***“They could be in the raptures of hell…”***

# Exploring Therapist Perceptions of Distress in Psychedelic-Assisted Therapy

Conor Coman

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## THESIS PORTFOLIO: CANDIDATE DECLARATION

| **Title of degree programme** | Professional Doctorate in Clinical Psychology |
|---|---|
| **Candidate name** | Conor Coman |
| **Registration number** | 21026151 |
| **Initial date of registration** | 17th September 2021 |

| **Declaration and signature of candidate** |
|---|
| • I confirm that the thesis submitted is the outcome of work that I have undertaken during my programme of study, and except where explicitly stated, it is all my own work.<br>• I confirm that the decision to submit this thesis is my own.<br>• I confirm that except where explicitly stated, the work has not been submitted for another academic award.<br>• I confirm that the work has been conducted ethically and that I have maintained the anonymity of research participants at all times within the thesis.<br><br>Signed: Date: 20/09/2024 |

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Finally, Dad. At a remote Neolithic tomb in the Boyne Valley in December 2016, you reminded me I was “well able” when I needed to hear it the most. That was the catalyst for this pursuit so this work is dedicated to you.

## Thesis Abstract

This thesis focuses on two topics in the realm of psychedelic assisted therapy.

The first section of the portfolio is a literature review of the existing research on the impact of sex/gender on outcomes in psychedelic assisted therapy and examines potential methodological barriers hindering the exploration of these differences. Despite growing interest in psychedelic-assisted therapy for psychological and substance misuse issues, research on the impact of sex/gender on treatment outcomes is limited. A systematic review of 13 studies found that six explored sex/gender differences, with mixed results. Unbalanced sampling was the most common methodological limitation. The influence of sex/gender in psychedelic therapy remains underexplored, highlighting the need for improved research designs and strategies to better assess this variable in future studies.

The second section of this portfolio outlines the results of an empirical paper, qualitatively exploring the therapist's perceptions of participant distress in psychedelic assisted therapy. This study interviewed 12 experienced PAT therapists to explore their perceptions of distress. Reflexive thematic analysis identified three themes: "Making Sense of Distress," "Therapist as the Safe Base," and "Navigating Distress." Findings reveal that distress in PAT can be intense and can lead to both positive and negative outcomes. It may also be an internal process, which can be challenging for therapists to detect. A trusting relationship between therapist and participant is crucial. The study emphasises refining non-directive approaches, improving therapist training, and addressing ethical concerns, contributing to a deeper understanding of distress in PAT.

The third section of this portfolio comprises an executive summary of the empirical paper. It is intended for distribution to psychedelic-assisted therapists, as well as individuals with an interest in research related to psychedelic-assisted therapy.

# Paper one: Literature Review

**Sex/Gender in Psychedelic-Assisted Therapy Research: A review of outcomes, design and implementation**

**Word count:**

**7897**

***This paper has been written in accordance with submission guidelines for The Journal of Psychoactive Drugs (Appendix A). Please note, there have been slight deviations from the guidelines in this version to ensure adherence to thesis requirements.***

## Abstract

Despite the growing interest in investigating the safety and efficacy of psychedelic-assisted therapy for addressing psychological and substance misuse challenges, there is a gap in research regarding the potential impact of sex/gender on treatment outcomes. A systematic review of existing psychedelic studies was conducted to assess variations in treatment outcomes based on sex/gender and to examine potential methodological barriers hindering the exploration of these differences. Out of the 13 studies meeting the comprehensive review criteria, six studies explored variations in outcomes, yielding mixed results. The most prevalent design limitation hindering the effective exploration of outcome differences was unbalanced sampling. The influence of sex/gender on treatment outcomes in psychedelic-assisted therapy remains an underexplored aspect of research. Addressing this crucial question necessitates a focus on refining research design and implementation strategies.

KEYWORDS: Psychedelic-assisted therapy, sex differences, gender differences, research design, sampling strategies

## Introduction

### *What is Psychedelic-Assisted Therapy?*

Psychedelica-assisted therapy (PAT) can be defined as the professionally supervised use of MDMA, psilocybin, LSD, ibogaine and other psychedelic compounds as part of elaborated psychotherapy programs (Schenberg 2018). PAT is showing considerable therapeutic potential with some proponents describing it as potentially paradigm-shifting (Schenberg 2018). In recent years, interest has been resurgent in the use of psychedelics focusing on PAT (Carhart-Harris and Goodwin 2017).

