included in the Meta-Analysis

Original Trial Name	N=656	Publication Paper	Timepoint	Blinding	Control	Outcome	Drug
Holze et al (2023)	37	Holze et al (2023)	Short	Double Blind	Inactive Placebo	Anxiety	LSD
		Holze et al (2023)	Medium			Anxiety	
		Holze et al (2023)	Short			Depression	
		Holze et al (2023)	Medium			Depression	
Sloshower et al (2023)	19	Sloshower et al (2023)	Short	Double Blind	Inactive Placebo	Anxiety	Psilocybin
		Sloshower et al (2023)	Short			Depression	
Goodwin et al (2022)	312	Goodwin et al (2023)	Short	Double Blind	Active Placebo	Anxiety	Psilocybin
		Goodwin et al (2023)	Short			Anxiety	
		Goodwin et al (2023)	Short			Depression	
		Goodwin et al (2023)	Short			Depression	
D'Souza et al (2022)	6	D'Souza et al (2022)	Short	Open Label	None	Depression	DMT
Carhartt-Harris et al (2021)	30	Carhartt-Harris et al (2021)	Short	Double Blind	Escitalopram	Depression	Psilocybin
		Carhartt-Harris et al (2021)	Short			Anxiety	
Davis et al (2021)	24	Davis et al (2021)	Short	Single Blind	Waiting List	Anxiety	Psilocybin
		Gukasyan et al (2022)	Short			Depression	
		Gukasyan et al (2022)	Medium			Depression	
		Gukasyan et al (2022)	Long			Depression	
Von Rotz et al (2023)	52	Von Rotz et al (2023)	Short	Double Blind	Inactive Placebo	Depression	Psilocybin
		Von Rotz et al (2023)	Short			Anxiety	
Ross et al (2016)	29	Ross et al (2016)	Short	Double Blind	Active Placebo	Anxiety	Psilocybin
		Ross et al (2016)	Short			Depression	

		Agin-Libes et al (2020)	Long			Anxiety	
		Agin-Libes et al (2020)	Long			Depression	
Carhart-Harris et al (2016)	19	Carhart-Harris et al (2018)	Medium	Open Label	None	Depression	Psilocybin
		Carhart-Harris et al (2018)	Short			Anxiety	
		Carhart-Harris et al (2018)	Medium			Anxiety	
		Carhart-Harris et al (2018)	Short			Depression	
Griffiths et al (2016)	51	Griffiths et al (2016)	Short	Double Blind	Active Placebo	Depression	Psilocybin
		Griffiths et al (2016)	Short			Anxiety	
Bogenschutz (2015)	19	Bogenschutz (2015)	Short	Open Label	None	Depression	Psilocybin
		Bogenschutz (2015)	Medium			Depression	
Gasser et al (2014)	11	Gasser et al (2014)	Short	Double Blind	Active Placebo	Depression	LSD
		Gasser et al (2014)	Short			Anxiety	
Grob et al (2011)	12	Grob et al (2011)	Short	Double Blind	Active Placebo	Depression	Psilocybin
		Grob et al (2011)	Medium			Depression	
		Grob et al (2011)	Short			Anxiety	
		Grob et al (2011)	Medium			Anxiety	
Osorio et al (2015)	6	Osorio (2015)	Short	Open Label	Active Placebo	Depression	Ayahuasca
Palhano-Fontes et al (2019)	29	Palhano-Fontes et al (2019)	Short	Double Blind	Inactive Placebo	Depression	Ayahuasca

Note: Short = 0-2 months, Medium = 2-6 months, and Long = 6-12 months

Defining Problematic Variance

Heterogeneity of study-level effects may reflect methodological diversity, measurement errors, or uncontrolled individual difference factors within the literature. Higgins I^2 is a measure of heterogeneity, which reflects the percentage of between-studies variation that is attributable to heterogeneity as opposed to sampling error (Deeks et al., 2023). Higher values of I^2 indicate greater heterogeneity. It was expected that the distribution of effects in the treatment efficacy studies in this review are likely to reflect differences in study design and trial methodology, differences in dose and (perhaps unknown) uncontrolled individual difference factors in the included participants. Accordingly, problematic heterogeneity was defined by the I^2 value exceeding 75% (Deeks et al., 2023). Where problematic heterogeneity is identified, subsequent analyses are focused on identifying sources of heterogeneity among the effect estimates in the primary studies.

Study Design Hierarchy

Studies included within the analysis were each provided a numerical value based on the design of the trials, with more robust designs being awarded a higher score, to be used for the Overall Quality Index Score described in detail below. The full list of study designs, the points attributed to each design, and their descriptions are provided in Table 4.

Table 4

Study Design Hierarchy

Study Design	Quality Score	Description
Randomised controlled trial/experiment	25	These are experimental studies comparing groups (usually two) to establish the effectiveness of specific interventions The most common design is to compare a new intervention against normal practice (treatment as usual). Participants in the trials are randomly assigned to the treatment groups to minimise bias.
Prospective case-cohort study	20	A cohort Study (prospective) is a study of a group of individuals, some of whom are exposed to a variable of interest (e.g., drug or environmental exposure), in which participants are followed up over time to determine who develops the outcome of interest and whether the outcome is associated with the exposure.
Retrospective Case Cohort Study	15	A cohort Study (retrospective) is when data is gathered for a cohort that was formed sometime in the past. Exposures and outcomes have already occurred at the start of the study. You are studying the risk factor and seeing if you can associate a disease with it. Individuals are split by exposure.
Non-randomised controlled trial/experiment	15	These trials are run when it is not possible to incorporate randomisation into the design. There is an increased risk of biases being introduced into the research and this should be considered carefully when the analysis is reported.
Before and after the study	10	Before and After Study is a study in which within-subject observations are made before (pre) and after (post) the implementation of an intervention/exposure.
Case-control study	10	A case-control study is a study in which patients who already have a specific condition or outcome are compared with people who do not. Researchers look back in time (retrospective) to identify possible exposures. They often rely on medical records and patient recall for data collection.
Cross-sectional study	10	Cross-Sectional Study is the observation of a defined population at a single point in time or during a specific time interval to examine associations between the outcomes and exposure to interventions. Exposure and outcome are determined simultaneously. Often rely on data originally collected for other purposes.

Single case experimental study	5	These studies report an interrupted time series within one or a small cohort of participants.
Uncontrolled case study	0	The report of a single case or small cohort without control

Risk of Bias Assessment

To evaluate potential bias in this literature, a set of quality criteria was devised. These criteria drew inspiration from established risk-of-bias frameworks, particularly The Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011) and the Risk of Bias Assessment Tool for Nonrandomised Studies (Kim et al., 2013) but also reflect criteria specific to the topic of this review. The current framework scrutinises bias across six domains: selection bias, performance bias, detection bias, statistical bias, reporting bias, and generalisation. Definitions of these domains are detailed in the following table, along with criteria for categorising studies as Low, Unclear, or High risk.

Table 5

Sources of Bias

Domain	Definition	Low risk of Bias	Unclear risk of bias	High risk of bias
Selection Bias	Systematic differences between participants selected for a study and those not selected.	Selection bias and/or unusual participant characteristics are unlikely to have had a meaningful effect on the outcome	Is unclear but possible that selection bias and/or unusual participant characteristics will have had a meaningful effect on outcome.	Selection bias and/or unusual participant characteristics are highly likely to have had a meaningful effect on outcome
Performance Bias	Systematic differences in participants' motivation to complete the study, especially within or between groups.	Performance bias is unlikely to have had a meaningful effect on the outcome	Is unclear but possible that performance bias will have had a meaningful effect on the outcome.	Performance bias is highly likely to have had a meaningful effect on outcome

Detection Bias	Potential systematic differences in outcome assessment or measurements influenced by participants' or assessors' awareness of the treatment group assignments, especially when blinding is challenging due to the noticeable effects of psychedelic substances. Minimising detection bias involves implementing blinding procedures to ensure unbiased and objective outcome assessments.	Detection bias is unlikely to have had a meaningful effect on the outcome	Is unclear but possible that detection bias will have had a meaningful effect on the outcome.	Detection bias is highly likely to have had a meaningful effect on the outcome
Statistical Bias	Bias arising from inappropriate statistical treatment of data; use of appropriate statistical methods is essential. Considers factors such as: was a power analysis conducted? Was the study pre-registered and were all outcomes included in the analysis? Were outcomes corrected for multiple comparisons?	Statistical bias is unlikely to have had a meaningful effect on the outcome	Is unclear but possible that statistical bias will have had a meaningful effect on the outcome.	Statistical bias is highly likely to have had a meaningful effect on the outcome
Reporting Bias	Systematic differences between reported and unreported findings are often seen as outcome reporting bias. Completeness of outcome data and potential attrition should be considered.	Reporting bias is unlikely to have had a meaningful effect on the outcome	Is unclear but possible that reporting bias will have had a meaningful effect on the outcome.	Reporting bias is highly likely to have had a meaningful effect on the outcome
Generalisability	The extent to which research findings can be applied to settings beyond the original study, considering differences between study participants and the target population for the review.	Sufficient sample for generalisation and representative of the target population. A sample size justification, estimate and power analysis were provided. The sample size is adequate to detect an effect	Sufficient sample for generalisation but with some idiosyncratic features. A sample size justification, estimate and power analysis were not provided	Small sample with or without idiosyncratic features. The sample size is not adequate to detect an effect.

The application of the risk of bias criteria to the included studies is reported in Table 5. Each study was assessed for its risk level in each domain: Low, Unclear, or High Risk of Bias, with corresponding scores of two, one, and zero points, respectively. The overall quality index was determined by combining these risk scores and then adding the total to the overall study design score (refer to Table 4). This process results in a single value representing study

quality out of maximum of 37 points that is expressed as a percentage for the Overall Quality Index. Higher scores indicate higher quality study designs with lower bias risk.

Table 6

Table of Bias Rating from Studies

Trial	Study Duration	Selection Bias	Performance Bias	Detection Bias	Statistical Bias	Reporting Bias	Generalisability	Overall Quality Score	Overall Quality Index
Holze et al (2023)	Short	High risk	Low risk	High risk	Unclear risk	Low risk	High risk	30	81%
	Medium	High risk	Low risk	High risk	Unclear risk	Low risk	High risk	30	81%
	Short	High risk	Low risk	High risk	Unclear risk	Low risk	High risk	30	81%
	Medium	High risk	Low risk	High risk	Unclear risk	Low risk	High risk	30	81%
Sloshower et al (2023)	Short	High risk	High risk	High risk	Low risk	Low risk	High risk	19	51%
	Short	High risk	High risk	High risk	Low risk	Low risk	High risk	19	51%
Goodwin et al (2022)	Short	Low risk	Low risk	Low risk	High risk	Low risk	High risk	33	89%
	Short	Low risk	Low risk	Low risk	High risk	Low risk	High risk	33	89%
	Short	Low risk	Low risk	Low risk	High risk	Low risk	High risk	33	89%
	Short	Low risk	Low risk	Low risk	High risk	Low risk	High risk	33	89%
D'Souza et al (2022)	Short	High risk	High risk	High risk	High risk	High risk	High risk	15	41%
Carhartt-Harris et al (2021)	Short	High risk	Low risk	High risk	Low risk	Low risk	High risk	31	84%
	Short	High risk	Low risk	High risk	Low risk	Low risk	High risk	31	84%
Davis et al (2021)	Short	High risk	High risk	High risk	High risk	High risk	High risk	25	68%
	Short	High risk	High risk	High risk	Low risk	High risk	High risk	27	73%
	Medium	High risk	High risk	High risk	Low risk	High risk	High risk	27	73%
	Long	High risk	High risk	High risk	Low risk	High risk	High risk	27	73%
Von Rotz et al (2023)	Short	Low risk	Unclear risk	High risk	High risk	High risk	High risk	28	76%
	Short	Low risk	Unclear risk	High risk	High risk	High risk	High risk	28	76%
Ross et al (2016)	Short	High risk	Low risk	Unclear risk	High risk	Low risk	High risk	30	81%
	Short	High risk	Low risk	Unclear risk	High risk	Low risk	High risk	30	81%
	Long	High risk	Low risk	High risk	High risk	Low risk	High risk	29	78%
	Long	High risk	Low risk	High risk	High risk	Low risk	High risk	29	78%
Carhatt-Harris et al (2016)	Medium	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
	Short	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
	Medium	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
	Short	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
Griffiths et al (2016)	Short	High risk	Low risk	Low risk	High risk	High risk	High risk	29	78%
	Short	High risk	Low risk	Low risk	High risk	High risk	High risk	29	78%
Bogenschutz (2015)	Short	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
	Medium	High risk	High risk	High risk	High risk	Low risk	High risk	17	46%
Gasser et al (2014)	Short	High risk	Unclear risk	Low risk	High risk	High risk	High risk	28	76%
	Short	High risk	Unclear risk	Low risk	High risk	High risk	High risk	28	76%
Grob et al (2011)	Short	High risk	High risk	Unclear risk	High risk	Low risk	High risk	28	76%
	Medium	High risk	High risk	Unclear risk	High risk	Low risk	High risk	28	76%
	Short	High risk	High risk	Unclear risk	High risk	Low risk	High risk	28	76%
	Medium	High risk	High risk	Unclear risk	High risk	Low risk	High risk	28	76%
Osorio et al (2015)	Short	High risk	High risk	High risk	High risk	High risk	High risk	15	41%
Palhano-Fontes et al (2019)	Short	Low risk	High risk	High risk	Low risk	Low risk	High risk	31	84%

Note: In the study duration column S = Short, M = Medium, L = Long. Outcome column, Anx = Anxiety Outcome Data, Dep = Depression Outcome Data. Note: For Goodwin et al. (2022) trials there were two active doses (25mg and 10mg), which are referred to in the trial name, as they were calculated as separate trials.

Selection Bias

There was a high level of selection bias across the studies included in this meta-analysis with 33 of the 39 trial data points having a high risk of bias in this category. This was largely due to the majority of the studies having a self-selected sample included in their trials or they did not report the recruitment methods employed within their methodology. The trials that were low risk of bias, such as Goodwin et al. (2022), Von Rotz et al. (2023) and Palhano-Fontes et al. (2019) all employed a mixed recruitment strategy to gain participants from a range of different settings.

Performance Bias

There was also a high risk of bias for the majority of studies regarding performance bias. This was because some of the trials did not do any analysis to assess whether there were any systematic differences between the groups that could identify a source of bias (i.e. Von Rotz et al, 2023, Grob et al, 2011, Palhano-Fontes et al, 2019). Moreover, open-label trials or those that had no control were also considered to be part of the high risk of bias within this category.

Detection Bias

There was an overall high risk of detection bias within the studies. This was because many of the studies either used open-label or inactive placebo designs. Moreover, of the studies that used an active placebo, some (i.e. Grob et al, 2011 and Ross et al, 2016) used Niacin to induce a small physiological response (flushing) that could help to reduce the risk of detection, whereas others used low doses of psychedelic drugs. Only the trials that used low doses of psychedelic drugs as a placebo were considered to have a low risk of detection bias.

Statistical Bias

There was a high risk of statistical bias within the studies that were included in this meta-analysis. Many of the studies, despite using multiple outcome measures in their analysis did not conduct a Bonferroni correction to account for this (e.g. Holze et al., 2023, Davis et al., 2021, Ross et al., 2016; Griffiths et al., 2016). Moreover, some studies did not conduct power analyses (e.g. Griffiths et al, 2016) for sample size, and some did not conduct statistical analyses on all the outcomes that were measured in the trial (e.g. D'Souza et al., 2022).

Reporting Bias

Reporting bias within these trials was mixed, with the slight majority of trials having a low risk of bias in this category. This was because most of the studies reliably reported all p values, and effect sizes regardless of whether they were significant or not. Moreover, most of the trials reported all the outcomes that were registered on clinical trial registries before publication. However, this was not true for all trials; some did not report all outcomes that were preregistered (i.e. Davis et al, 2021, Griffiths et al, 2016); some did not register the trial before undertaking (i.e. Osorio et al, 2015); others did not properly address limitations of the study (i.e. Gasser et al, 2014) within the paper.

Generalisability

There was a risk of generalisability bias within all the studies within this meta-analysis due to the low participant numbers; the smallest study had 6, the largest had 312, and the mean was 29 participants per trial.

Summary

Overall, there was a high level of bias across most of the domains covered in this analysis. There were no studies that did not have at least some risk of bias in at least two of the areas, with some demonstrating risk of bias in all the areas. Resultantly, the findings of this

meta-analysis should be interpreted with caution. Nonetheless, the included trials are thought to be representative of the literature at this point.

RESULTS

For the analysis, the data will be divided into two separate meta-analytic foci based on outcomes related to symptoms of anxiety and depression in psychedelic-assisted psychotherapy. The analyses for each category will encompass evaluations against any mental health condition recorded in the clinical trial data; the effects of psychedelic-assisted psychotherapy on anxiety symptoms for individuals with any mental health condition (not limited to anxiety disorders) and on depression symptoms for individuals with any mental health condition (not limited to depression).

ANXIETY

Selection of the Meta-Analytic Model

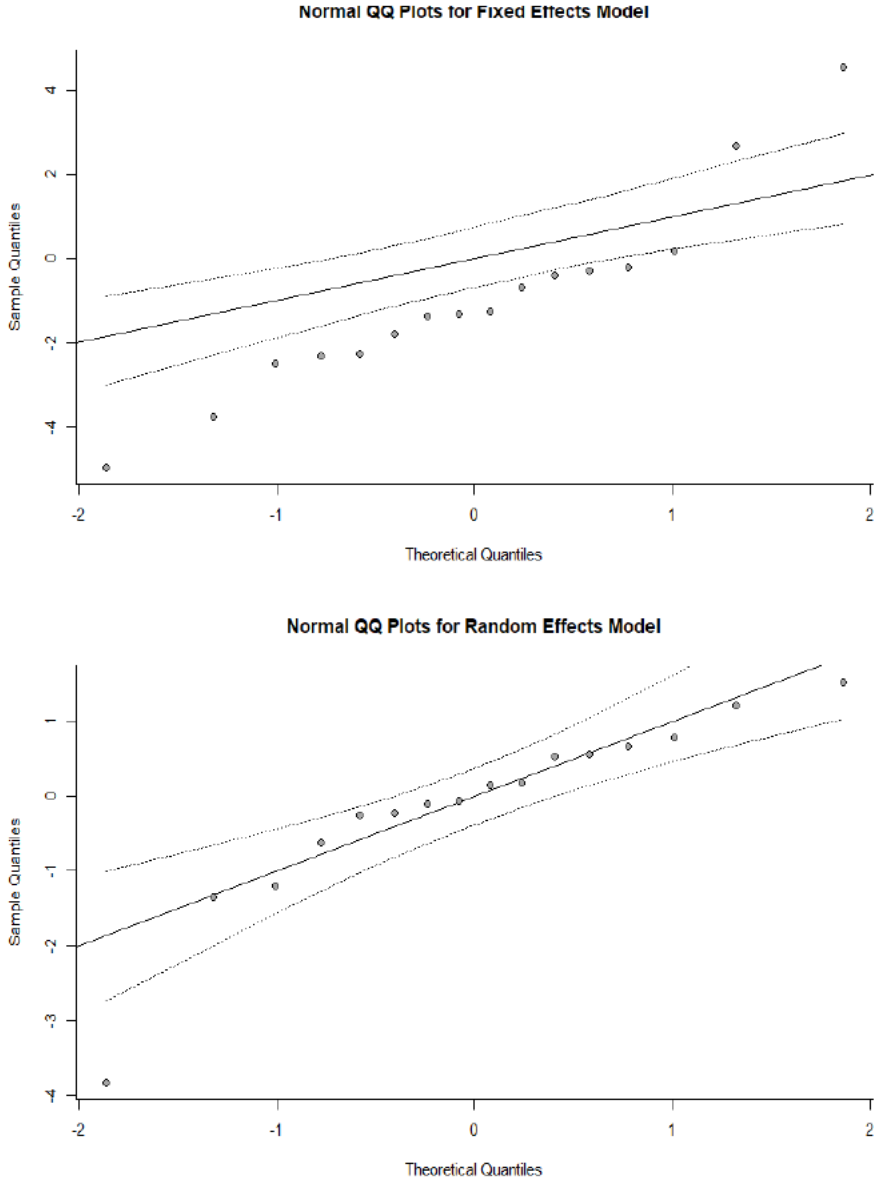
In deciding between the most appropriate meta-analytic model, the nature of the research and the potential impact of methodological variations were considered. While a fixed-effect model is typically appropriate when all included studies share a similar high-quality methodology, it falls short in accounting for the inherent variability often found in psychological studies through factors such as methodological differences, uncontrolled moderators, and inherent fluctuations in measured effects.

Given the diverse methodological strengths and weaknesses observed in the selected studies, assuming functional equivalence became untenable. Differences in participant characteristics, study methods, and intervention protocols could significantly affect the reported treatment effects. Relying solely on sample size to estimate the precision of measurement in such cases would be unjustified.

Unlike the fixed-effect model, the REM incorporates both between-study variation and sample size in weighting study-level effects. This feature makes REM better suited for meta-analyses dealing with studies exhibiting marked heterogeneity, which was particularly relevant to our research context. Therefore, we opted for the REM to ensure a more robust analysis of our data.