### *PAT as an Emerging Treatment for Psychological Distress*

While research is still preliminary and should be viewed as such, reviews indicate promising results for several mental health conditions including, depression, end-of-life anxiety, obsessive-compulsive disorder and substance misuse (including smoking cessation) and post-traumatic stress disorder (Wheeler and Dyer 2020; Cavarra et al. 2022). Follow-up studies indicate that these benefits are lasting (Jerome et al. 2020; Johnson, Garcia-Romeu and Griffiths 2017). Large-scale epidemiological surveys suggest that many who use psychedelics recreationally experience benefits to their well-being. Finally, experimental studies using healthy volunteers have demonstrated an association between these compounds and increased psychological well-being and openness to experience (Erritzoe et al. 2019). The mechanistic action of PAT using classic psychedelics appears to be the attainment of an altered state of

consciousness, often described as a 'mystical experience' (Kangaslampi 2023) in which the self of sense is dramatically altered (Nour et al. 2016).

### *Why study sex/gender[1] differences in mental health research?*

There are calls for more understanding of sex and gender in the context of health research due to potential implications for the safety and effectiveness of treatments. Gahagan, Gray and Whynacht (2015) describe a "growing recognition" of the importance of including sex and gender considerations in health research, positing that this bolsters the evidence base, allows tailoring of care to individuals, specifies health policy and facilitates equity in care. Cavanaugh and Hussein (2020) extend the importance of gender and sex considerations to psychological research, arguing that its absence affects replicability and can put women, in particular, at risk from adverse effects of pharmaceuticals. Zucker and Prendergast (2020) suggest that prescribing equal drug doses to men and women in clinical trials risks overmedicating women and potentially contributing to adverse drug reactions. Women are twice as likely to experience adverse drug reactions as men, consistently manifesting as elevated blood concentrations and longer elimination times of drugs which are unrelated to differences in body weight (Zucker and Prendergast, 2020). The proposed Sex and Gender Equity in Research guidelines (Heidari et al. 2016) recommend that researchers report whether sex/gender differences are anticipated and provide planned sex and gender-based analyses of data within research design.

Concerning psychological interventions, there is a mixed picture of whether there are differences in outcomes between sex/gender and it is an under-researched area (Liddon, Kingerlee and Barry 2018; Parker, Blanch and Crawford 2011). There is some limited evidence to suggest gender differences in outcomes (Ogrodniczuk 2006), including that women benefit more from psychotherapy for PTSD than men (Békés et al. 2016; Stefanovics and Rosenheck 2020; Gross et al. 2023). There is evidence to indicate that, on average, men and women demonstrate psychological distress differently, (Tamres, Janicki and Helgeson, 2002). Male responses to distress are often described as externalising in nature i.e. expressed

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[1] The term sex refers to "the biological, genetic, and physiological processes related to sexual beings." Gender refers to "the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. Gender refers to "the roles, relationships, and relative power that people relate to or societies generally attribute to women and men, irrespective of their genetic make-up." (Jäncke 2018). As these terms are sometimes incorrectly used interchangeably within research (Gogover 2021; Gahagan et al. 2015), both terms will be investigated for the purposes of this review. For the purposes of this review, the term sex/gender will be used given the manner in which the terms are used interchangeably within research and the difficulties in disentangling their effects on outcomes (Jäncke 2018; Franconi et al. 2019).

outwardly (Sagar-Ouriaghli et al. 2019) through substance misuse, irritability and aggression (Angst et al. 2002). In contrasts, women are represented as more likely to experience internalising disorders (pathologies of subjectively experienced negative emotion) e.g. depression (Kessler 2005; Kornstein et al. 2000) and eating disorders (Van Eeden, Van Hoeken and Hoek 2021). Research should carefully consider these differences when exploring relative efficacy, due to the fiscal and ethical considerations of therapeutic prescribing.

Sex/gender are relevant when considering accessibility to services (Morison, Trigeorgis and John 2014). Men have been shown to have difficulties accessing mental health services (Sagar-Ouriaghli et al. 2019), holding more negative attitudes towards mental health services than women (Addis and Mahalik 2003, Yousaf, Popat and Hunter 2015) and adhere less to mental health treatment (Tibubos et al. 2021). Males are more likely to have negative attitudes toward seeking mental health support (Gonzalez et al. 2011) and surveys reflect a belief that there is a lack of "male-sensitive" psychological treatment options (Liddon, Kingerlee and Barry 2018). These attitudes are reflected in service use, with women in the UK 1.5 times more likely to receive mental health support in the form of medication or therapy, even when controlling for prevalence rates of mental health difficulties (Sagar-Ouriaghli et al. 2019; McManus et al. 2016). The importance of men accessing mental health services is clear. Suicide rates are consistently higher among males than females, with males 3.5 times more likely to complete suicide than females (Chang, Yip and Chen 2019) and more likely to engage in clinically significant substance misuse (National Institute of Health, 2020).