Figure 2

QQ Plot of the Distribution of Anxiety Scores Within the Primary Studies



The distribution of primary study effects is shown in Figure 2 using both the fixed effects model and the random effects model. The between-studies variance (τ^2) was calculated using the Restricted Maximum Likelihood estimator (REML), as this estimator is more robust to deviations from normality (Banks, Mao, & Walters, 1985).

As can be seen from Figure 2, there is clear evidence of non-normality in the distribution of study-level effects when using the fixed effects model, however, this non-normality is largely absent when using the random effects model. Therefore, this indicates that the use of the random effects model when between studies variation is calculated using the REML is an appropriate method for the estimation of the weighted average treatment effect.

The Omnibus Test for Anxiety Outcomes

The anxiety outcomes reported in the included studies are shown in Table 7. There was a total of 679 outcome data points from 15 clinical trial outcomes.

Participants were selected from a range of different groups. Some of the participant groups were people with a primary diagnosis of anxiety or depression, and three data points with anxiety or depression in addition to a diagnosis of life-threatening illnesses (Holze et al., 2023; Ross et al., 2016). There was a mix of different blinding methods included in the analysis as well as different control methods. Studies that had outcome measurements a different time points were grouped into short- (up to 2 months), medium- (2-6 months) or long-term (6-12 months) outcomes, based on the timepoint in the study that was closest to the meta-analysis categories.

Table 7

Anxiety Trials Within Meta-Analysis

Trial	*Year*	*Time*	*Drug*	*Blinding*	*Control*	*Participant Group*	*n*	*d*	*95% CI*
Carhartt-Harris et al	2016	Short	Psilocybin	Open Label	None	Depression	19	-2	-2.44; -0.42
Carhartt-Harris et al	2021	Short	Psilocybin	Double Blind	Escitalopram	Depression	30	-1.47	-2.27; -0.66
Carhartt-Harris et al	2016	Medium	Psilocybin	Open Label	None	Depression	19	-1.43	-3.1; -0.9
Davis et al	2021	Short	Psilocybin	Single Blind	Waiting List	Depression	24	-2.68	-3.7; -1.66
Gasser et al	2014	Short	LSD	Double Blind	Active Placebo	Anxiety	11	-1.19	-2.50; 0.12
Goodwin et al (10mg)	2022	Short	Psilocybin	Double Blind	Active Placebo	Depression	154	-0.10	-0.42; 0.22
Goodwin et al (25mg)	2022	Short	Psilocybin	Double Blind	Active Placebo	Depression	158	-0.37	-0.68; -0.05
Griffiths et al	2016	Short	Psilocybin	Double Blind	Active Placebo	Depression	51	-0.8	-1.33; -0.27
Grob et al	2011	Short	Psilocybin	Double Blind	Active Placebo	Anxiety	12	-2.76	-4.34; -1.18
Grob et al	2011	Medium	Psilocybin	Double Blind	Active Placebo	Anxiety	12	-1.61	-2.92; -0.31
Holze et al	2023	Short	LSD	Double Blind	Inactive Placebo	Anxiety/LTI	37	-1.60	-2.34; -0.86
Holze et al	2023	Medium	LS D	Double Blind	Inactive Placebo	Anxiety/LTI	37	-0.87	-1.54; -0.2
Ross et al	2016	Short	Psilocybin	Double Blind	Active Placebo	Depression/LTI	29	-1.24	-2.04; -0.44
Ross et al	2016	Long	Psilocybin	Double Blind	Active Placebo	Depression	15	-7.35	-9.95; -4.75
Sloshower et al	2023	Short	Psilocybin	Double Blind	Inactive Placebo	Depression	19	-0.88	-1.82; 0.07
Von Rotz et al	2023	Short	Psilocybin	Double Blind	Inactive Placebo	Depression	52	-0.69	-1.25; -0.13

Note: /LTI = Diagnosis associated with a Life-Threatening Illness. Short = up to 2 months, Medium = 2-6 months, Long-term = up to 6-12 months follow-up post-drug administration

Random effects models were calculated for short-, medium- and long-term outcomes using the generic inverse variance method. The omnibus estimates for each of the outcome timepoints are shown in Table 8.

Table 8

Omnibus Estimates for Anxiety Outcomes at Each Timepoint

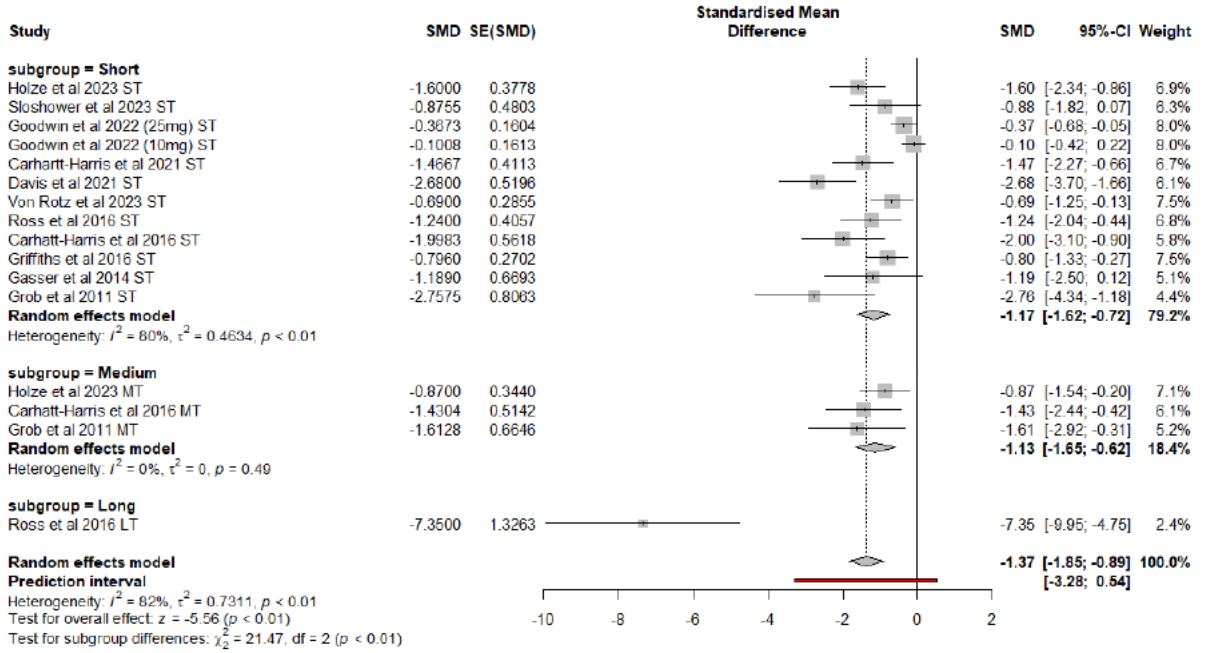
			95%-CI				
	k	**SMD**	**Lower**	**Upper**	**τ**	**τ²**	***I²***
Short	12	-1.17	-1.62	-0.71	0.68	0.46	80%
Medium	3	-1.13	-1.65	-0.62	0	0	0%
Long	1	7.35	-9.95	-4.75	-	-	-
Total	16	-1.37	-1.85	-0.89	0.86	0.73	82%

In the short term, there was a weighted large overall effect (SMD = -1.17, 95% CI -1.62 to -0.71) favouring the treatment condition. In the medium term, there were also weighted average effects favouring the treatment condition (SMD = -1.13, 95% CI -1.65 to -0.62). However, the long-term effect was calculated from a single study, resulting in an effect size (SMD = -7.35, 95%CI -9.95 to -4.75) disproportionately larger than the effects from the short- and medium-term outcomes.

The random effects model yielded a large overall effect size (SMD -1.37, 95% CI -1.85 to -0.89), indicating a substantial and statistically significant impact favouring the treatment condition across the three timeframes. With an SMD of 1.37, 91.5% of the treatment group will be above the mean of the control group, and 49.3% of the two groups will overlap. Additionally, there is an 83.4% chance that a person randomly selected from the treatment group will have a higher score than a person picked at random from the control group (probability of superiority). Moreover, to have one more favourable outcome in the "treatment" group compared to the "control" group, on average, two people would need to be treated. See Figure 3 below for a forest plot of these outcomes

Figure 3

Forest Plot of Outcomes by Timepoint



The analysis reveals significant heterogeneity among the studies (I^2 = 80%; τ^2 = 0.46, 95% CI: 0.38 to 4.6, p < .01) for short-term outcomes. However, there was lower and non-significant heterogeneity for medium-term outcomes (I^2=0%; τ^2< 0.01, p=0.49). The overall between-study variance remained large and statistically significant (I^2 = 82%; τ^2 = 0.73, 95%CI 0.38 to 4.6, p < .01).

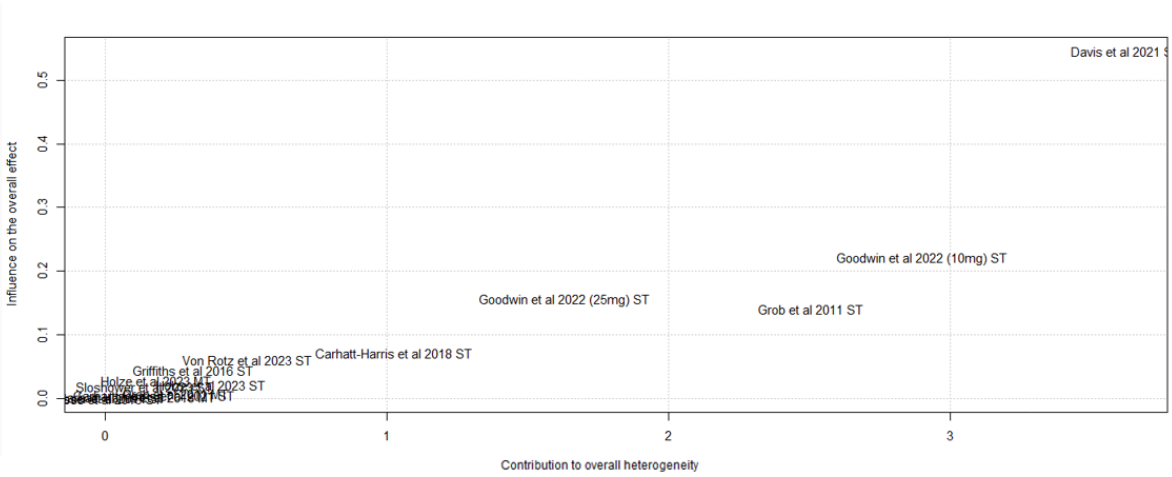
Heterogeneity could not be calculated for the long-term outcomes as this consisted of a single study reporting a disproportionately large effect size. Therefore, the focus of the subsequent analyses will be on the identification of the sources of heterogeneity between the anxiety outcomes in the short- and medium-term outcomes. This reduces the overall meta-analytic effect (SMD = -1.16, 95%CI -1.54 to -0.79) as well as the overall between studies heterogeneity (I^2=77%; τ^2< 0.36, p=0.01).

THE IMPACT OF INFLUENTIAL PRIMARY STUDIES

The impact of disproportionately influential studies was assessed using a "leave-one-out" analysis, in which the random effects model was calculated with each of the primary studies removed in turn and the change in weighted average effect size (i.e., influence) and the change in heterogeneity were recorded. The result of this "leave-one-out" analysis is presented on the Baujat plot (Baujat et al., 2002) in Figure 4.

Figure 4

Baujat Plot of Influential Studies for Anxiety Outcomes



As can be seen from Figure 4, the Davis et al. (2021) short-term trial showed high levels of influence and heterogeneity.

After reviewing Davis et al. (2021) several factors may be contributing towards its overall levels of influence and heterogeneity within this meta-analysis. Firstly, the study has the lowest overall quality index rating of all the trials included in the anxiety analysis; with

Davis et al.'s (2021) short-term data receiving a high risk of bias rating in all five domains. Some key factors contributing to this are that, although the trial was pre-registered, none of the anxiety measures reported in the publication were included in the trial registration. Moreover, despite reporting data for multiple outcome measures, there was no correction for multiple comparisons. Finally, the control group within this trial consisted of a waiting list group, rather than employing any placebo methodology. These reasons together may explain why, despite its relatively modest sample size for the group, this trial produces one of the greatest effect sizes within the sample and contributes towards a disproportionate influence and heterogeneity within the analysis.

When this trial was omitted from the analysis, the recalculated weighted average effect size decreased from SMD -1.16 to -1.04, representing a 10.3% shift (95%CI -1.38 to -0.7, $p<.01$). Omitting Davis et al. (2021) reduces τ^2 from 0.6 to 0.5, and overall I^2 variance from 77% to 72% suggesting a reduction in the estimated between-study variance and overall heterogeneity of the data. Moreover, when omitting Davis et al. (2021) the probability of superiority of the treatment condition over the control group was reduced by 6.5% (from 83.4% to 76.9%). The following analysis was then conducted after removing Davis et al. (2021) from the analysis.

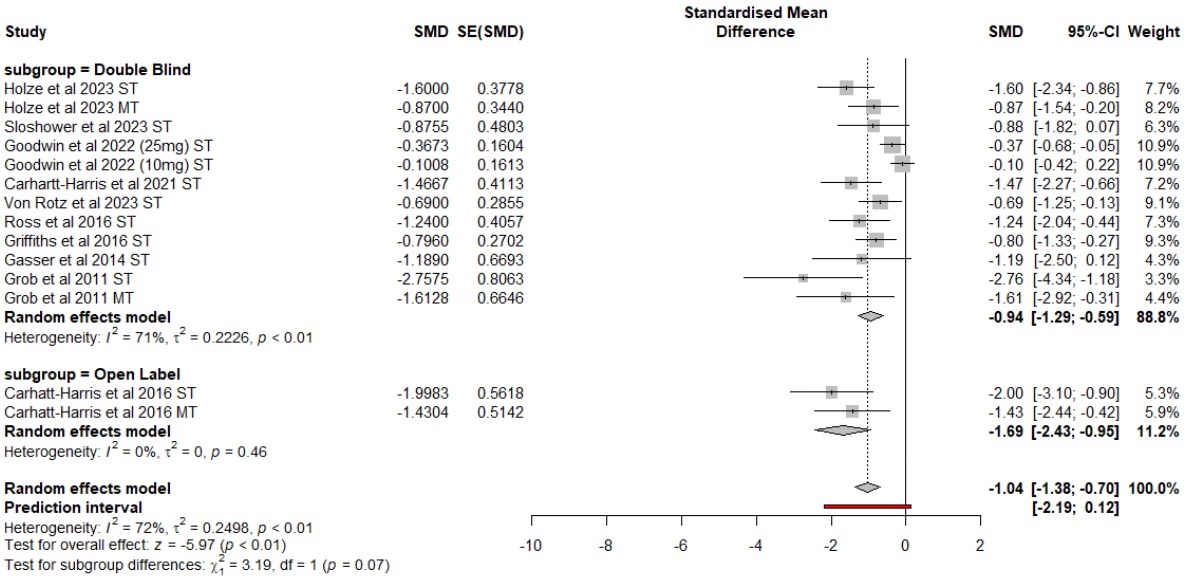
THE EFFECT OF RISK OF BIAS IN THE PRIMARY STUDIES

The Effect of Blinding

Figure 5 illustrates the difference in anxiety outcomes in which subgroup analysis within the random-effects model did not reveal statistically significant differences between trials based on blinding methods employed ($\chi^2=3.19$, $p<.07$)

Figure 5

Forest Plot of Outcomes by Blinding Type

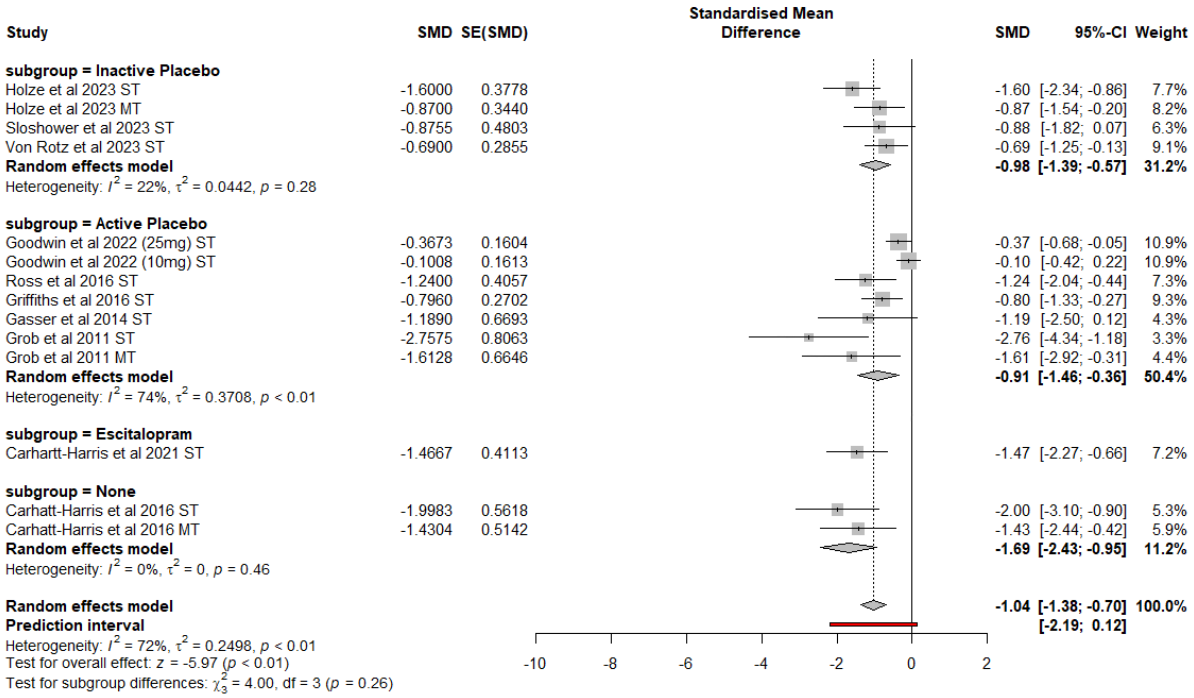


Effect of Control Type

A subgroup analysis was undertaken to examine whether the type of control affected the size of the reported treatment effect The test for subgroup differences within the random effects model did not yield a statistically significant difference in effect size based on the type of control group employed ($\chi^2 = 4$, p=0.26).

Figure 6

Forest Plot of Outcomes by Control Type



Notably, the Escitalopram group had only one data point, and the None (no control) group had two data points (from one trial). Moreover, when comparing solely the Active versus Inactive Placebo groups, no statistically significant differences were observed.

Effect of Sources of Bias

Selection Bias

A significant effect between groups based on the risk of selection bias was identified (χ^2 = 20.7, p < 0.01). The low-risk group demonstrated a smaller overall effect size (SMD -0.32, 95% CI -0.61 to -0.04), while the group with a high risk of selection bias exhibited a larger effect size (SMD -1.26, 95% CI -1.55 to -1.97).

Performance Bias

There was a small but significant effect of subgroup differences based on the risk of performance bias ($\chi^2 = 3.92$, $p = .05$), with a larger treatment effect in the any risk group (SMD = -1.55, 95%CI -2.11 to -0.99) versus the low-risk group (SMD = -0.84, 95% CI -1.27 to -0.41).

Detection Bias

There also appears to be a significant impact on effect size based on the risk of detection bias within the studies. This category is similar to control type as most of the studies within the active placebo would also be considered to be low risk of detection bias. However, some of the studies that were classified as 'Active Placebo' used low doses of psychedelic drugs (i.e. LSD or Psilocybin) whereas others used substances such as Niacin to induce physiological effects (i.e. flushing). Within this category of "detection bias" only studies that used low doses of psychedelic drugs as placebo were considered to be low risk of detection bias.

A significant effect between groups based on the risk of detection bias was found ($\chi^2 = 12.55$, $p < 0.01$). The low-risk group presented a smaller overall effect size (SMD -0.43, 95% CI -0.79 to -0.07), whereas the trials with a risk of detection bias showed a larger effect size (SMD -1.27, 95% CI -1.59 to -0.95), with non-overlapping confidence intervals.

Statistical Bias, Reporting Bias and Generalisability

There were no significant differences in outcomes between groups based on statistical bias ($\chi^2 = 0.26$, $p = 0.61$), reporting bias ($\chi^2 = 1.41$, $p = 0.22$), generalisability ($\chi^2 = 0$) or Performance Bias ($\chi^2 = 2.10$, $p = 0.15$).

Overall Effect of Methodological of Bias

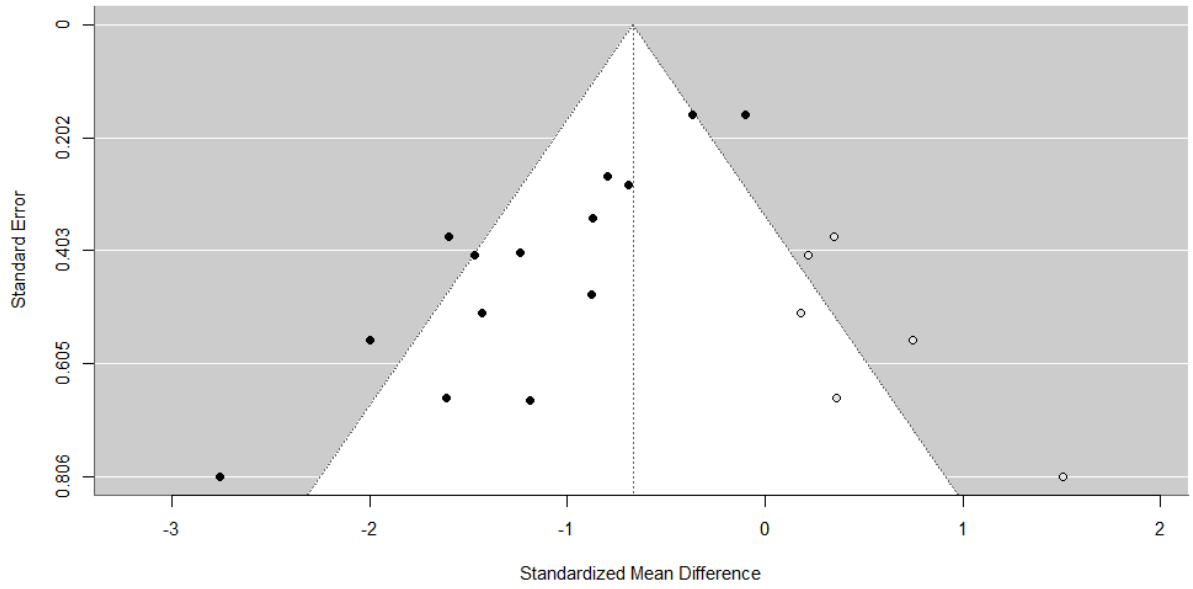
Overall, significant effects for the presence of selection bias, performance bias, and detection bias were observed. For each type of bias, higher levels of risk were associated with larger reported treatment effects. This suggests that the presence of risk of selection-performance- and detection bias serves to inflate the reported treatment outcome and to overestimate the weighted average treatment effect. The overall effect of Risk of Bias within the data was large and statistically significant ($\chi^2 = 30.31$, $p = 0.01$)

The Impact of Publication and Small Study Biases

Publication bias arises from the inclination to publish studies with statistically significant results while being hesitant to publish those with non-significant findings (Duval & Tweedie, 2000). Small study bias occurs when studies with smaller sample sizes exhibit greater variability in measuring treatment efficacy (Schwab et al., 2021). These biases become evident in a funnel plot, which illustrates the study's SMD (indicating its importance in the synthesis) and gauges the study's deviation from the meta-analytic average (highlighting its discrepancy within the literature). In the absence of publication bias, studies with smaller sample sizes and greater variability scatter widely at the plot's bottom, while larger studies cluster closer to the overall meta-analytic effect at the top, creating a symmetrical funnel shape. However, an absence of studies in the region associated with small sample sizes and non-significant results suggests potential publication bias, leading to an overestimation of the true effect.

Figure 7

Funnel Plot of Anxiety Outcomes



Note. Filled circles represent observed data from trials, Empty circles represent imputed data

As depicted in Figure 7, clear evidence of publication bias emerges in the distribution of anxiety outcomes, revealing an absence of small studies in the graph section associated with null findings. To assess the impact of publication bias, a trim and fill procedure (Duval & Tweedie, 2000) was employed with the assumption that publication bias would result in an asymmetrical funnel plot. This process addresses publication bias by iteratively trimming extreme effect sizes and imputing potentially missing studies to the opposite side of the distribution. Initially, studies with large effect sizes are removed to mitigate the influence of publication bias. Then, the procedure estimates the number of potentially missing studies with non-significant or negative results. Mirror-image 'filler' studies are imputed to balance the distribution symmetrically around the mean effect size.

In the funnel plot, observed studies are shown as dark circles, with an effect size estimate of -1.04 (95% CI -1.4 to -0.69). Imputing studies, represented by empty circles, yielded an adjusted estimate of -0.67 (95% CI -1.05, -0.3), indicating a 35.4% decrease in treatment efficacy compared to the original analysis. This adjusted estimate suggests a 68.2% likelihood of a lower depression score in the treatment group than the control group, with an average of 4.3 treated individuals needed for one additional favourable outcome compared to the control group.

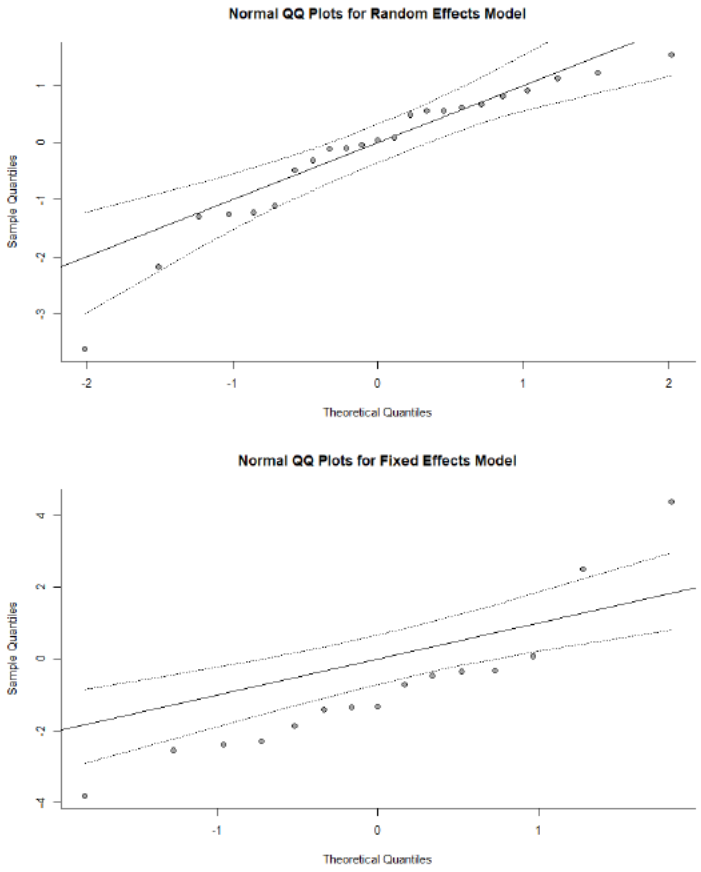
Accordingly, it would appear that publication bias may have had an impact on the estimate of treatment efficacy, but the revised estimate remains statistically significant and of moderate-to-large size.

DEPRESSION

SELECTION OF THE META-ANALYTIC MODEL

Figure 8

QQ Plot of the Distribution of Anxiety Scores Within the Primary Studies



The distribution of primary study effects is shown in Figure 8 using both the fixed effects model and the random effects model. The between-studies variance (τ^2) was again calculated using the REML estimator.

The depression outcomes described in the primary studies are reported in Table 9. There is a total of 825 outcome data points from 23 clinical trial outcomes. Participants were selected from a range of different groups. Some were people with diagnoses of anxiety or

depression, and some with additional diagnoses of life-threatening illnesses. There was a mix of different blinding methods included in the analysis as well as different control methods. Studies that had outcome measurements a different time points were grouped into short- (up to 2 months), medium- (2-6 months) or long-term (6-12 months) outcomes, based on the time point in the study that was closest to the meta-analysis categories

Table 9

Table of Depression Trials and Outcomes Within Meta-Analysis

Trial	*Year*	*Time*	*Drug*	*Blinding*	*Control*	*Participant Group*	*n*	*d*	*95%CI*
Bogenschutz	2015	Short	Psilocybin	Open Label	None	Alcohol Dependence	19	-0.61	0.31; -1.53
Bogenschutz	2015	Medium	Psilocybin	Open Label	None	Alcohol Dependence	19	-0.29	0.61; -1.20
Carhartt-Harris et al	2021	Short	Psilocybin	Double Blind	SSRI	Depression	30	-1.5	-0.75; -2.25
Carhartt-Harris et al	2016	Short	Psilocybin	Open Label	None	Depression	19	-2.33	-1.21; -3.46
Carhartt-Harris et al	2016	Medium	Psilocybin	Open Label	None	Depression	19	-1.35	-0.35;-2.35
Davis et al	2021	Short	Psilocybin	Single Blind	Waiting List	Depression	24	-2.35	-1.31;-3.39
Davis et al	2021	Medium	Psilocybin	Single Blind	Waiting List	Depression	24	-2.31	-1.28;-3.34
Davis et al	2021	Long	Psilocybin	Single Blind	Waiting List	Depression	24	-2.19	-1.18;-3.20
D'Souza et al	2022	Short	DMT	Open Label	None	Depression	6	-0.68	0.96;-2.33
Gasser et al	2014	Short	LSD	Double Blind	Active Placebo	Depression	11	-0.41	0.92;-1.75
Goodwin et al (25mg)	2022	Short	Psilocybin	Double Blind	Active Placebo	Depression	158	-0.52	-0.22;-0.81
Goodwin et al (10mg)	2022	Short	Psilocybin	Double Blind	Active Placebo	Depression	154	-0.24	0.05;-0.54
Griffiths et al	2016	Short	Psilocybin	Double Blind	Active Placebo	Depression	51	-0.79	-0.27;-1.32
Grob et al	2011	Short	Psilocybin	Double Blind	Active Placebo	Depression	12	-1.37	-0.12;-2.63
Grob et al	2011	Medium	Psilocybin	Double Blind	Active Placebo	Depression	12	-1.71	-0.39;-3.04
Holze et al	2023	Short	LSD	Double Blind	Inactive Placebo	Anxiety/LTI	37	-1.3	-0.59;-2.01
Holze et al	2023	Medium	LSD	Double Blind	Inactive Placebo	Anxiety/LTI	37	-0.91	-0.23;-1.59
Osorio et al	2015	Short	Ayahuasca	Open Label	Active Placebo	Depression	6	-4.80	-1.88;-7.74
Palhano-Fontes et al	2019	Short	Ayahuasca	Double Blind	Inactive Placebo	Depression	29	-1.23	-0.50;-1.97
Ross et al	2016	Short	Psilocybin	Double Blind	Active Placebo	Depression/LTI	29	-1.2	-0.41;-1.99
Ross et al	2016	Long	Psilocybin	Double Blind	Active Placebo	Depression	15	-5.87	-3.72;-8.02

Sloshower et al	(2023)	Short	Psilocybin	Double Blind	Inactive Placebo	Depression	38	-0.83	0.03;-1.69
Von Rotz et al	(2023)	Short	Psilocybin	Double Blind	Inactive Placebo	Depression	52	-0.83	-0.26;-1.40

Note. LTI = Diagnosis associated with a Life-Threatening Illness. Short = up to 2 months, Medium = up to 2-6 months, Long-term = 6-12 months follow-up post-drug administration

A random effects model was calculated using the generic inverse variance method. The omnibus estimates for each of the outcome timepoints are shown in Table 10.

Table 10

Omnibus Estimates for Depression Outcomes at Each Timepoint

			95%-CI				
	k	SMD	Lower	Upper	τ	τ^2	I^2
Short	16	-1.05	-1.36	-0.73	0.47	0.22	69%
Medium	5	-1.25	-1.93	-0.58	0.59	0.35	58%
Long	2	-3.9	-7.5	-0.3	2.46	6.05	89%
Total	23	-1.27	-1.61	-0.93	0.67	0.45	76%

Both the short-term (SMD = -1.05, 95% CI -1.36 to -0.73, $p < .01$) and medium-term analyses showcased a significant effect (SMD = -1.25, 95% CI -1.93 to -0.58, $p < .05$) with low levels of heterogeneity (short term $I^2 = 69\%$, $\tau^2=0.22$, $p < .01$; medium-term $I^2 = 58\%$, τ^2 0.22, $p=.05$). The long-term effects also demonstrated significant effects (SMD = -3.90, 95% CI -7.5 to -0.3, $p < .01$); however, this is derived from limited data (k=2) with substantial and statistically significant heterogeneity ($I^2 = 89\%$; $\tau^2 = 6.05$, $p < .01$) between the studies.

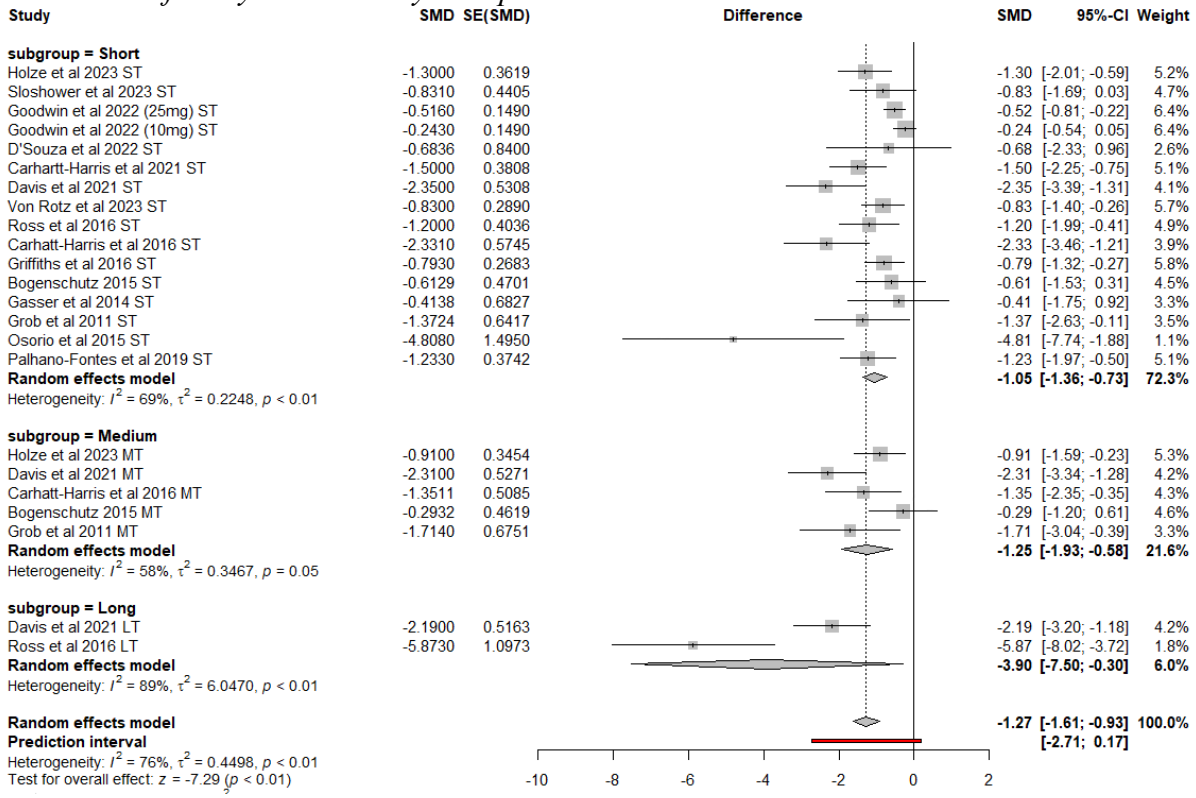
The overall omnibus estimates for the depression outcomes revealed a significant large effect size (SMD = -1.27, 95% CI -1.61 to -0.93, $p < .01$). With an effect size of this magnitude, the treatment group is expected to surpass the control group for 89.8% of its members, with a 52.5% overlap between the two groups. Additionally, there is an 81.5% chance that a randomly selected person from the treatment group will have a lower depression score than a randomly

selected person from the control group (probability of superiority). On average, treating 2.1 individuals is required to observe one more favourable outcome in the treatment group compared to the control group.

The overall level of heterogeneity within the analysis was moderate ($I^2 = 76\%$; $\tau^2 = 0.45$, $p < .01$), with the largest source of heterogeneity coming from the long-term treatment group. The overall proportion of total variability in effect estimates that is due to heterogeneity in this analysis is high ($I^2 = 76\%$, 95%CI 63.6% to 83.7%).

Table 11

Forest Plot of Study Outcomes by Timepoint



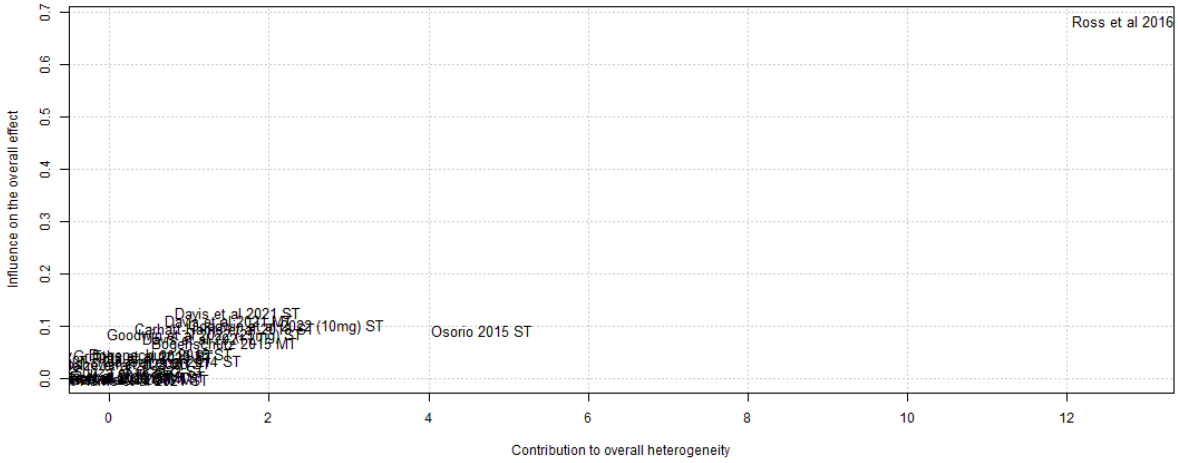
THE IMPACT OF INFLUENTIAL PRIMARY STUDIES

In the assessment of individual study impact on the meta-analysis, Ross et al. (2016) long-term outcome data emerged as a significant contributor to both influence and heterogeneity (see Figure 9). The exclusion of Ross et al. (2016) from the analysis yielded noticeable effects on the overall meta-analysis outcomes. Specifically, the recalculated weighted average effect size (SMD) decreased from -1.27 to -1.15, indicating a substantial 9.4% shift (95% CI: -1.43 to -0.86, $p < 0.01$). Furthermore, the removal of Ross et al. (2016) led to a decrease in between-study variance, with τ^2 decreasing from 0.45 to 0.27, and a corresponding reduction in the proportion of the overall meta-analytic effect attributed to heterogeneity, as I^2 decreased from 75.6% to 69.6%. These findings underscore the considerable impact of the Ross et al. (2016) long-term data on observed heterogeneity, highlighting its influential role in shaping the overall effect size estimate.

The Ross et al. (2016) trial is notable from other studies in that it is the only study that is gathering long-term follow-up data on participants (6-12 months) for this outcome. It is also a study with a relatively small sample size (n=15) though not the smallest sample size within the review. Moreover, within the Ross et al. (2016) trial, there was a large (51%) attrition rate between the short-term and long-term follow-up data within the study. As such the following analysis will be completed with the Ross et al. (2016) long-term data omitted.

Figure 9

Baujat Plot of Influential Studies for Depression Outcomes



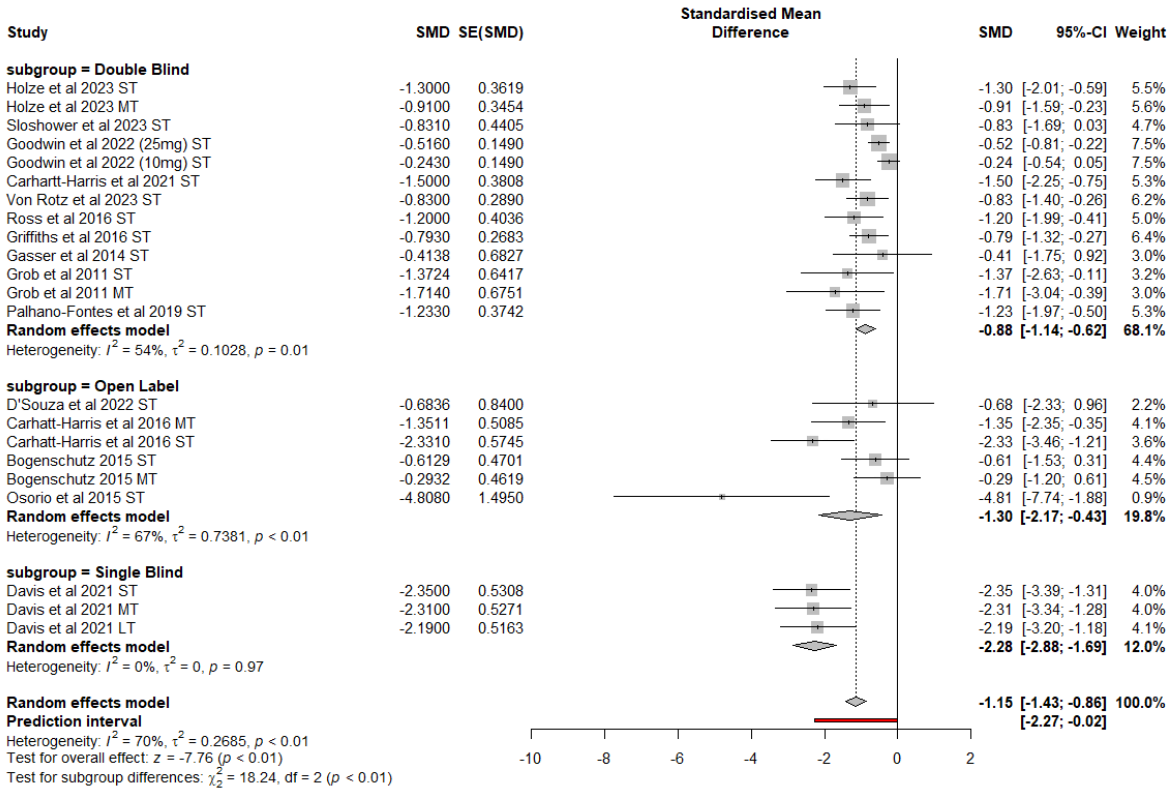
THE EFFECT OF RISK OF BIAS IN THE PRIMARY STUDIES

Blinding

Figure 10 illustrates the difference in depression outcomes between blind, double-blind and open-label trials. Subgroup analysis within the random-effects model revealed distinct and statistically significant differences between trials based on the blinding methods employed. Specifically, the weighted average effect size (SMD) exhibited significant variation across different blinding conditions: Double Blind (SMD -0.88, 95% CI -0.14 to -0.62), Open Label (SMD -1.3, 95% CI -2.17 to -0.43), and Single Blind (SMD-2.28, 95% CI -2.88 to -1.69). The overall prediction interval for the random-effects model indicated a statistically significant difference in effect sizes by subgroup (χ^2=18.24, p<.01), highlighting substantial heterogeneity in treatment effects associated with varying blinding methodologies in the included studies, with double-blind studies exhibiting a smaller overall effect than for open-label or single-blind studies.