Psychedelics could challenge traditional barriers to engagement from men with mental health services due to an apparent existing interest from this population with rates of lifetime use of psychedelics greater in males than females (Krebs and Johansen 2013). Previous epidemiological research indicates disproportionately higher psychedelic use among males (Davis et al. 2022) and male mental health service users (Corrigan et al. 2022). While many internet surveys exploring psychedelic experiences are male-dominated (Palmer and Maynard 2022; Haijen et al. 2018), this could bias our emerging understanding of psychedelic experiences in favour of males. However, such findings offer encouraging evidence that psychedelics may be a potential tool to engage a cohort that services have traditionally found difficult to reach.

### *Sex/Gender in psychedelic research*

There are some noteworthy findings in qualitative studies of PAT relating to sex/gender. In a randomised controlled trial for treatment-resistant depression, Watts et al. (2017) described how some male participants achieved insight into how social expectations of gender norms i.e. masculinity had narrowed their emotional range, one participant reported he *"had always found it difficult to be emotional, found it uncomfortable to be around other people if they were emotional"* and saw *"emotions as weakness."* This participant described how, as a child, his parents had told him that *"boys don't cry,"* and as he matured, he had learned to *"put his feelings in a box because you can't be upset, you're a man."* In a smoking cession trial, Noorani et al. (2018) reported interesting gender-related findings. It was identified that all five of the female participants in the trial reported psilocybin occasioned insights into self-identity whereas this phenomenon was only reported in two out of the seven male participants. Furthermore, in this trial all those who expressed an openness to further psilocybin experiences were male. Finally, in a randomised control trial targeting social anxiety in autistic adults conducted by Danforth et al. (2018), two participants reported feeling more at ease with expressing and exploring their gender identities.

There has been some attention given to sex/gender differences in the subjective effects of psychedelics. A large-scale internet survey investigating adverse events after using ayahuasca in a ceremonial setting, Bouso et al. (2022) identified being female as predictive of negative mental health outcomes. Liechti, Gamma and Vollenweider (2001) and Pardo-Lozano et al. (2012) examined gender differences in the subjective effects of MDMA and found that women experienced more intense psychoactive effects than men in the form of perceptual changes, thought disturbances, and fear of loss of body control. They also found that acute adverse effects were more common in females than males. Furthermore, Verheyden et al. (2002) found that female MDMA users reported greater depression in the days following MDMA ingestion.

Studerus et al. (2012) and Garcia-Romeu et al. (2021) conducted studies examining the effects of psilocybin and reported no discernible sex/gender differences. However, Garcia-Romeu et al. (2021) observed that women exhibited higher scores on the self-reported Challenging Experiences scale (Barrett et al. 2016). Challenging experience is a term used to describe acute negative psychological responses during a psychedelic encounter, including fear, panic, paranoia, depressed mood, anger, confusion, dissociation, depersonalization, and physiological symptoms. Barrett et al. (2016) specifically noted slightly higher scores among

women on the "fear" subscale of the Challenging Experiences questionnaire. Notably, during the development of the Challenging Experiences questionnaire via internet survey concerning psilocybin use, all individuals who reported enduring and impairing psychotic symptoms as a consequence of psychedelic consumption were male (Carbonaro et al. 2015).

Recent advancements in neuroimaging, particularly the utilization of deep learning models (AI), as demonstrated by Ryali et al. (2024), have provided insights into structural disparities within the male and female brain. Notably, these disparities encompass regions such as the Default Mode Network (DMN), which is implicated in self-referential thought processes. The DMN holds particular significance in the context of psychedelic research, as it is hypothesized to be intricately involved in the neural mechanisms underlying psychedelic experiences (Gatuso et al. 2023; Barnett et al. 2020; Carhart-Harris et al. 2014). Should divergent structural characteristics exist within the DMN between genders, this could potentially influence how individuals experience PAT.

Notwithstanding the above findings, gender considerations are notably scarce in psychedelic research development and literature (Gukasyan and Narayan 2022). Most research relating to gender in the realm of psychedelics has related to physiological/biological differences in response to the compound being used and dosing, although, this research is limited. Given the potential for adverse lasting effects of psychedelic experiences, along with evidence of greater acute adverse effects of MDMA on females, the question of sex/gender differences in psychedelic therapy warrants closer examination.