Figure 10

Forest Plot of Outcomes by Blinding Method



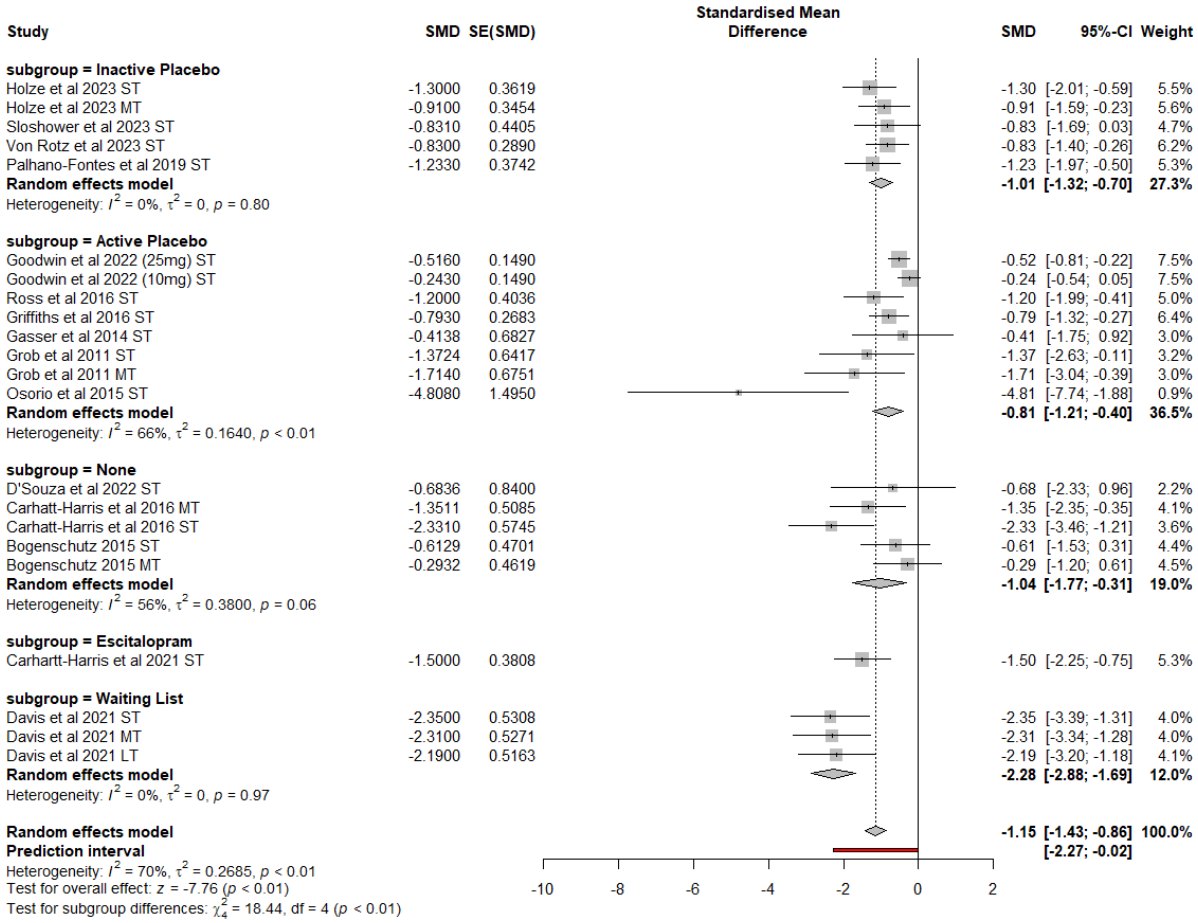
Effect of Control Type

A subgroup analysis was conducted, revealing notable variations among trials based on different control groups within the data. The differences in effect sizes, presented in ascending order from smallest to largest, show distinct impacts within by subgroup: Active Placebo (SMD -0.81; 95%% CI -1.21 to -0.4), Inactive Placebo (SMD -1.01, 95% CI -1.32 to -0.7), None (SMD -1.04, 95% CI -1.77 to -0.31), Escitalopram (SMD -1.5, 95% CI -2.25 to -0.75), and

Waiting List (SMD -2.28, 95% CI -2.88 to -1.69). Significantly, the test for subgroup differences within the random-effects model yielded a highly significant result (X^2 = 18.44, df = 4, p < 0.01), emphasising the existence of statistically significant differences in effect sizes among the subgroups. Notably, the trials utilising waiting list controls yielded a statistically significant larger effect than the meta-analytic average with non-overlapping 95% confidence intervals.

Figure 11

Forest Plot of Outcomes by Placebo Type



EFFECT OF SOURCES OF BIAS

Detection Bias

The low-risk group had a significantly reduced effect size (SMD 0.46, 95% CI -0.71 to -0.20) compared to the any-risk (high or unclear risk) group (SMD 1.33, 95% CI -1.62 to -1.04) with non-overlapping confidence intervals. The overall effect by group is depicted by the χ^2 value of 19.69 ($p<.01$).

Selection Bias

There was a selection bias effect within the meta-analysis, with studies at a low risk of selection bias demonstrating a smaller overall effect size (SMD -0.6, 95% CI -0.97 to -0.24) compared to studies that had a risk of selection bias (SMD -1.31, 95% CI -1.62 to -1.) with non-overlapping confidence intervals. This conferred a statistically significant difference between groups based on this variable ($\chi^2 = 8.2$ df = 1, $p<.01$).

Statistical Bias

There was a paradoxical effect when analysing for statistical bias with the Low-Risk group finding an overall larger effect (SMD -1.66, 95%CI -2.16 to 1.17) than the any risk group (SMD-0.89, 95%CI -1.17 to -0.62). This revealed an overall significant effect between groups ($\chi^2 = 7.04$, df = 1, $p <.01$).

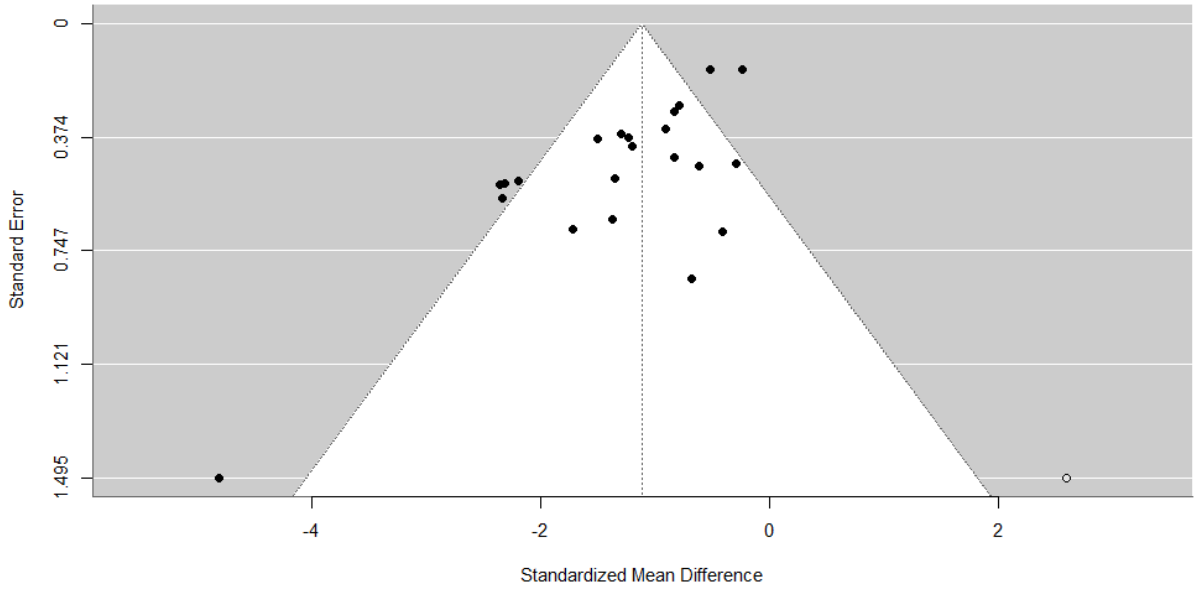
Reporting Bias, Generalisability and Performance Bias

There were no significant differences between groups based on reporting bias ($\chi^2 = 2.03$, $p = 0.15$), generalisability bias ($\chi^2 = 0$) or performance bias ($\chi^2 = 0.3.89$, $p = 0.05$).

Impact of Publication and Small Study Bias

Figure 12

Funnel Plot of Depression Outcomes



Note. Filled circles represent observed data from trials, Empty circles represent imputed data

The omnibus estimate of the effect size stands at -1.27 (95% CI -1.6 to -0.93). Imputed studies are denoted by empty circles, and the imputed estimate is -1.12 (95% CI -1.41, -0.78). The adjusted point estimate reflects an 11% decrease in treatment efficacy compared to the original omnibus analysis. Accordingly, it would appear that publication bias may have had an impact on the estimate of treatment efficacy, but the revised estimate remains statistically significant and of large effect size. This adjusted estimate suggests a 78.62% likelihood of a lower depression score in the treatment group than the control group, with an average of 2.44 treated individuals needed for one additional favourable outcome compared to the control group.

DISCUSSION

This meta-analysis aimed to evaluate the literature of clinical trial studies that have investigated and assessed the efficacy of treating symptoms of depression or anxiety in people with diagnosable mental health conditions. Overall, 15 unique clinical trials were included in the analysis, which included any follow-up data published in subsequent reports. This analysis looked at clinical trials that were open-label, single-blind, double-blind and uncontrolled.

SUMMARY OF MAIN RESULTS

Anxiety

Regarding studies assessing anxiety outcomes, the findings of this meta-analysis revealed a significant overall treatment effect favouring the treatment condition across all timeframes. However, caution is necessary due to the disproportionately large effect size observed in the long term, primarily influenced by data from a single study. Utilising a random effects model, a substantial and statistically significant treatment impact across all timeframes was confirmed (SMD -1.37), with notable heterogeneity among short-term outcomes ($I^2 = 80\%$) and lower heterogeneity in the medium-term ($I^2 = 0\%$).

Upon excluding the only long-term study from the analysis, along with the short-term data from Davis et al. (2021) due to its significant contribution to heterogeneity and influence over the meta-analytic effect, attributed to methodological biases within the study, the overall meta-analytic effect reduced to SMD -1.04. Furthermore, there were additional reductions in the overall effect sizes of studies when controlling for methodological variation. For instance, when considering only double-blind trial data, the effect sizes decreased further to SMD -0.94.

Similarly, when focusing on studies employing an active placebo, the effect size was also reduced to SMD -0.91.

Notably, subgroup analysis also demonstrated reductions in the overall effect when examining only studies with low risk in selection bias (SMD = -0.32), performance bias (SMD = -0.84), and detection bias (SMD = -0.43). Similarly, the analysis identified the presence of publication bias, which may have influenced the estimated treatment efficacy, although the revised estimate following adjustment for publication bias remained statistically significant and of moderate-to-large size (SMD = -0.67)

Overall, this suggests that the likelihood of superiority of the treatment condition for anxiety symptomology ranges between 83% (number needed to treat 2) and 59% (number needed to treat 9.9) based on the highest and lowest effect size estimates, respectively.

Depression

This meta-analysis revealed significant treatment effects across all periods but with notable heterogeneity in long-term outcomes (I^2 = 89%). The overall effect size was substantial and statistically significant (SMD = -1.27), but excluding influential studies, like Ross et al. (2016) from the long-term data, reduced effect size (SMD = -1.15) and heterogeneity (I^2 = 69.6%). Further analyses showed decreased effect sizes when considering only double-blind trials (SMD -0.88) or studies with an active placebo (SMD -0.81). Subgroup analyses based on bias risk indicated reductions in overall effect sizes for studies with low risks of detection bias (SMD = -0.46), and selection bias (SMD = -0.6). The presence of publication bias was indicated, but after adjusting for it, the revised estimate remained statistically significant and of large size (SMD = -1.12). Overall, the findings suggest moderate to high effect sizes for psychedelic therapies on depression symptoms, with varying likelihoods of treatment condition

superiority ranging between 82% (number needed to treat 2.15) and 62.8% (number needed to treat 6.61) based on the range of effect size estimates above.

QUALITY OF EVIDENCE

The overall quality of the evidence in this meta-analysis was good, with most of the trials receiving Overall Quality Index scores above 75%. The majority (66.7%) of the studies employed a double-blind methodology with a placebo control (40% active placebo, 26.7% inactive). However, several studies carried a high risk of bias, with none of the trials included having a low risk of bias in all areas. Particularly, the studies exhibited issues with selection bias, as most participants were self-selected or recruited from specific cohorts, such as patients from a single clinic with life-threatening illnesses.

This meta-analysis also provided more evidence for the need for robust blinding techniques in the trial designs. For example, when comparing groups with a low- (i.e. using low doses of psychedelics as active placebo) versus high-risk of detection bias there was a statistically significant difference in effect sizes for both the anxiety and depression trials.

Other common sources of bias arose from studies omitting power analyses or failing to conduct statistical adjustments for multiple comparisons in their outcome data. Furthermore, while most studies were preregistered, some trials did not report all registered outcome data, potentially leading to a bias towards reporting significant findings while omitting null results.

Overall, the sample sizes in the included trials were low, with the smallest studies (D'Souza et al., 2022; Osorio et al., 2015) having just 6 participants each, and the mean number of participants per trial being 29. Goodwin et al. (2022) had the largest number of participants in any single study (n=312), which is relatively large within the field of clinical psychology; however, it is still modest compared to psychiatric clinical trials more broadly (Jakobsen et al.,

2017). Moreover, the total number of participants (*n*=656) across all clinical trials within this meta-analysis still represents a generally low figure for trials related to drugs before gaining approval for clinical practice (U.S. Food and Drug Administration, 2018).

Another important factor to note is the overall lack of evidence for the longer-term impact of psychedelic therapies on mental health. Within this analysis, only one study was found reporting long-term data for anxiety outcomes, and two studies reporting long-term data for depression outcomes.

LIMITATIONS

This meta-analysis did not examine adverse event data from the clinical trials. Therefore, no conclusions can be drawn regarding potential side effects or negative outcomes associated with psychedelic drugs, which is crucial for conducting a cost-benefit analysis of their therapeutic use.

Some studies have indicated that psychedelic drugs may have negative psychiatric outcomes for individuals with specific risk factors, such as diagnosed personality disorders (Marrocu et al., 2024) or genetic predispositions to mania or schizophrenia (Simonsson et al., 2024). However, a recent review by Romeo et al. (2024) found that serious adverse events are rare in controlled settings. Across 1,072 drug administrations in psychedelic trials, they found 13 instances of participants experiencing temporary psychotic symptoms during the acute phase of the drug's effect. In the post-acute period (days to weeks after administration) five instances of participants experiencing suicidal thoughts were also noted, compared to one in a control group, along with four instances of self-harm versus none in control groups. They also found that participants receiving high doses of psychedelics had a greater risk of nausea, dizziness,

and anxiety during the acute phase, and an increased risk of headaches and loss of appetite in the post-acute phase compared to placebo controls (Romeo et al., 2024).

Furthermore, it is acknowledged that since this meta-analysis investigated the effects of psychedelic treatments on symptoms of anxiety or depression across various client groups with mental health conditions, the results may differ from analyses focusing solely on anxiety symptoms in individuals with anxiety or depressive symptoms in those with depression. However, this approach was deemed the most comprehensive strategy for capturing clinically relevant data on psychedelic trials.

Moreover, it is recognised that strategic decisions within the meta-analytic method may have influenced the findings. For instance, considering short-, medium-, and long-term data for clinical trials as independent entities could yield different results compared to combining all effect sizes within each trial across all timeframes to generate a single SMD for each trial.

Another limitation is the absence of a systematic assessment of COIs among the included studies. Previous research has indicated that COIs might represent an important source of bias in the psychedelic literature (van Elk & Fried, 2023). While Table 12 provides the sources for all data included in this meta-analysis, with associated COIs that are declared within those publications, no statistical analysis was conducted to evaluate outcome differences based on those COIs within the data. However, most of the trials included have clear COIs, potentially introducing an unaccounted-for bias. This aspect was not systematically assessed due to the near ubiquity of COIs among the studies. It should be noted that although three studies were categorised as 'unknown' regarding COIs, this does not necessarily indicate their absence; rather, that they were not declared or apparent within the publication itself.

Table 12

Summary of Data Sources for Meta-Analysis and COIs

Trial Name	*Drug*	*Conflict of Interest*
Holze et al (2023)	LSD	Authors are consultants for pharmaceutical companies Mind Medicin, Inc, Compass Pathways, and Reconnect Foundation.
Sloshower et al (2023)	Psilocybin	Funding and design by Heffter Research Institute
Goodwin et al (2022)	Psilocybin	Supported by Compass Pathways Ltd that manufactures COMP360 (psilocybin)
D'Souza et al (2022)	DMT	Unknown
Carhartt-Harris et al (2021)	Psilocybin	Authors receive consulting fees from pharmaceutical companies that synthesise psychedelics: Compass Pathways Pathway and SmallPharma
Davis et al (2021)	Psilocybin	Authors are board members and received grant funding from Heffter Research Institute, Beckley Psychedelics Ltd, Entheogen Biomedical Corp, Field Trip Psychedelics Inc., Mind Medicine Inc., and Otsuka Pharmaceutical Development & Commercialization Inc
Von Rotz et al (2023)	Psilocybin	Author is an employee of Reconnect Labs AG pharmaceutical company that develops psychedelic drugs.
Ross et al (2016)	Psilocybin	Funding by the Heffter Research Institute and the RiverStyx
Carhart-Harris et al (2016)	Psilocybin	Funding from Servier and Lundbeck pharmaceutical companies. Affiliated with large psychedelic research centres i.e. Psychedelic Research Group, Imperial College London.
Griffiths et al (2016)	Psilocybin	Funded by Heffter Research Institute and the Riverstyx Foundation. Author on Board of Directors for Heffter Research Institute
Bogenschutz (2015)	Psilocybin	Grants from the Lundbeck Foundation and the Heffter Research Institute
Gasser et al (2014)	LSD	Funded in part by Multidisciplinary Association for Psychedelic Studies
Grob et al (2011)	Psilocybin	Funding from Heffter Research Institute
Osorio et al (2015)	Ayahuasca	Unknown
Palhano-Fontes et al (2019)	Ayahuasca	Unknown

Comparison to Previous Meta-Analyses

The overall findings from this meta-analysis were consistent with those of other meta-analyses, showing large effect sizes for the efficacy of psychedelic therapies on mental health outcomes. However, in contrast to the previous meta-analyses reported, this study was able to conduct subgroup analyses based on methodological variation between studies, which had significant effects on treatment efficacy. In these cases, the treatment outcome, while maintaining its efficacy, was attenuated at times into the moderate effect size range. Based on

this, it may be that as more large and robust clinical trials emerge within the literature, the overall effect size for psychedelic therapies may trend towards more moderate values. This highlights the need for clear messaging about the effectiveness of these therapies and, as has been documented elsewhere (see van Elk & Fried, 2023), a more cautious approach to reporting these interventions.

Implications for Future Research

The findings of this meta-analysis highlight several areas that should guide future research in the field. Firstly, robust blinding techniques and careful selection of placebos may be important for the validity of findings for randomised control trials in psychedelic research. In this regard, active placebos using small doses of psychoactive drugs may be the most efficacious methods for blinding participants in such a way that blinding is maintained.

Furthermore, larger and more diverse participant samples are needed to enhance the generalisability of findings across demographic groups and mental health conditions, with the majority of the studies published thus far using small sample sizes. To understand the long-term effects of psychedelic therapies, longer-term follow up studies should be implemented tracking the outcomes for participants for longer than 6 months post administration.

CONCLUSION

This meta-analysis found overall positive effects of psychedelic-assisted therapies on symptoms of depression and anxiety among people with mental health conditions. This was the largest meta-analysis to date evaluating the efficacy of psychedelic therapies as a mental health treatment. Treatment effect sizes were in the moderate to large range for both anxiety and

depression symptoms. However, the attenuation of this effect based on study methodology highlights the need for larger and more robust clinical trials going forward.

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PRESS RELEASE

GROUNDBREAKING META-ANALYSIS REVEALS SIGNIFICANT BENEFITS OF PSYCHEDELIC THERAPIES FOR DEPRESSION AND ANXIETY

A groundbreaking meta-analysis of clinical trial studies investigating the efficacy of psychedelic therapies in treating symptoms of depression and anxiety has unveiled promising results, indicating significant benefits for individuals with mental health conditions. Led by a team of researchers at the University of Birmingham, this meta-analysis represents the largest and most exhaustive review of its kind to date, encompassing 15 unique clinical trials and analysing data from a total of 656 participants.

Exploring the frontiers of psychiatric research, this study delves into short-acting psychedelics, a class of mind-altering drugs with roots dating back to ancient civilisations. Coined by Humphrey Osmond, "classic psychedelics" encompasses substances like mescaline, LSD, psilocybin, and DMT, known for their profound effects on consciousness. Despite historical obstacles, the resurgence of psychedelic research in the 1990s reignited scientific interest in these compounds. Clinical trials have showed promising potential for psychedelic-assisted psychotherapy (PAP) in treating depression and anxiety, signalling new possibilities for mental health treatment. Against this backdrop, the meta-analysis aimed to advance our understanding of psychedelic therapies by examining recent developments and employing comprehensive methodologies to evaluate their therapeutic potential.

The findings underscore the transformative potential of psychedelic-assisted therapies in addressing the pervasive challenges of depression and anxiety. Across all timeframes examined - short-term, medium-term, and long-term - the meta-analysis revealed consistently positive treatment effects favouring participants who took psychedelic drugs when compared to the control groups.

In terms of anxiety outcomes, the analysis demonstrated a substantial and statistically significant treatment impact, with effect sizes ranging from moderate to large. Notably, even in the long term, a significant treatment effect was observed. However, caution is warranted due to the influence of a single study on the long-term outcomes.

Similarly, for depression symptoms, the meta-analysis unveiled significant treatment effects across all periods. While there were large differences among studies with long-term outcomes, the overall effect size remained substantial and statistically significant. Excluding studies that added to the large variation in long-term data led to a reduction in effect size, further emphasising the importance of rigorous methodological approaches in clinical trials.

Importantly, subgroup analyses based on bias risk and blinding methodologies shed light on the nuances of treatment efficacy. Studies employing robust blinding techniques, such as double-blind trials, showed slightly reduced effect sizes compared to open-label or single-blind studies, suggesting the importance of blinding in minimising bias.

Furthermore, the analysis identified the presence of publication bias, indicating the need for transparency and comprehensive reporting in psychedelic research. Despite this, the revised results following adjustment for publication bias remained statistically significant, reaffirming the robustness of the findings.

However, the meta-analysis also highlighted several areas for future research. Robust blinding techniques, careful selection of placebos, and larger, more diverse participant samples are crucial for enhancing the validity and generalisability of findings. Additionally, longer-term follow-up studies tracking outcomes beyond six months post-administration are needed to understand the full scope of psychedelic therapies' long-term effects.

This meta-analysis represents a significant milestone in the field of psychedelic mental health research, offering promising potential for individuals struggling with depression and anxiety. As the momentum behind psychedelic-assisted therapies continues to grow, further research and collaboration will be essential in unlocking their full potential.

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CHAPTER 2 EMPIRICAL PAPER:

A PHENOMENOLOGICAL EXPLORATION OF EXPERIENCES WITH SHORT-ACTING PSYCHEDELICS FOR LOW MOOD AND DEPRESSION

ABSTRACT

Background: Previous research suggests that psychedelic drugs such Psilocybin and Lysergic acid diethylamide may offer therapeutic benefits distinct from traditional antidepressants, relying not only on the pharmacological mechanisms of action but also the subjective phenomena that people experience while using the drugs. Integration of these experiences is central to psychedelic-assisted psychotherapy. However, exploration of short-acting psychedelics, like Dimethyltryptamine (DMT), remains largely unexplored to date.

Methods: This qualitative study investigates the experience of peoples who have used short acting psychedelics in an attempt to help with their low mood or depression. Nine participants were recruited from online psychedelic forums and engaged in text-based interview to provide their accounts of these experiences. Following the interviews, Interpretative Phenomenological Analysis (IPA) was used to identify and analyse themes emerging from the transcripts.

Results: Four primary themes were found: 1) Journey to Using DMT for Mental Health, 2) Psychological and Spiritual Insights, 3) Emotional Healing Through DMT, and 4) Personal Growth Following DMT. Participants typically spoke about turning to DMT after conventional treatments failed, experiencing profound insights, emotional healing, and personal growth. They described encounters with otherworldly entities, dissolution of the ego, and transformative effects on behaviour and attitudes following using the drug.

Conclusion: This study represents the first of its kind to shed light on the types of experiences people have using short-acting psychedelics, particularly DMT, for mental health.

Its findings highlight the significance of subjective experiences in outcomes described by participants and may help inform future research into the area going forward.

INTRODUCTION

Psychedelic Drugs

The term ‘psychedelics’ was first coined in 1957 by Humphrey Osmond, who authored a review on the effects of ‘psychomimetic’ drugs. These substances, primarily utilised in clinical and research contexts, were noted for their capacity to mimic mental illnesses such as psychosis and schizophrenia, particularly through inducing hallucinations (Osmond, 1957). Osmond contended that the drug-induced experiences were qualitatively distinct from mental illness, as they could engender positive experiences and facilitate introspection. He proposed the term ‘psychedelic’, meaning ‘mind manifesting’, as a more apt descriptor (Osmond, 1957). Thus, originally, ‘psychedelic’ referred to a phenomenological attribute of these drugs, implying potential benefits for users. Over time, both ‘psychedelic’ and ‘hallucinogenic’ have been employed in literature, with the latter focusing on the perceptual and hallucinatory effects of these substances, devoid of mental health connotations (Johnson et al., 2019). However, ‘psychedelics’ has become the preferred term, deemed to more comprehensively represent not only altered perceptions and hallucinations but also shifts in self-awareness, cognition, and autobiographical memory (Johnson et al., 2019).

It remains a matter of debate as to which drugs are within the ‘psychedelic’ category, leading to a distinction between ‘classic’ and ‘atypical’ psychedelics (Mitchell & Anderson, 2023). Classic psychedelics include phenethylamines like mescaline, tryptamines such as 5-MeO-DMT, N,N-DMT, and Psilocybin Mushrooms, and ergolines like lysergic acid diethylamide (LSD), which primarily act as agonists or partial agonists at serotonin receptors (Calvey & Howells, 2018). For this study, psychedelic drugs will refer to this class of ‘classic

psychedelic', as these have been the subject of much of the recent research literature on psychedelic-assisted psychotherapy.

Early Psychotherapeutic Research into Psychedelics

In the 1940s, early investigations into the therapeutic potential of psychedelics began with studies on LSD's effects on healthy subjects and schizophrenia patients, noting its potential to aid psychotherapy by facilitating access to repressed content in the consciousness (Nichols & Walter, 2021). By the 1960s, LSD had become recognised as an analgesic for patients with severe illnesses and was researched extensively by Kast and Collins (1964) who also documented its psychological effects on these patients. They noted that LSD induces excitatory symptoms like tremors and panic, followed by a phase of enhanced beauty perception and vivid imagery. Significantly, it shifted patients' focus from basic survival-related sensations to more abstract perceptions, including a deeper appreciation of beauty and emotional experiences. Following LSD use, patients' attitudes towards their terminal conditions altered, leading to a disregard for the seriousness of their situations and a beneficial change in their mental states, particularly in their discussions about death (Kast & Collins, 1964; Nichols, 2021). Around this time, psychedelics had also started to be investigated for more broad psychotherapeutic properties. In 1962, the "Good Friday Experiment" reported that participants who were given psilocybin underwent deep mystical states, resulting in lasting improvements in their spiritual and psychological well-being. These included enhanced spirituality, greater life appreciation, and an expanded perspective on religious and philosophical matters (Doblin, 1991).

Short-Acting Psychedelics

While there has been a modest amount of research into the therapeutic use of psychedelics, with several clinical trials and meta-analyses indicating positive effects for

mental health conditions with psilocybin (Irizarry et al., 2022) and LSD (Li et al., 2022), little research has been conducted regarding the therapeutic use of short-acting psychedelics. Short-acting psychedelics refers primarily to the two subtypes of dimethyltryptamine (DMT), N,N-DMT and 5-MeO-DMT, which are not typically orally active and usually administered through non-oral routes (i.e. smoking), leading to a brief duration, with acute effects typically lasting just 20 minutes (Timmermann et a., 2018), and qualitatively difference experiences from other psychedelics (Sherwood et al., 2020). 5-MeO-DMT is more potent than N, N-DMT often inducing an experience characterised by a more intense onset coupled with ego-dissolution (i.e. losing a sense of self as differentiated from the external world) compared to more visually vivid and detailed hallucinations associated with N,N-DMT (Ermakova et al., 2022; Reckweg et al., 2022; Sherwood et al., 2020).

Qualitative Research on Short-Acting Psychedelics

Initial studies into the effects of short-acting psychedelic drugs started with Strassman et al.'s (1994) double-blind placebo-controlled trial documenting the first recorded administration of N, N-DMT with 11 human participants. The study demonstrated that DMT's psychoactive effects were nearly instantaneous, eliciting distinct experiential phenomena depending on the dose. At low (0.05mg/kg) doses participants described comforting and "warm" physical effects without perceptual distortions. Whereas at the highest dose (0.4mg/kg), participants reported an overwhelming intensity with rapid hallucinogenic effects that led to a complete disruption of normal mental functioning. They described vivid hallucinations (visual and auditory), intense physiological sensations akin to fear and a feeling of heaviness and detachment from their body. Despite this, the participants generally reported

the experience to be exciting and euphoric, while maintaining their sense of intellectual clarity throughout the experience with some reporting new perspectives on their lives as a result.

More recent studies have used online questionnaires (Cott & Rock, 2010) and analysis of internet forum content (Lawerence, 2022) to explore the experiences of short-acting psychedelics. Cott and Rock (2010), conducted a thematic analysis of DMT experiences from 19 participants who completed an online questionnaire. From this, the authors identified 9 themes among the users' experiences: 1) hallucinations, 2) entering other realities, 3) lucidity, 4) affective distortions, 5) ineffability, 6) extreme intensity, 7) spirituality, 8) distortion in sense of time, space, self and 9) a sense of familiarity. A more recent naturalistic field study (Michael et al., 2023) interviewing 36 participants following DMT use found some commonalities with the previous study in which participants described intense emotions from their experiences but with a sense of lucidity and difficulty putting those experiences into words (ineffability). However, they also found notable experiences related to the often-difficult onset of the drug's effects. This was frequently followed by positive emotional (94%) as well as mind-manifesting (83%) content in which the drug produces visual or hallucinogenic phenomena as representations of an emotional state within them.

Lawrence et al. (2022) identified common themes based on a large sample (n=2,277) of participants documenting 3,778 DMT experiences via 3,305 Reddit posts. These included common physical effects like somesthesis, auditory ringing, visualisations of fractals and vivid colours. Moreover, 74% of cases involved encounters with entities, often leading to some kind of mission or insight imparted upon the participant from the entity (46%). The entities were most often described as conscious (92%) and intelligent (72%), but also sometimes negative or difficult experiences (11%). These entities were also frequently perceived as feminine (24%),

often divine, God-like (17%) or alien (16%). Other common descriptions featured alternate dimensions, specific rooms, and tunnels, with experiences commonly encompassing mystical elements and ego-dissolution. Participants also reported a sense of familiarity and reduced fear of death, with 6.1% expressing profound beauty in their experiences (Lawrence et al., 2022). However, this study did not capture information about mental health diagnoses, or changes in mental health status as a result of the experiences.

Dimethyltryptamine and Mental Health

Several clinical trials have examined the safety of inhaled DMT in healthy individuals (Falchi-Carvalho et al., 2024; Vogt et al., 2023), alongside initial investigations assessing mental health outcomes. Timmerman et al. (2018) reported statistically significant reductions in depression, but not trait anxiety, ratings up to two weeks post-DMT administration compared to a placebo control group in healthy participants (*n*=30). Additionally, in an open-label trial, D'Souza et al. (2022) studied the effects of intravenous DMT in individuals with major depressive disorder (MDD) (*n*=7) and healthy controls (*n*=3), revealing a significant decrease in depression symptoms among MDD participants the day after treatment.

Furthermore, internet-based surveys have identified potential psychotherapeutic benefits as a primary motivation for DMT use. Cakic et al. (2010) found that 31% of Australian DMT users reported taking DMT for possible mental health benefits. Davis et al. (2018) investigated epidemiological factors of 5-MeO-DMT use from an online-based sample of users (*n*=515). They found that the most common frequency of DMT use was less than once per year (38%), typically taken at home (50%), and often sourced from a psychedelic guide or leader (30%). While the most commonly reported reason for use was spiritual exploration (68%), a substantial proportion (14%) reported healing or psychological treatment as their motivation.

Furthermore, the majority of the sample reported experiencing personal growth (90%), spiritual growth (89%), and psychotherapeutic effects (84%) from using the drug.

The Present Study

Previous research has predominantly focused on qualitative aspects of individuals' experiences with short-acting psychedelics, particularly examining perceptual, somatic, cognitive, and affective dimensions while under the influence of these drugs. Additionally, some studies have highlighted potential psychotherapeutic benefits as significant factors contributing to their use, with preliminary research indicating positive effects on mental health, but with small samples and typically on healthy participants.

However, to date, no studies have investigated how participants who have used DMT to address mental health concerns interpret the phenomenological aspect of their DMT experiences within this context. The current study aims to address this gap, by exploring the experiences of individuals who report low mood or depression and have attempted to use short-acting psychedelics therapeutically for this. It seeks to understand how they perceive and make sense of their psychedelic experiences in relation to their mental health. Low mood and depression were chosen as the condition of interest in this study, as it is the condition with the greatest evidence base for psychedelic assisted psychotherapies (Ko et al., 2023) and the only condition for which DMT has been tested in a clinical trial (D'Souza et al., 2022).

METHOD

Ethics

Ethical approval for this project was gained from the University of Birmingham's Research Science, Technology, Engineering and Mathematics Ethics Committee.

Due to the sensitive nature of the research topic, with DMT being illegal in most countries around the world, participant safety was key to the undertaking of this study. As a result, several processes were implemented as part of the ethics to maintain the anonymity of the participants (see the Anonymity and Confidentiality section below for more details).

Position Statement

This research adopted a neutral stance on the potential therapeutic use of psychedelic drugs for mental health difficulties. Multiple randomised control trials have investigated psychedelic-assisted psychotherapy with substances like LSD or Psilocybin. However, there is a notable lack of comparable research on short-acting psychedelics, such as N,N-DMT and 5-MEO-DMT. Consequently, this study refrains from forming hypotheses about the utility of these substances and does not prioritise either positive or negative accounts from individuals who have used these drugs, instead, the study focuses on the individual's perceptions (see interview structure in Appendix 6 for details of how this was achieved).

The author of this paper conducted this study while completing their doctoral thesis in clinical psychology. Over a decade ago, the researcher became aware of DMT, initially learning about it through the popular podcaster Joe Rogan, followed by independent research involving videos and documentaries, such as DMT: The Spirit Molecule documentary and the book How to Change Your Mind. Initially, the researcher held a positive view of DMT due to the described

potential benefits for mental health. This positive outlook was maintained during a Master's Degree module in neuropharmacology, where the researcher wrote essays on the use of psychedelic drugs and psychedelic-assisted psychotherapy.

In recent years, however, the researcher has taken a more sceptical stance towards claims of a breakthrough in the treatment of mental health conditions. This is largely due to increased awareness of the limitations and biases in psychedelic research more generally (see van Elk & Fried, 2023). As a result, at the time of this study, the researcher maintains a more moderated stance about the effectiveness of DMT in improving mental health. Nevertheless, the author still possesses a tentatively positive attitude regarding the likelihood of potential benefits, but the degree of these benefits may not be as transformative as is sometimes claimed. The researcher has no personal experience of using short-acting psychedelics for mental health or any other reason therefore has no direct bias due to personal experience of the drugs.

Recruitment

Nine participants were recruited using a purposive sampling methodology whereby advertisements were posted online across a range of Internet discussion groups and forums. This number was established, as a greater number than is typically suggested in Interpretative Phenomenological Analysis (IPA) (Smith et al., 2022), to enhance the information power due to limitation on the quality of dialogue via text-based interviews (Malterud et al., 2016).

Notably, adverts were posted to a large number of DMT, Psychedelic and drug-related communities on Reddit (subreddits) as well as Telegram groups, BlueLight.org and the University of Birmingham's website. The communities were chosen through the researcher's knowledge of online communities in which there would likely be people who would have experience using short-acting psychedelics for low mood or depression. Moreover, some of

these communities have been utilised in similar studies, such as Ryan et al. (2023), Lawerence et al. (2022), and Carhartt-Harris and Nutt (2010).

Communication with potential participants typically took place within these specific forums. The researcher created accounts of the respective platforms specifically for advertising and conducting the interviews. Participants were given the option of conducting the interviews via direct message within the website or via end-to-end encrypted messaging software.

Inclusion and Exclusion Criteria

Full details of the inclusion and exclusion criteria are described in Table 1.

Table 13

Inclusion and Exclusion Criteria for Participants

Inclusion Criteria	Exclusion Criteria
Age Requirement: At least 18 years old	**Recreational Use Only:** DMT use was solely for recreational purposes, and not to explore its effects on mood or depression.
Language Proficiency: Competent in reading and writing English	**Current Acute Treatment:** Individuals undergoing acute treatment for substance withdrawal at the time of the study
Recent Use of DMT: via inhalation at some point in the past year	**Method of DMT Ingestion:** Those whose only experience with DMT compounds was through oral ingestion (such as taking Ayahuasca) or who had used DMT only while intoxicated with other substances

Intention Behind Use: Have used with the intention of exploring its effects on their low mood or depression as self-reported by the participant

Consent

The study advertisement included a link to the research website, where the Information Sheet and Consent Form were hosted. The advertisement requested that participants read these documents. If they met the study's requirements and agreed to the points in the consent document, they could then contact the researcher to express their interest in participating.

If potential participants contacted the researcher before reading these documents, they were directed to review them before proceeding further. Once participants confirmed and agreed, via the messaging application, that they had read the information provided, an interview time was arranged.

Anonymity and Confidentiality

To ensure privacy, participants remained anonymous throughout the study. The researcher and academic supervisors did not have access to participants' names or contact details. This was ensured by making clear within the information sheet and consent form that potential participants should only contact the researcher to volunteer their interest in the study via the messaging application using an account that was not created in their real name. If participants' full names were evident from the username on their account, then they were told that they would not be able to proceed with the study.

Following the interviews, each participant was assigned a random identifier and referred to by a pseudonym in the study's documentation. Excerpts of anonymised data were reviewed by academic supervisors and shared with other students and trainees as required for analysis purposes, adhering to an approved data management plan. Participants were made aware through the information sheet that the research would be contributing towards a doctorate research thesis. This overall plan was in place to maintain the confidentiality and security of the information.

Despite these measures, it was acknowledged that there are still inherent limitations in maintaining absolute confidentiality and anonymity due to the electronic and internet-based nature of the study, and this was made clear in the Participant Information Sheet (see Appendix 4).

Control Over Information Provided by Participants

Participants had autonomy over the information they provided. They were free to opt out of the interview at any point without needing to justify their decision. If a participant chose to withdraw during the interview, all information collected up to that point was permanently deleted. Additionally, participants had a two-week window post-interview to request the withdrawal of their data. After this period, the data was stored separately, making it impossible to retract individual contributions.

Post-Study Data Usage:

After the study's completion, participants were informed that their data would contribute to a doctoral thesis and that, while verbatim quotes might be used, no identifiable information would be included. Their data is referred to only by pseudonyms, and the thesis will be archived

at the University of Birmingham library. Should the data be published in journal articles, it will similarly exclude any identifiable information.

Participants

No demographic data from the nine participants were collected to ensure anonymity. Therefore, no information was available about the age, sex, occupation or nationality of any of the participants who were interviewed for this study.

Two interviews conducted within the study's data-collecting phase were not included in the final analysis. The first of these interviews involved a participant who commenced the interview and spoke about their experiences with short-acting psychedelics for the treatment of low mood and depression. However, partway through the interview process, the participant was unable to continue due to other commitments. Despite efforts to reschedule and conclude the interview at a later date, the participant did not attend.

The second interview, also excluded from the analysis, featured a participant who had initially confirmed their understanding and agreement with the study's information sheet and consent document. However, during the interview, it became apparent that the participant did not fulfil the study's specific eligibility criteria. They revealed that their use of short-acting psychedelics was for recreational purposes and had only taken the substances within the context of other drug use. Consequently, the interview was ended, and the participant was told that their data would not contribute to the study's findings.

Interview Procedure

The study employed a semi-structured interview format to explore participants' experiences of using short-acting psychedelics for low mood and depression. This approach

was designed to best reflect participants' perspectives, while also encompassing essential aspects of the short-acting psychedelics experience pertinent to the study's objectives. The development of the interview protocol involved creating open-ended questions and topics to ensure participant flexibility in expressing their views. This method allowed participants to prioritise and discuss topics in a sequence that resonated with their personal experiences. The detailed interview schedule is presented in Appendix 6. In addition, the interview framework was established to maintain neutrality regarding the potential benefits or risks of short-acting psychedelics for low mood and depression, ensuring the interviewer refrained from posing leading questions or forming presuppositions about the participants' experiences.

Participants were required to read and agree to an information sheet and consent document before engagement. Interview durations ranged from 69 to 110 minutes (mean 85 minutes) and were each conducted in one sitting (i.e. from start to finish of each interview with no break).

The initial segment of the interview aimed to provide a broad overview of how participants first encountered short-acting psychedelics. This was intended to set the stage for an in-depth exploration of their specific phenomenological experiences to be discussed in later parts of the interview.

In line with ethical considerations, participants were instructed, as detailed in the consent documentation, to avoid disclosing personal or identifiable information during the interview. This guidance was reiterated as necessary throughout the interview process. In cases where participants incidentally mentioned identifying information such as age, gender, or country, they were advised against further personal disclosures. Subsequently, all such information was redacted from the interview transcripts to ensure participant anonymity.

Upon the conclusion of the interviews, participants were thanked for their contributions and informed of their right to withdraw their data from the study within two weeks. Following this period, the retraction of data was no longer feasible. All participants consented to the use of their interviews, with no requests for data withdrawal.

Queries from participants regarding the study's results were addressed by informing them that direct updates were not possible; however, a summary of the study's findings would be published on the study's website, a resource they had previously accessed for the information sheet and consent documents.

Upon completion of the interviews, the transcripts were copied to a word processing file and anonymised further by removing their account username. Any accidental personal disclosures were also removed, such as age or country of origin. The file was then uploaded to a secure document store hosted by the University of Birmingham.

Interpretative Phenomenological Analysis

An IPA approach was chosen as the method for analysing the data in this study due to its alignment with the exploratory nature of the research topic (Smith et al., 2022). Given the limited existing research on short-acting psychedelics, particularly regarding their potential therapeutic use for mental health issues such as low mood and depression, a qualitative approach like IPA offers the flexibility and depth necessary to comprehend the nuanced experiences of individuals who have used these substances for this purpose. As an ideographic approach, IPA emphasises the importance of meaning-making in these experiences for individual participants, allowing for a thorough exploration of their subjective realities (Smith et al., 2022). With theoretical underpinnings in hermeneutics, IPA also acknowledges the interpretative nature of this process, wherein participants make sense of their own experiences

of using short-acting psychedelics for mental health, which will subsequently be re-interpreted by the researcher (Smith et al., 2022). In this sense, epistemologically, IPA is a constructionist approach to knowledge, making use of how the participants created knowledge about their own experiences, and subsequently how the researcher comes to understand the participant's experiences.

Overall, this approach provides an analytic method that can help elucidate the types of experiences people have concerning the use of short-acting psychedelics for mental health, particularly how they interpret their experiences of short-acting psychedelics within the context of their low mood or depression.

Analysis

The interview data was analysed using the method outlined by Smith et al. (2022). This IPA method began with reading and re-reading each interview transcript to begin the process of familiarisation and active engagement in the material and participants' experiential world. After this step is an exploratory noting stage in which semantic, linguistic and contextual notes were made to identify the specific way in which participants spoke about, understood and thought about their experiences with short-acting psychedelics. Following this, experiential statements were constructed to capture the essence of the participants' experiences by condensing and articulating the most salient aspects of the exploratory notes while also connecting them to the original transcript. Personal Experiential Themes (PETS) were then constructed for each participant, to identify connections across experiential themes within participants, then finally Group Experiential Themes (GETS) were created to summarise connections between participants (see appendices 7-10 for examples of this process).

RESULTS

Based on the interviews from the nine participants interviewed, four themes were generated from the data, which are summarised in Table 2.

Table 14

Group Experiential Themes and Contributing Participants

Theme	Subtheme	Participants
Journey To Using DMT Therapeutically	Long-Term Mental Health Difficulties and Struggles with Conventional Treatment	Alex, Avery, Casey, Jamie, Morgan, Quinn, Taylor
	Interest and Hopes for DMT	All
Revealing Psychological and Spiritual Insights Through DMT		Alex, Avery, Casey, Casey, Jamie, Morgan, Quinn, Taylor
Experiencing Emotional Healing Through DMT		All
Personal Growth Following DMT use		Avery, Casey, Jamie, Jordan, Morgan, Taylor

All quotations used in this section were copied verbatim from the interviewees' original transcripts. Therefore, there may be spelling, typographical or grammatical errors that are direct representations of the original data.

Table 15

Symbols Used within Quotations for the Analysis

Symbol	Description
[…]	An ellipsis within square brackets indicates that textual material has been omitted from the portion of the quotation in which the ellipsis is placed. An ellipsis without square brackets indicates that it was added by the participants in the original transcript
[ ]	Any text within square brackets has been added by the author to provide additional information within a quotation

THEME 1: JOURNEY TO USING DMT THERAPEUTICALLY

This theme refers to the first part of the participants' journeys, which for many started with long-term mental health difficulties and disillusionment with mainstream methods of mental health treatment. For many, this was followed by some initial introduction to DMT that left a strong impression upon them, followed by a period of interest and curiosity towards the substance and having hopes that it would be able to help them beyond previous treatments they have tried.

Subtheme 1.1: Long-Term Mental Health Difficulties and Struggles with Conventional Treatments

Most of the participants in the interviews spoke about their mental health difficulties being long-term and feeling as though they had not been able to sufficiently alleviate this through conventional methods. For example, Jamie spoke about their lifelong feeling that something is missing:

> There's always been something missing for me. Like I look around and I think right everything is in place to be happy. Like what we would normally say adds to happiness or satisfaction or whatever you want to call it. But still something I'm missing. All about my life and what I'm supposed to be what I want to achieve what I am supposed to or expected to achieve...who actually am I what actually am I (Jamie; 52-65)

Later in the interview, Jamie also went on to speak about their perception of conventional treatment methods, suggesting that they did not have a positive perception of antidepressant drugs:

> I went through a bit of not so great life for maybe 10 to 15 year....nothing to do with substances or that just a really tough time....and through my experience of watching or knowing anyone who took a tablet for the way they were feeling never ever worked. And I'm not one to reach out to someone I know and discuss (Jamie; 143-145)

This sentiment of being disillusioned by conventional treatments was also echoed by other participants. For example, Alex stated they were:

> Diagnosed with and treated for depression since late teenage years. depression has never been severe, just an ever-present low mood/low energy feeling. usually managed by medication, but don't like the numb feeling it gives either so have gone on and off over the years (Alex; 87-91)

Taylor also spoke about their experiences with depression, seeing it as something they have had since their teenage years and their belief that it is, to some extent, familial:

> I think it is chronically in my family, as far as i can remember my mother have depression, till now she isnt cured from it, nor looking for ways to do it. For me personally it was somewhere in my teenage years. I always wasnt feel best, but when I started smoking weed it definatelly unlocked it and since than i had really dark times (Taylor; 125-132)

Taylor then went on to speak about their struggles to find any other methods for alleviating their depression, despite efforts to do so:

> Unable to find another way to beat depression. I tried with food diet, sport activities, overtime working, hobbies , going out with friends, antidepressants and somehow I still felt empty inside (Taylor; 285-287)

While many of the participants spoke similarly about their experiences of low mood or depression being a long-term struggle, they each spoke about their struggles with conventional treatments in a different way. For example, Jamie spoke about their experiences of other people trying antidepressants and their reluctance to try this due to their negative expectations of them, as well as their reluctance to talk to others for support: “I'm not one to reach out to someone I know and discuss”. This is somewhat different to Alex who had previously tried antidepressants but did not like the side effects, and also Taylor who spoke about trying various, more conventional treatment methods, but had always found them to be unsatisfactory in their effectiveness for alleviation of their low mood.

These two components of a long-term struggle with mental health, coupled with a negative perception of conventional treatments were spoken about by many of the participants. However, it was also not limited to just antidepressant pharmaceutical medication as some of the participants also spoke about their struggles with therapy. For example, Morgan said they

have "[…] tried talking therapy. It was too difficult open up to someone I barely knew and the cost was prohibitive" (135-136). This was also similar to the sentiment expressed by Quinn who spoke about their dissatisfaction with talking therapy and struggling to work with a therapist who would not have the firsthand experiences they have had in going to war:

> CBT useless, talking therapy was OK but doesn't change anything and your talking to someone that probably hasn't had to kill someone so doesn't really get it. Citalopram just numbed my senses/pain so it helps but not in the right way. I don't want to be numb/dead (Quinn; 160-164)

These two components of this theme were discussed by the majority of participants except for Jordan (who did not speak about conventional treatments) and Riley (who did not speak about conventional treatments nor allude to the long-term chronicity of their depression).

These narratives highlight the pervasive dissatisfaction with traditional mental health approaches among participants, setting the stage for their exploration of alternative methods such as short-acting psychedelics.

Subtheme 1.2: Interest and High Hopes for DMT

This subtheme refers to the participants' experiences of discovering DMT and their perceptions of it before taking. This period was typically characterised by most of the participants developing a keen interest in DMT, spending time learning about the subject and having hopes that it would be able to help with their mental health in a different way than had been possible through other methods.

All the participants spoke about DMT being interesting to them, for example, Jamie stated that they first learnt about DMT through a documentary called 'The Spirit Molecule'

which piqued their interest leading them to research more about the substance "I started researching extensively about it[…]and read everything I could on it" (71-72) they also added that they felt compelled to try it "everything I had read and watched about dmt told me you need to try this you need to see what this is about" (71-72).

Jordan also spoke about first being intrigued by other people's descriptions of their experiences with DMT: "I started watching more videos on it and reading other peoples expiriences" (71-72) and following this had "fantastical expectations of other worlds and beings, i thought it was amazing all this could be found with a substance that only lasts a few minutes" (81-83) and "no doubts about others experiences and the fact that it is a rather simple and natural molecule made me trust that it could benefit me" (84-86).

Casey spoke about being initially interested in DMT but went through a process of changing their perception of the drug before taking it. They stated that initially "it was described to me as a key that 'opened doors to alternate universes' which at the time peaked my interest as something that could potentially allow me access to new 'recreational' experiences" (75-77). However, they went on to add:

> I never had chance to come into contact with the substance until around a year ago, when I found someone who could supply me with the opportunity. And I'm glad for the fact as the mindset I was in when I was first introduced to the idea, was not one that would lend itself to the experience at all (Casey; 78-82)

Casey is glad that they first took DMT after they knew more about the purported spiritual and therapeutic aspects of the substance, as opposed to the recreational perception they had of it initially. They went on to explain that over a period of time, through their own research:

> DMT seemed to keep cropping up in my research…as the quickest and most profound method of changing perspective, so I made it my mission to obtain the substance and experience this change myself (Casey; 111-114)

They then described what they hoped they would be able to achieve through DMT, based on their research:

> I was hoping to be given the opportunity to see life from a perspective beyond my own self. To be shown a bigger picture and offered the chance to take my negative experiences and view them as a passing event, and be able to then continue on a path that I could enjoy without having to dwell and let past events influence my life in a negative manner (Casey; 121-126)

Riley, however, went in a somewhat different direction with their journey. When they first learnt about DMT the profound and potentially transformative nature of the experiences are what initially piqued their interest:

> I came across it somewhere and it caught my interest […] I don't remember what I exactly saw about DMT on the internet beceause its a long time ago. But what made DMT in general interesting to me is the weirdness of the experience that it provides .It's really interesting to me how ingesting some molecule can alter your reality in such an extreme way. So when I learned about the existence of DMT I had to see it for myself (Riley; 76-93)

However, their decision to eventually take DMT to help with their low mood appeared to be more spontaneous and without any reference to any expectations of profound or deep experiences, but rather as a more superficial mood boost: "I woke up on a random morning

feeling really tired, lethargic, and bored. And after laying in bed for a few minutes I got the idea to smoke some DMT to get something like a kickstart" (152-155). They then went on to explain that "in my own experience with DMT I always had a mood boost after" (171-172).

Morgan also had a different experience before going into their first experience. Though they spoke about DMT as being interesting, they did not have any strong expectations about its healing potential: "My initial thoughts were that it must be fun to hallucinate. It sounded like an interesting experience. I didn't buy into the healing/spiritual aspect at the time" (97-99). However, they later went on to explain that they eventually decided to take it therapeutically after noticing some positive, mood-enhancing effects after taking it for more recreational reasons.

In this subtheme, participants shared their fascination with DMT, driven by the prospect of transformative experiences and therapeutic potential. While Jamie, Jordan, and Casey embraced profound spiritual expectations, Riley's interest stemmed from curiosity about altered realities but later spontaneously hoped to use it as a mood enhancer. Morgan initially viewed DMT as recreational but later explored its therapeutic benefits after experiencing mood enhancement.

THEME 2: REVEALING PSYCHOLOGICAL AND SPIRITUAL INSIGHTS THROUGH DMT TRIPS

Another theme that was present throughout the majority of the interviews was the concept of the DMT trip revealing psychological or spiritual insights to the participants about themselves, others, or the world via the content of their trips. This theme was discussed by all

but one of the participants (Riley). However, the impact and nature of these insights differed between the participants.

Alex, for example, spoke about having “some moment of these brilliant-seeming insights into my personality or things in my past” (197-198) but then went on to say, “but not in a way that has influenced my depression, especially not long-term” (198-199). They later described that:

> Although I'd really wanted a more profound experience, after the trip it just felt like I had taken a really fun drug and saw some crazy things. I didn't really feel the need to process or make sense of the trip, like I have with mushrooms (Alex; 221-224)

They suggest that, unlike psilocybin mushrooms, they did not feel that there was any need to make sense of the DMT trip. They then explained their reasoning for this:

> I think its the short nature of the trip, they're 15min long tops. and it sets on very quickly. and then its just a barrage of colors and patterns. your headspace is definitely different than your sober mind, but I really just felt in awe and overwhelmed (Alex; 233-236)

Others felt differently to Alex, where the experiences produced strong and profound insights that required substantial time to process and left a lasting effect. For example, Casey, when discussing the nature of their experiences described them in the following way:

> The experience of DMT isn’t one that you would consider as a recreational experience, it is a very personal and spiritual experience that you may only need once, personally I felt I had more to learn and would benefit from future experiences but the lessons and change in perspective from the experience

> before can take weeks or months to process and come to terms with, each time is slightly different based on your current state I would say (Casey; 206-213)

Casey feels as though the “lessons” from their experiences can take a long time for them to fully understand and alludes to the possibility that one may only need to have such an experience on one occasion for it to have a lasting effect. Alternatively, Morgan described insights that they felt that they received while under the influence of DMT that were somewhere between those described by the previous two participants. In the following passage, Morgan speaks about receiving insights from DMT that helped with their low mood but also went on to say that for these to lead to permanent benefits would require extra “work” while they are not under the influence. When describing the benefits they have got from DMT they say “It doesn't magically solve all my problems on its own. But it does bring light to them and foster new ways of looking at them" (202-204). They explain:

> It broadens my perspective. Lets me see things more objectively […] almost like I can look at the situation as if it happened to someone else. Then I ask myself what would I say to someone who went through that? I would be kinder than how I am treating myself (Morgan; 218-228)

When asked to elaborate on this, Morgan said “If I intentionally keep [my change in perspective] in mind then it lasts a while, easily weeks. But sometimes life gets in the way and I'm back to the default mind set in a few days" (266-268) and that “[…] sober work is necessary for any sort of permanent progress” (279-280).

Many of the participants also described the insights they felt while under the influence of DMT as being difficult as it can show them aspects of themselves or their life of which they were either in denial or not aware. For example, Avery describes how their experiences with

DMT allowed them to acknowledge aspects of their low mood, stating that “DMT helped me realise I *do* have anhedonia because I was in denial before” (220-221). Avery describes how this was occasioned by a vision while hallucinating on DMT:

> I saw pure blackness with a tiny point, a tiny tiny point, I tried to look away but I felt a presence force me to look at that point, I moved my eyes but I saw anger itself force my eyes back into the point, so I look at the point. The point is behind a blurred screen, or a smudge. I try so hard to look inside, in small glimpses I see beautiful visuals of what I love, but once again, it is obscured. How I processed this was "wow, I have anhedonia, my mind is a tool that is ever so slightly misconfigured (Avery; 250-263)

However, they also described some of the insights as being pleasant and leading to positive realisations or insights about their life:

> Another experience I had was seeing my future, it wasn’t bad or lonely. I was with my partner and our family, in a nice sunny field. It also showed me the hopes I have for my little brother’s future, and how I love him and how I just want to protect him. It made me realise others also love me and want to protect me, they also have hopes for my future (Avery; 266-271)

This view of psychological insights precipitated by DMT were common among many of the interviewees. Jamie emphasised, “[…] who I see and what I communicate with” (167) as being important vectors for their insights when under the influence of DMT. Jamie stated that “I have seen clown jesters who point and laugh and that's the message. Relax be at peace and experience. Experience the good and the bad and let it be” (188-194). Later, they explained the following:

> Like dmt has shown me ‘hello oo wake wake dummy’. Do u really think its just yous existing on earth and that's it be all and end all. That's the message I have gotten from them all […] Dmt has also taught me that we all have divine within us and that we actually create our own reality (Jamie; 287-300)

Similarly, Quinn described a hallucinatory experience while under the influence of DMT with a female entity that revealed aspects of their mind to them:

> The emotions I was faced with, she pulled them out when I wanted them buried and forgotten. I felt like an energy exchange. But when I got to the bad bits it felt like they were pulled out and she said "what about this?" Like an exposé (Quinn; 310-313)

They interpreted this as:

> Like maybe I haven't dealt with a lot of stuff properly. Things happen and I just bury it. Just soldier on. I don't know how to deal with stuff properly but maybe that trip was just confirmation of that fact (Quinn; 319-321)

In summary, this theme centred around the revelation of psychological and spiritual insights through DMT trips among participants, with variations in the depth and impact of these. While some, like Alex, perceived the experience as transient and recreational, others, like Casey and Morgan, saw them as leading to profound and lasting changes. Moreover, within this, participants, such as Avery, also noted the confrontational nature of the experience, revealing aspects of their mental health about which they were in denial.

THEME 3: EXPERIENCING EMOTIONAL HEALING THROUGH DMT

The majority of participants spoke about DMT providing them with some form of emotional experience that they would frequently describe as inherently therapeutic. This is in contrast to the previous theme in which participants often felt they gained some explicit knowledge that was helpful. Instead, this theme refers to the inherent emotional components of the participants. In some cases, these experiences were so intense that the participants felt it gave them a permanent change.

Jamie spoke about their feeling before using DMT, of something being missing from their life (described in Theme 1.1), as being fulfilled through the DMT trip. They stated that “I [no] longer feel like that ...there isn't anything missing now....I still get low mood from time to time as anyone would but that missing thing is found” (111-112). Jamie also spoke about their experiences with DMT as providing them with a sense of emotional peace that was not present beforehand: “I have an inner peace now that never goes....no matter happy or sad” (270-271).

Based on this, Jamie appears to be communicating that the emotional relief that they have felt since taking DMT is permanent. Alex differed slightly in that they also felt some positive emotional effects from DMT but explained that these were only temporary, stating “there was an afterglow period of slight euphoria for a couple of hours after, but the effects didn't really last or feel meaningful outside of the drug itself” (163-165) and “I did look forward to the euphoric afterglow, and sometimes the enhanced mood would last into the next day. but that's really it unfortunately” (210-212).

Casey spoke about the DMT experience as providing them with peace that was brought to them via entities they experienced while using the drug: "I could only say that my request to the universe to settle my soul and bring me the peace I longed for was answered by the entities that I met with while in the other realm”. And another occasion they spoke about an emotionally

therapeutic experience which was provided by an entity that they encountered during their DMT trip:

> I was greeted by what I instinctively knew as a 'mother' figure, but not mother in the human biological sense, this entity was mother energy, Mother Earth, the source, and was shown with love that the life I have dedicated to my family was one that was 'noticed' and approved of (Casey; 193-197)

They also said:

> I can safely say that during the process I have only ever been filled with the feeling of welcome, love and acceptance, the after effects even after my first experience have been an instant change (Casey; 171-174)

Furthermore, Quinn, who previously shared encounters with feminine entities (as discussed in the previous theme), recounted another interaction with another female entity. This entity provided emotional comfort to Quinn that helped with their low mood:

> The first time I had a breakthrough I danced with a female energy who cuddled me and reassured me everything was OK. It was pure love/bliss. […] I realised immediately I was in the presence of a strong feminine energy and she was looking after me there was all love and no malice (Quinn; 212-236)

Unlike Quinn's previous experience with another entity, where they discussed the insights and revelations gained, Quinn's interpretation of this experience was different. When asked about it, Quinn responded simply "Why wouldn't that help your mood […] u taking the piss" (246-249), suggesting that the emotional impact of the experience was inherently

therapeutic, without requiring further analysis or understanding beyond the immediate emotional response.

Taylor spoke about having a feeling of anxiety taking DMT followed by more beneficial emotional experiences that have provided a sense of relief and humility:

> Well the initial anxiety is what is keeps me away from using it too ofter, maybe once a year. But if you go beyond it and let go, just see where the experience will bring you you get a feeling of relieve, more humble (Taylor; 185-188)

However, Avery spoke about difficult emotional experiences while using DMT. They recounted feelings of loneliness being induced by the DMT experience:

> Everything in my room felt lonely. I felt lonely. Though I found my sadness to be humorous and comical. I didn't feel any less sad or lonely, but I was able to be detached from this sadness and loneliness (Avery; 300-303)

In framing it in this way, Avery describes how the loneliness could be put into context, and they can perceive this emotion in a more detached way. They spoke about their experiences with DMT becoming more "dark and gloomy but also more beautiful and meaningful" (320-321) viewing these dark emotional experiences as beneficial, "They felt sort of like a shower for my mind" (321).

In this theme, participants shared their experiences of emotional healing facilitated by DMT trips. Overall, the group reflected a diversity of responses, with some finding lasting peace and fulfilment, such as Jamie and Casey, while others, like Alex, experienced only transient euphoria. Taylor's journey involved overcoming anxiety to discover relief and humility, whereas Avery navigated feelings of loneliness, ultimately finding detachment and

significance in the emotional journey. These varied responses underscore the individual nature of emotional healing through DMT experiences. In contrast to the previous theme, focused on insights gained during DMT trips, this theme delves into the emotional healing experienced by participants, highlighting a shift from explicit acquisition to inherent therapeutic emotional experiences.

THEME 4: PERSONAL GROWTH FOLLOWING THEIR EXPERIENCE WITH DMT

This theme refers to the way that some of the participants spoke about their experiences of using DMT as a catalyst for practical change in their lives. For some, it was something that led to changing their behaviours towards people, while others viewed the DMT experience as leading to changes that made them a better person towards themselves or led to an increased sense of agency and personal responsibility in their life.

Jamie, for example, spoke about DMT leading to them making positive behavioural changes:

> It has helped me fill that missing piece of who I am and it is a permanent change not only has it helped me do that i…started to look into all other areas of my life where I could make subtle changes to improve like diet exercise etc..saunas swimming regularly (Jamie; 152-154)

They also spoke about DMT changing their attitude towards others, such as in this example of seeing a man outside of a shop asking for money:

> Before dmt I don't even think I just go uch alcoholic not getting my money blah blah.....but [...] I said to the wee man do u want a hand like a fiver....he just said he was starving I said OK will I get you something and he said yes so I got him chips and gravy [...]and see if I give him a fiver and he does go and buy a can of beer...maybe thats the only joy left in his life and I'm in a position to help [...] I was the first way before dmt and after I realised oh my god what an arsehole you are (Jamie; 350-357)

Jordan, spoke about how, after using DMT, they gained a sense of personal responsibility towards themselves and others, stating that it "[…] forced me to accept that i was responsible for my own isolation and mood" (155-156). They also reported that through DMT they learnt "accept your own feelings, dont push them to the side in hopes that they will resolve themselves. you are responsible for your own well being and once you arrive there you can be there for others" (304-307).

Furthermore, they went on to explain that the greatest benefit they got from their experiences with DMT was through their increased sense of responsibility towards themselves and their relationships: "it made me realize that i was not just responsible for myself but also that i am importent to other people that need me, be it as a son or brother, or an emotional support" (168-171).

This idea of personal responsibility also played a part in Morgan's narrative about the beneficial effects that they felt following DMT use:

> It forces me into the present moment which makes it clear that I am on some level causing my own suffering — there's no immediate danger in my vicinity, I'm just recriminating and ruminating and obsessing (Morgan; 156-159)

However, Taylor approached this differently. They believed that DMT was the sole means of escaping negative mental states, which they found intimidating. Paradoxically, their fear of DMT motivated them to implement lifestyle changes aimed at avoiding situations that might necessitate its use:

> If i behave in my day to day life bad and dont hustle to achieve something good each day i think i will end in dark places again, and the only way out i found working so far is taking 5 meo dmt and N N dmt for getting out of such bad states of mind, where one see ego death…so i prefer as far as i can not to go mentally down, to help people, to do as best i can in my job (Taylor; 229-241)

Avery described how their depression hampers motivation and task initiation, but when using DMT, they feel a sense of control and clarity. They spoke about this in terms of achieving goals in their life as DMT helped them trust themselves with problem-solving:

> Part of my depression […] is that I struggle with motivation and task-initiation. Even with introspection and breaking down my goals and motivations I feel like it seems like an impossible task. My sober mind is so lazy, it hates thinking….On DMT, and other psychedelics, I feel like this heaviness just evaporates. I feel so much more in control and I trust my mind so much more (Avery; 365-374)

Overall, this theme centres on the collective notion of DMT acting as a catalyst for practical change among these participants. It encompasses shifts in behaviour, attitudes, and personal responsibility remarked upon by those within the group. They discussed how their experiences with DMT led to changes in their interactions with others, a heightened sense of agency in their lives, and a greater willingness to confront and address personal challenges. This builds upon the previous two themes by highlighting transformative nature of the

participants' experiences in terms of its broader impact on their practical approach to life and self-improvement.

DISCUSSION

The experiences of people using short-acting psychedelic drugs in an effort to improve their low mood and depression were explored in this study. Through the use of an IPA approach to analysing the interview transcripts of nine participants, four primary themes were identified: 1) Journey to Using DMT for Mental Health, 2) Revealing Psychological and Spiritual Insights Through DMT, 3) Experiencing Emotional Healing Through DMT, and 4) Personal Growth Following DMT. Theme one was subdivided into two subthemes: 1) Long-Term Mental Health Difficulties and Struggles with Conventional Treatment and 2) Interest and Hopes for DMT.

Summary of Findings

Based on the interviews conducted in this study, there was a common pattern observed among most participants regarding their experiences with DMT in addressing low mood or depression. Generally, participants began their journey with longstanding mental health issues that conventional treatments had failed to alleviate satisfactorily over many years. Some had experimented with treatments such as antidepressant medication or talking therapy but found them ineffective or experienced undesirable side effects. Conversely, other participants hesitated to pursue conventional methods, sometimes influenced by their own or others' experiences of ineffectiveness or inaccessibility. Nevertheless, a prevailing sentiment among participants was a lack of confidence in conventional depression treatments as satisfactory or effective solutions for their low mood. This component of the study may reflect some of the wider psychedelic literature that suggests that prospective users may have more favourable perceptions of psychedelics than established treatments due to known adverse side effects of the latter (Lowe et al., 2022).

As participants progressed in their journeys, they delved into understanding DMT, often describing strong reactions upon learning about the substance. Most of the participants described their initial perceptions of DMT as “fascinating”, “interesting” or “profound” and was typically followed by a period of learning about the drug, which for some went on for many years before taking the drug. Some of the participants’ first introduction to DMT came within the context of it being something that may have therapeutic potential. Other participants spoke about being initially interested by the strangeness of the hallucinatory experiences they heard about and thought about it as more of a fun, recreational experience before learning about therapeutic phenomena that are sometimes discussed with these drugs. This process reflects a deliberate and researched approach to therapeutic psychedelic use, as observed in previous research (Ryan et al., 2023) that is in contrast with impulsive or risk-taking traits associated with other illicit substance use (Butler et al., 2004),

Participants provided accounts of their experiences with this short-acting psychedelic, reflecting on its effects on their mental health. The first theme that emerged from these accounts was the revelation of insights. Within the first theme around revelation of insights, participants spoke about experiences they had after taking the drug that revealed or imparted information that was associated with new ways of understanding themselves, others, their relationships, or the world. These insights varied in their duration and impact; some were fleeting, lasting little longer than the acute period of intoxication, while others had a profound and lasting resonance. Some participants described these as having an immediate effect on their understanding of their low mood or its contributing factors, while others spoke about these insights requiring a substantial amount of time to process and fully understand the “lesson” they could take from the experience. Many of the participants spoke about these insights being imparted by entities or impressions of figures, such as elves, jesters, and mother figures, while others spoke about

more abstract, visual hallucinations that represented metaphorical insights relevant to their mental health. This theme relates back to Osmond's (1957) original concept of psychedelics as "mind manifesting", implying that these substances may unveil facets of one's own psyche. Such effects are commonly observed in DMT (Davis et al., 2020) and psychedelics overall (Peill et al., 2022). However, within this study, participants contextualise this phenomenon with regards to its relevance to the effects of short-acting psychedelics on their low mood.

Another shared theme among all participants was of DMT providing an emotionally valuable experience that was helpful for their low mood. For some, this experience was temporary, lasting little longer than the day of the trip, whereas others spoke about impactful emotional content that they found inherently therapeutic. These ranged from a simple "mood boost" to experiences of profound love. Additionally, many participants noted the presence of uncomfortable emotions, such as fear, during their DMT experiences. However, all participants who discussed these feelings framed them as valuable and integral to the therapeutic process. Quinn elaborated on this aspect extensively, summarising it with, "I think bad trips don't happen, you have challenging trips from time to time but there's usually some sense you can make from it" (332-334). Some of these experiences are similar to a cathartic-type experience referred to as Emotional Breakthrough, whereby users experience a release of difficult emotions that result from a “breaking through” or overcoming of psychological defences (Roseman et al., 2019). These experiences are thought to be important components of the psychedelic experience that mediate enduring psychotherapeutic change (Roseman et al., 2018).

Finally, many of the participants described personal growth following their experiences with DMT. In this theme, the participants spoke of the transformative effects that DMT had on their personalities. Discussions centred on observed changes in behaviour, attitudes, and self-

awareness. Some individuals found that DMT acted as a catalyst for positive behavioural shifts, leading them to adopt healthier habits and lifestyles. Others experienced a heightened sense of empathy and understanding towards others, prompting them to reevaluate their interactions and judgments. Participants often highlighted how DMT use was associated with confronting their emotions, taking responsibility for their well-being, and helping them to have a deeper connection with themselves and those around them. This personal growth was sometimes characterised by a sense of agency and accountability as some of the participants discussed recognising their ability to shape their reality and contribute positively to their lives. However, not all experiences within this theme were described in this manner; some individuals found apprehension towards using DMT as a fear-inducing substance. This motivated them to implement lifestyle changes that would help them avoid getting into poorer mental health, that they felt could only be resolved through the use of DMT. While behaviour change has not been studied in short-acting psychedelics, other research has documented spontaneous positive behavioural changes following psychedelic drug use (Teixeira et al., 2022). Similarly, Kähönen (2023) has discussed the concept of psychedelic experiences leading to a shift in one's personal values, as discussed by some of the participants, to becoming more self-transcendent through a process of "unselfing" whereby psychedelic states may assist in breaking down the egocentric perception of oneself as separate from the external world. However, this does not capture the shift towards a greater sense of personal responsibility and agency over their life that was described by participants within the current study.

Strengths and Limitations

At the time of writing, this study represented the first direct investigation into the qualitative, phenomenological aspect of individuals' experiences using short-acting

psychedelics in an attempt to manage their mental health. While previous studies have explored the qualitative experiences associated with these substances, they primarily focused on trip reports detailing the induced psychedelic experiences without contextualising them within the realm of mental health. Additionally, some studies have examined aspects of DMT experiences linked to mental health outcomes, with hypotheses suggesting that higher scores on measures like the Mystical Experiences Questionnaire (MEQ) during psychedelic trips may predict lasting therapeutic effects on mental health symptoms (Barsuglia et al., 2018). However, none of the prior studies have taken the approach of the current study, which utilised IPA to offer rich and detailed descriptions of participants' accounts regarding the DMT experiences and how they made sense of this in relation to their low mood. In this sense, the findings from this report are novel and provide a unique perspective of this area of research.

It should be noted, however, that this methodological approach is based upon ideographic principles and cannot make generalised, nomothetic claims about the experiences of individuals using DMT for psychotherapeutic purposes may encounter. Furthermore, this study was not designed around identifying or exploring whether short-acting psychedelics are efficacious as a substance that people can use for alleviating low mood, depression, or mental health difficulties more generally. Consequently, although as part of the study, the participants frequently provided their accounts of the perceived utility of short-acting psychedelics for themselves, as well as their subjective reasons for these outcomes, this study is not able to hypothesise about any mechanistic psychological processes that may contribute towards these effects. To establish generalised principles of subjective experiences of people using short-acting psychedelics for mental health, future studies could recruit greater numbers of participants. Furthermore, to establish the efficacy of these experiences for mental health outcomes -- including the safety profile of these drugs -- further clinical trials are necessary.

Furthermore, one of the unique components of this study was its emphasis on the anonymity and confidentiality of the participants. To do this, an anonymous, online text-based interview methodology was utilised. However, this approach introduces several limitations to the study's findings. Firstly, the text-based format of the interviews may have limited the richness of the data when compared to conventional, speech-based interviews that permit a more interactive dialogue, with greater room for elaboration. Moreover, in speech-based interviews a greater quantity of data can be gathered in the same duration of time. To mitigate this, a greater number of participants were recruited than would typically be for an IPA-based study of this nature. Secondly, because all the participants were recruited from online forums, data may be skewed towards people that are particularly interested in short-acting psychedelics than would be the average user of these substances. Additionally, due to the anonymity safeguards within the methodology, participants were not independently verified to confirm any diagnosis of depression but rather relied on their own testimony of these difficulties.

Another limitation of this study was the lack of demographic data collected from the participants. This decision was made to enhance anonymity for those involved, but it restricts the ability to contextualise the findings based on these factors. For instance, the study cannot account for differences that might exist between participants in terms of gender, age, nationality, and other demographic variables. Moreover, this limitation hinders the assessment of potential biases arising from shared demographic characteristics among the participants.

Further research may be able to build upon this study by conducting face-to-face interviews with participants who are recruited from more diverse sources, with data collected for basic demographic information from the participants. This will allow for a deeper exploration of the subjective experiences and nuances surrounding the use of short-acting

psychedelics for mental health purposes. Additionally, incorporating validated measures to assess mental health outcomes, such as standardised clinical assessments, could provide more robust evidence regarding the efficacy and safety of these substances in therapeutic contexts. Moreover, longitudinal studies tracking participants' experiences over time could offer insights of the long-term effects and sustainability of any observed benefits. By addressing these methodological considerations and expanding the scope of inquiry, future research has the potential to enhance our understanding of the role of short-acting psychedelics in the field of mental health beyond the current study.

Previous research has indicated that, unlike typical antidepressant medication, psychedelic drugs rely on their subjective effects for their proposed therapeutic benefits (Yaden et al., 2021). Furthermore, the subjective content of these experiences forms a central focus of psychedelic integration psychotherapy, an integral part of the psychedelic-assisted psychotherapy process (Bathje et al., 2022). This study contributes to existing literature as the first to investigate the types of subjective experiences individuals encounter when using short-acting psychedelics for mental health purposes. Consequently, the experiences documented in this study hold particular significance for future research into the effectiveness of short-acting psychedelics for these purposes, especially in the context of integration therapies for such drugs, with implications for possible clinical interventions in this field.

Conclusion

Overall, this study utilised an innovative methodology to explore a novel area (short-acting psychedelics) within a nascent area of research (psychedelic therapies). It explored the testimony of nine participants who have used these substances with the intention of helping with their low mood or depression, focusing on the qualitative, phenomenological components

of their experiences. Four key themes emerged: the journey to using DMT, revelation of insights, emotional healing, and personal growth through DMT use.

This study contributes to a deeper understanding of the complexities surrounding short-acting psychedelic approaches to mental health and its implications for mental well-being. However, further research in this area is necessary to understand the reliability of these findings as well as the safety, efficacy, and effectiveness of short-acting psychedelics.

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LITERATURE PRESS RELEASE

Unlocking the Therapeutic Potential of Short-Acting Psychedelics: A Groundbreaking Study

In recent years, the therapeutic promise of psychedelic drugs has captured widespread attention. While substances like LSD and psilocybin mushrooms have taken the spotlight, lesser-known short-acting psychedelics, such as Dimethyltryptamine (DMT), have remained in the shadows. However, a new study sheds light on the experiences of individuals who have turned to DMT as a potential treatment for mental health issues.

Initial investigations into DMT have revealed profound effects, including intense hallucinations and significant shifts in perception and self-awareness. Users commonly report encounters with otherworldly entities and experiences of ego dissolution. Surveys conducted online indicate that a notable proportion of DMT users are drawn to the substance by its purported mental health benefits. Preliminary clinical studies have shown promising results, with some participants reporting reductions in symptoms of depression following DMT use. Despite this growing interest, little research has explored how individuals with mental health concerns interpret their experiences with DMT.

In a pioneering study, researchers, led by Doctoral Researcher Ryan Little, delved into the subjective experiences of individuals using short-acting psychedelics, particularly DMT, to address issues of low mood and depression. Employing in-depth interviews and qualitative analysis, the study uncovered four primary themes among participants:

1. Journey to DMT for Mental Health: Participants embarked on their DMT journey after grappling with longstanding mental health issues that had proven resistant to conventional treatments. Dissatisfied with traditional approaches, they turned to psychedelic alternatives in search of relief.

2. Psychological and Spiritual Insights: DMT experiences revealed profound psychological and spiritual insights, often accompanied by encounters with entities or metaphorical hallucinations. Participants described these experiences as transformative and enlightening, offering new perspectives on their inner worlds.

3. Emotional Healing: Despite encountering discomfort during some sessions, participants reported experiencing emotional healing through DMT. Challenging experiences were viewed as integral to therapeutic progress, leading to profound shifts in emotional well-being.

4. Personal Growth: DMT facilitated personal growth, prompting behavioural changes, increased empathy, and a deeper connection with oneself and others. Participants expressed a heightened sense of agency and accountability over their lives, attributing these changes to their experiences with the substance.

This study represents a significant contribution to our understanding of the therapeutic potential of short-acting psychedelics in mental health treatment and integration therapies. By exploring the subjective experiences of individuals using DMT, it offers valuable insights that can inform future research and clinical interventions in the field of psychedelic-assisted therapy.

For more information, please contact Ryna Little, School of Psychology, University of Birmingham.

APPENDICIES

APPENDIX 1

Ethical Approval

UNIVERSITY OF BIRMINGHAM

Dear Dr Andrew Fox and Ryan Little

RE: Using Dimethyltryptamine (DMT) for Psychotherapeutic Purposes: A Phenomenological Analysis of Short-Acting Psychedelics for Low Mood and Depression

Application for Ethical Amendment: [redacted]

Thank you for your application for amendment to the above project, which was reviewed by the Science, Technology, Engineering and Mathematics committee.

On behalf of the Committee, I confirm that this amendment has full ethical approval.

Any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

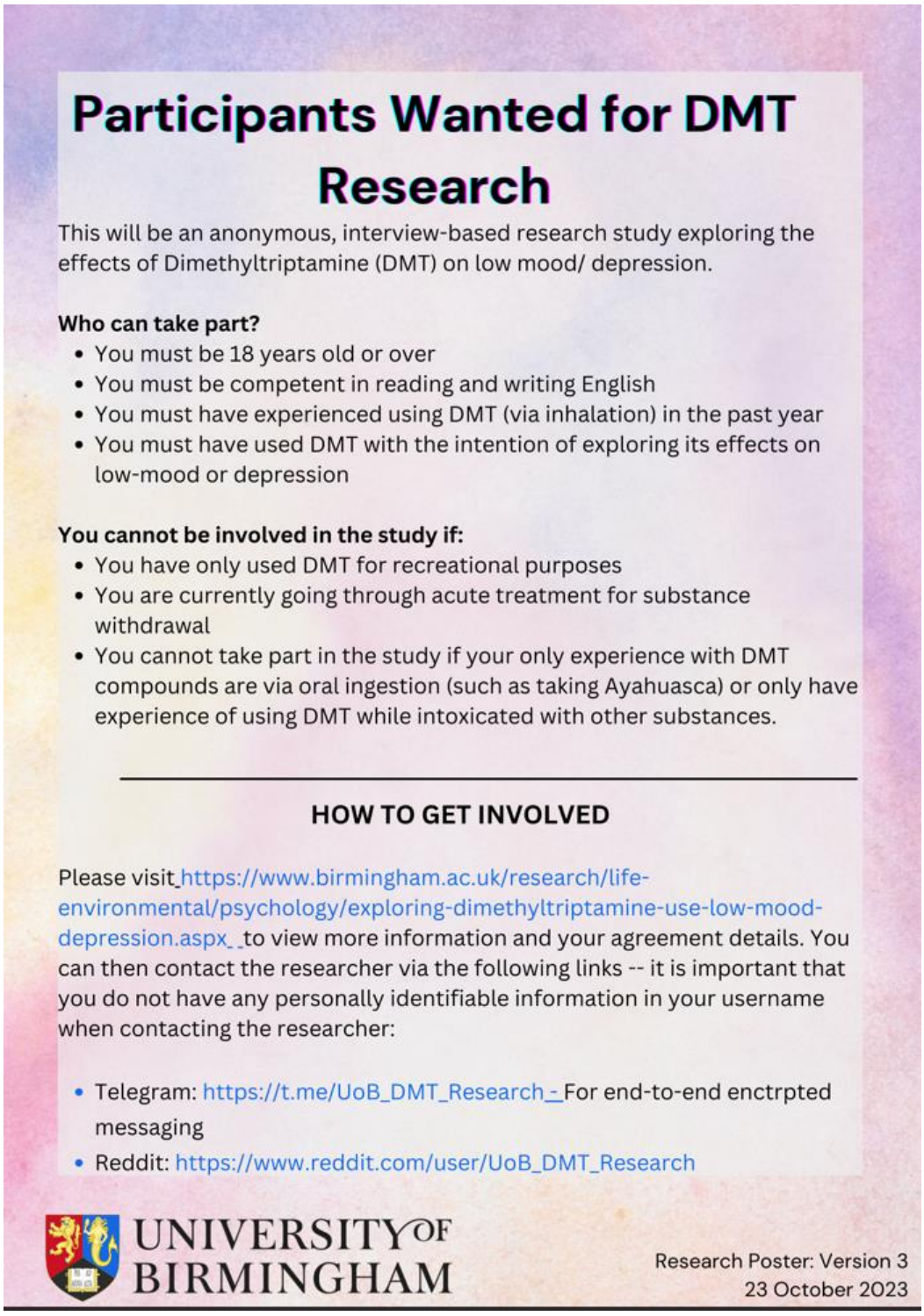
Kind regards,

The Co-Chairs of the Science, Technology, Engineering and Mathematics Committee

E-mail: [redacted]

APPENDIX 2

Research Advert



Participants Wanted for DMT Research

This will be an anonymous, interview-based research study exploring the effects of Dimethyltriptamine (DMT) on low mood/ depression.

Who can take part?

- You must be 18 years old or over
- You must be competent in reading and writing English
- You must have experienced using DMT (via inhalation) in the past year
- You must have used DMT with the intention of exploring its effects on low-mood or depression

You cannot be involved in the study if:

- You have only used DMT for recreational purposes
- You are currently going through acute treatment for substance withdrawal
- You cannot take part in the study if your only experience with DMT compounds are via oral ingestion (such as taking Ayahuasca) or only have experience of using DMT while intoxicated with other substances.

HOW TO GET INVOLVED

Please visit https://www.birmingham.ac.uk/research/life-environmental/psychology/exploring-dimethyltriptamine-use-low-mood-depression.aspx to view more information and your agreement details. You can then contact the researcher via the following links -- it is important that you do not have any personally identifiable information in your username when contacting the researcher:

- Telegram: https://t.me/UoB_DMT_Research - For end-to-end enctrpted messaging
- Reddit: https://www.reddit.com/user/UoB_DMT_Research

UNIVERSITY OF BIRMINGHAM

Research Poster: Version 3
23 October 2023

APPENDIX 3

Consent Form

UNIVERSITY OF BIRMINGHAM

Consent Form

Project Title: Using Dimethyltryptamine (DMT) for Psychotherapeutic Purposes: A Phenomenological Analysis of Short-Acting Psychedelics for Low Mood and Depression

Researcher: Ryan Little, Trainee Clinical Psychologist, University of Birmingham

1. I confirm that I have understood the participant information sheet for the above study and have had the opportunity to consider the information and ask questions.

2. I understand that this study is voluntary and I am free to withdraw at any time, up to two-weeks following the conclusion of the interview, without giving any reason.

3. I understand there are limitations to anonymity due to the study being conducted electronically and via the internet.

4. I understand that I am not to contact the researcher, or the University of Birmingham, in any other manner than via the end-to-end messaging platform.

5. I understand that when contacting the researcher, I must do so with a username that does not identify me.

6. I understand that following the interview, I have a two-weeks within which I may contact the researcher and withdraw my data without giving any reason.

7. I understand that after the two-week opt-out period has passed, my username will be replaced with a made-up identifier and I will no longer be able to withdraw my data.

8. I understand the data from this study will be reviewed by the researcher and academic supervisors at the University of Birmingham to ensure the analysis is a reasonable representation of the data.

9. I understand that verbatim quotes from the interview may be published in a write-up of the data, but no identifiable information will be attached to such quotes.

10. I agree that I meet the eligibility criteria outlined in the participant information sheet.

Please declare in your contact with the researcher on the forum-specific or encrypted messaging software that you consent to all of the following items and agree to take part in the study.

If you would like to speak via encrypted messaging (Telegram), please use the following link https://t.me/UoB_DMT_Research

APPENDIX 4

Participant Information Sheet

Participant Information Sheet

Study Title

Using Dimethyltryptamine (DMT) for Psychotherapeutic Purposes: A Phenomenological Analysis of Short-Acting Psychedelics for Low Mood and Depression

Summary of Aims

The aim of this study is to investigate people's experiences of using DMT for the purposes of helping with depression. It will explore your experiences before, during and after using the drug, how you made sense of these experiences, and whether you feel this was associated with any changes in your mental health.

The study will consist of anonymous text-based interviews that will be conducted on forum-specific messaging software or an end-to-end encrypted messaging application. By participating in this research, you will be contributing towards the currently small, but rapidly growing area of research into DMT.

Background

Research into the effects of classic psychedelic drugs have recently begun to be published looking into their effects on mental health. DMT is a short-acting substance within this category of drugs that has been reported to induce similar experiences to other, longer-lasting psychedelics. However, compared to other psychedelics there are relatively few studies investigating DMT.

Who can be involved?

To be involved in the study you must:

- Be aged 18 years old or over
- Be competent in reading and writing English
- Have experienced using DMT (via inhalation) at some point in the past year
- Have used DMT with the intention of exploring its effects on your own low mood or depression

You cannot be involved in the study if:

- You have only used DMT for recreational purposes
- You are currently going through acute treatment for substance withdrawal
- Your only experience with DMT compounds is via oral ingestion (such as taking Ayahuasca) or only have experience of using DMT while intoxicated with other substances.

What would taking part in the study involve?

By participating in the study, you will be interviewed via forum-specific messaging software or, if you choose, an end-to-end encrypted messaging application. After reading this document and the consent form, you may contact the researcher via the links within the advert. It is important for your safety that when contacting the researcher you do not disclose any identifiable information about yourself, either within the interview or from your username on the messaging platform. By using this messaging platform, the content of the interview will only be visible to the researcher and yourself and will be deleted for both parties within two weeks of the interview being completed.

Once you have contacted the research on the messaging application, you will be asked to confirm that you have read this information sheet and the consent form and agree to the points outlined within the form.

The interview will ask questions about your experiences leading up to using the drug, your experiences while using the drug and how you have made sense of these experiences since that time. There will also be some questions relating to your mental health and how you feel DMT may have impacted upon this. The questions will not be asking about any trauma that you may have experienced in your life, where or how you acquired the drug, or any information that would make you identifiable. The interview is expected to take roughly 1 hour but will be flexible.

Further Information

What control do you have over the information that you provide?

During the interview, you are free to opt-out at any time without the need to provide a reason. All information collected during the interview up to that point will be permanently deleted and no further data collected.

Following the interview, you will have a two-week window during which you will be able to contact the researcher and withdraw your interview without providing any reason. If you choose to withdraw during this two-week window, all of the data collected from you will be permanently deleted from the record. Following this, you information will be deleted from the messaging app, stored separately and anonymously. Therefore, after the two-week window has elapsed, you will no longer be able to withdraw your data from the study.

How will anonymity and confidentiality be maintained?

For your own safety, it is important that you remain anonymous throughout the process. This means that the researcher should not know your name or contact details at any point. Instead, you will be allocated a random identifier and referred to by a pseudonym within the write-up of the study.

The data will be reviewed by the researcher as well as academic supervisors at the university to ensure that any analysis is a fair representation of the data. Anonymised data may also be looked at by other students and Trainees as part of analysis and training.

A data management plan will be adhered to ensure that your information is kept confidential and safe.

However, it should be noted that despite all of the above, there may still be limitations in confidentiality and anonymity that are difficult to avert due to the study being conducted electronically and via the internet.

All data will be kept in accordance with the Data Protection Act (2018)

What will happen after the study?

Your data will be used as part of a doctorate thesis. Some verbatim quotes may be used within the write up. However, no identifiable information will be presented and your data will be referred to by a pseudonym within the thesis. The final thesis will be kept within an archive at the University of Birmingham library. The data may be used for publishing in journal articles based on the findings of the study and again, this will not include any identifiable information but will use quotes.

Duty of Care

Due to the nature of the interview, it is possible that sensitive topics may arise that you could find distressing, or other issues related to risks you may disclose to the researcher.

As the research will be recruiting participants globally and anonymously, support will not be able to be provided to you by the researcher. Moreover, the researcher will not be able to direct you to any specialist support services. You should therefore be aware of what services (such as emergency services) you can contact prior to your involvement in the study. Moreover, any advice regarding DMT, its effects or medical issues will not be able to be provided during the interview.

Statement of Ethical Approval

Prior to being conducted, this study has been reviewed and granted approval by the University of Birmingham's Science, Technology, Engineering, and Mathematics Ethics Committee.

Further Information

The research is being funded by the University of Birmingham and organised by the researcher

Lead Researcher

Ryan Little, Trainee Clinical Psychologist, University of Birmingham.

- Contact via email on [redacted]
- Or contact securely via telegram at https://t.me/UoB_DMT_Research

Supervisors

Andrew Fox, Assistant Professor, University of Birmingham

Alexandre Copello, Honorary Professor of Addiction Research, University of Birmingham

Rebecca Ryan, Honorary Research Fellow, University of Birmingham

APPENDIX 5

Script for Confirming Consent with Participants

Script for Initial Contact with Potential Participants

Opening statement:

> "Hi, thank you for registering your interest in the DMT research. Can you please advise me at to whether you have read the information and consent form already?"

If no:

> **"***That is fine. Can you please take a look at the study information form and research agreement using the following link [insert link to information sheet and consent form]."*

If Yes (once they have confirmed they have read the documents):

> "Great, thank you for that. Before I enlist you as a participant in the study can you please conform that you agree to the following:

1. I confirm that I have understood the participant information sheet for the above study and have had the opportunity to consider the information and ask questions.

2. I understand that this study is voluntary and I am free to withdraw at any time, up to two-weeks following the conclusion of the interview, without giving any reason.

3. I understand there are limitations to anonymity due to the study being conducted electronically and via the internet.

4. I understand that I am not to contact the researcher, or the University of Birmingham, in any other manner than via the end-to-end messaging platform.

5. I understand that when contacting the researcher, I must do so with a username that does not identify me.

6. I understand that following the interview, I have a two-weeks within which I may contact the researcher and withdraw my data without giving any reason.

7. I understand that after the two-week opt-out period has passed, my username will be replaced with a made-up identifier and I will no longer be able to withdraw my data.

8. I understand the data from this study will be reviewed by the researcher and academic supervisors at the University of Birmingham to ensure the analysis is a reasonable representation of the data.

9. I understand that verbatim quotes from the interview may be published in a write-up of the data, but no identifiable information will be attached to such quotes.

10. I agree that I meet the eligibility criteria outlined in the participant information sheet."

If they consent to the above:

Confirm that they can take part in the study and proceed to made agreement for further contact or to arrange a date and time to complete the interview

If they do not consent:

Kindly inform participant they in order to become a participant in the study they must meet the inclusion/exclusion criteria and agree to all of the points in the consent form.

APPENDIX 6

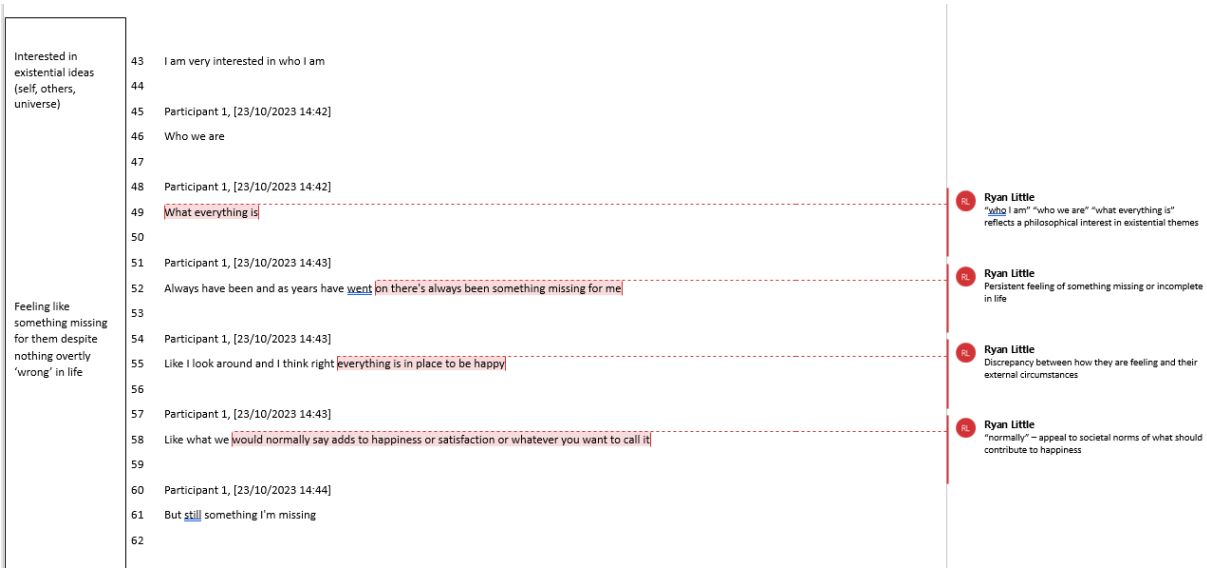
Interview Schedule

Semi-structured question topics

1. What can you tell me about how you first learned about DMT?
2. Could you know the type of DMT you have used?
3. How would you describe your experiences with low mood? How long have you been dealing with this?
4. What led you to try using DMT to help with your low mood/depression?
5. What were you hoping to achieve by using DMT to address your low mood/depression?
6. Could you describe your experiences using DMT to address your low mood/depression?
7. What effects, positive and/or negative, have you noticed since using DMT to address your low mood/depression? If so, could you describe them?
    a. Anything harmful or beneficial…
8. In terms of your experiences while using doing DMT did you experience anything significant in relation to your wellbeing and mental health
9. How did you make sense of your experiences on DMT after the 'trip' [use their language]?
10. How have your experiences using DMT changed over time, if at all?
11. Is there anything else you would like to share about your experiences with DMT and low mood/depression?

APPENDIX 7

Example of Initial Note Taking



APPENDIX 8

Example of Generating Personal Experiential Statements

#	Personal Experiential Statement (PESs)	Quote	Line Numbe
1	Long term interest prior to taking	watched the dmt spirit mole	35
2	Strong Initial Interest	"was really interested in it",	35, 127-128
3	Not much information initially	as there wasn't that much in	36
4	Interested in existential ideas (self, others, universe)	I am very interested in who	43-49
5	Feeling like something missing despite nothing overtly 'wrong'	there's always been someth	55-65
6	Shocked at finding out they could get DMT followed by extensiv	point I was in shock because	68-72
7	Extensive research through different sources	watched every documentary	84-86
8	Aware of type of DMT (N,N)	NN.DMT	92
9	Feeling like they had the "ingredients" for happy life	I had all the ingredients for h	102
10	A change in their mental state to feel like there is no longer som	I know longer feel like that .	111-112
11	Stopped searching for the answer "to their happiness"	...but yeah as far as I'm conc	113-114
12	Have found the answers they were looking for (why they are not	.....the first time I felt like th	113-114
13	Lifelong seach for existential questions	I've just always known that t	126-127
14	Initial disbelief about reports of how DMT has helped others	.....how could they possible	128-130
15	Desire for a teaching expereince via DMT	I have to try this I have to se	130
16	Lack of confidence in conventional treatments	through my experience of w	144-145
17	DMT as a catalyst for change in their life	as I said it has helped me fill	154-154
18	DMT allowed them to accept themself and their feelings	Dmt for me let me know tha	157-159
19	Important messages communicated during trips via entities	I think in my case personally	167
20	Entities that they encountered showing them that they do not n	And now I'm going to sound	188-194
21	A sense of "inner knowing" conributes to a consistency across tr	I have lots of trips where I've	206-209
22	A feeling that what they are saying sounds unbeleivable	Forgive if I sound crazy	240
23	The experiences have turned their life around	This has turned my whole er	236-237
24	"Beings" having a temprement and behaviour that conveys mea	The jesters and clowns are p	246-259
25	mind	There are existences upon e	269-270
26	A feeling of new inner peace that is always with them now	I have an inner peace now th	270-271
27	A new realisation that there is something bigger than oneself, b	dmt has shown me "hello oc	287-300
28	A progression of experiences which has culminated in a spiritual	....in the beginning I just saw	317-320
29	Experiences with bad entities associated with feeling of infinite	I have also been in some ter	325-327
30	Changes me permanently for the better	....dmt can be a very very cha	328-329
31	You find thing out about yourself that you may not want to face	Negatives would be and I do	339-340
32	DMT expanded empathy, leading to a shift from judgment to co	maybe before dmt I don't ev	350-352
33	DMT experience clarifying values already held	I kinda already knew this but	363-369
34	Uncomfortable process of unlearning and relearning	It unlearn you of everything	378-381
35	Cannot go back to being how you were before taking DMT	Once you have woken up an	408-411
36	Want it to be explored further	but it's shown me so much a	429
37	Feeling like DMT experiences are as real as normal world	as far as I am concerned dmt	429-450

APPENDIX 9

Example of Generating Personal Experiential Themes from Personal Experiential Statements

PETs	Quotes	Line Number
Initial Fascination and Curiosity with DMT		
Long term interest prior to taking	*watched the dmt spirit molecule documenta*	*35*
Strong Initial Interest	*"was really interested in it", "everything I ha*	*35, 127-128*
Not much information initially	*as there wasn't that much information on it*	*36*
Shocked at finding out they could get DMT fo	*point I was in shock because I just thought i*	*68-72*
Extensive research through different sources	*watched every documentary...different web*	*84-86*
Search for Meaning of Existential Questions		
Interested in existential ideas (self, others, u	*I am very interested in who I am...who we ar*	*43-49*
Lifelong seach for existential questions	*I've just always known that this world is not*	*126-127*
Desire for a teaching expereince via DMT	*I have to try this I have to see it for myself ar*	*130*
A progression of experiences which has culm	*....in the beginning I just saw shapes....so I d*	*317-320*
Emotional Void Prior to DMT use		
Feeling like something missing despite noth	*there's always been something missing for r*	*55-65*
Feeling like they had the "ingredients" for ha	*I had all the ingredients for happy life*	*102*
Finding Fulfulment through DMT		
A change in their mental state to feel like the	*I know longer feel like that ...there isn't anyt*	*111-112*
Stopped searching for the answer "to their h	*...but yeah as far as I'm concerned that has*	*113-114*
Have found the answers they were looking fo	*.....the first time I felt like that feeling of why*	*113-114*
Integration and Acceptance of DMT Insights		
DMT allowed them to accept themself and th	*Dmt for me let me know that I am great as I*	157-159
Important messages communicated during tr	*I think in my case personally...Its what and w*	*167*
Entities that they encountered showing them	*And now I'm going to sound crazy but I have*	*188-194*
Lessons about suffering being temporary and	*There are existences upon existences and ev*	*269-270*
A new realisation that there is something big	*dmt has shown me "hello oo wake wake du*	*287-300*
Permanent Self Growth via DMT Experiences		
DMT as a catalyst for change in their life	*as I said it has helped me fill that missing pie*	154-154
The experiences have turned their life aroun	*This has turned my whole entire life around.*	*236-237*
Changes me permanently for the better	*....dmt can be a very very challenging experi*	*328-329*
Cannot go back to being how you were befor	*Once you have woken up and your consciou*	*408-411*
Want it to be explored further	*but it's shown me so much and it definitely n*	*429*
DMT expanded empathy, leading to a shift fo	maybe before dmt I don't even think I just g	350-352
A feeling of new inner peace that is always w	*I have an inner peace now that never goes..*	*270-271*
Unfomfortable self discovery		
A sense of "inner knowing" conributes to a c	*I have lots of trips where I've forgotten alot*	*206-209*
A feeling that what they are saying sounds u	*Forgive if I sound crazy*	*240*
You find thing out about yourself that you ma	*Negatives would be and I don't know if it is o*	*339-340*
DMT experience clarifying values already hel	*I kinda already knew this but dmt confirms o*	*363-369*
Uncomfortable process of unlearning and rel	*It unlearn you of everything you have learne*	*378-381*

APPENDIX 10

Example of Generating Group Experiential Themes from Personal Experiential Themes

Participant 1	Participant 2	Participant 3	Par
Initial Fascination and Curiosity with DMT	Initial Fascination and Expectations	Exploration and Discovery with Psychedelics	Lon Exp The
Search for Meaning of Existential Questions	Hope and Intentions for Therapeutic Transformation Beyond Conventional Treatment	Relationship Between Naturalness and Trust	DM Per
Emotional Void Prior to DMT use	Intense but temporary emotion improvements	Importance of Relationships with Others	Inte Imp Exp
Finding Fulfulment through DMT	Insights that were only temporary	Emotional Insights and relief via DMT trips	Cha Bel
Integration and Acceptance of DMT Insights	Physical and Cognitive Side Effects	DMT as a Catalyst for Personal Responsibility and Behaviour Change	Res Acc
Permanent Self Growth via DMT Experiences		Enduring Emotional Change	Des Acc
Unfomfortable self discovery		Evolution and Control of DMT Experiences	
Journey to DMT			
Curiosity and Fascination about DMT	Struggle with conventional MH treamtent		
Insights			
Emotional Intensity and Healing			
Personal Growth			