### *Aims*

Given the diverse findings on the effects of sex and gender on psychedelic experiences, the potential for divergent outcomes in PAT exists. This study aimed to systematically review PAT studies, focusing on those that investigated and documented the potential influence of sex and gender on therapy outcomes. The review aims to elucidate the current understanding of sex and gender-specific outcomes, assess whether researchers consider these factors in study design, and evaluate if results relating to sex and gender are reported accordingly. Additionally, the study will appraise the methodological quality of research exploring sex and gender differences to scrutinize the validity of reported distinctions.

### *Research Questions:*

1. Do therapeutic outcomes differ between sexes/genders in PAT studies, and is there an exploration into the reasons behind any observed differences?
2. Are there considerations in research design and implementation that may hinder the effective investigation of divergent outcomes related to sex/gender?
3. What is the methodological quality of the studies that examine the role of sex/gender or refer to it in design/analysis?

## Methods

### *Criteria for study inclusion*

*Inclusion criteria:*

- Studies using quantitative randomised controlled designs, quantitative non-randomised designs, quantitative descriptive studies and mixed methods studies
- Studies that use LSD, DMT/ayahuasca, psilocybin, ibogaine, mescaline/peyote or MDMA.
- Adult participants with a mental health diagnosis including substance misuse (may include a healthy control group).
- Studies that refer to sex and/or gender in their design or analysis.
- Studies published in a peer-reviewed journal.
- Studies that include psychological therapy to support psychedelic dosing.

*Exclusion criteria:*

- Studies using animals.
- Studies in a language other than English.
- Studies that focus on micro-dosing psychedelics. Micro-dosing refers to the use of low sub-perceptual doses of psychedelics which are usually self-administered (Hutten et al. 2019).
- Single case studies, studies that don't list male and female participant numbers in their demographics.
- Studies published prior to 1990 due to the challenges of women being routinely excluded from research trials at this time (Pinn 2003) and different conceptualisations of mental health conditions and the language used to describe mental illness (Johansen et al. 2022).

- A recent review examining sex differences in outcomes in the use of ketamine for mood disorders concluded that there were few significant differences (Benitah et al. 2022). As such ketamine was excluded from this review and the search.
- Furthermore, cannabis, which is argued by some to have psychedelic properties, was also excluded from the review.

*Population*

This review focused on participants in studies of PAT. To be included in the review, studies must have collected data, or commented on sex/gender, in their methods, analyses or discussion.

*Intervention*

Studies reported on and discussed using a psychedelic (psilocybin, LSD, DMT/ayahuasca, mescaline/peyote or MDMA) in conjunction with talking therapy.

*Comparison*

Male/female/other, men/women/other.

*Outcome*

Outcomes of PAT and whether there are sex/gender-related differences. Methodological issues in PAT relating to sex/gender.

### ***Procedures***

#### *Search strategy*

A search of the literature on psychedelic-assisted psychotherapy was conducted using PubMed and PsycINFO with the following search terms: (*psychedelic* OR *hallucinogen* OR *entheogen* OR *lysergic acid diethylamide [LSD]* OR *LSD* OR *dimethyltryptamine* OR *DMT* OR *psilocybin* OR *ayahuasca* OR *3,4-Methylenedioxy methamphetamine [MDMA]* OR *MDMA* OR *ibogaine*) AND (*psychedelic-assisted psychotherapy* OR *-assisted psychotherapy* OR *psychotherapy* OR *mental health* OR *psychology* OR *therapeutic* OR *therapy* AND *sex* OR *gender).* The search terms “sex” and “gender” were removed however due to the lack of relevant results. Given that sex/gender differences in psychedelic therapy is an under-researched area, it was clear that there was an absence of articles that addressed the research question directly.

Articles deemed suitable for screening were read closely and internally searched for the following individual keywords: “sex”, “gender”, “male”, “female”, “man”, “woman.” “men” “women” Relevant results were then noted.

The following limits were added to the search:

PsychInfo: Published between 1990-2023, English language, adults, quantitative, follow-up, clinical trial, prospective, retrospective, treatment outcome, human

PubMed: Published between 1990 - 2023, clinical study, clinical trial, RCT, humans, adult.

PRISMA guidelines were followed (Page et al. 2021). *Figure 1* shows the PRISMA flow diagram reflecting the number of studies identified, screened and reviewed as eligible, and included in this review.

To control for the risk of publication bias, a search was carried out on the Dart.en search engine of electronic theses exploring the research question.

### *Quality Appraisal*

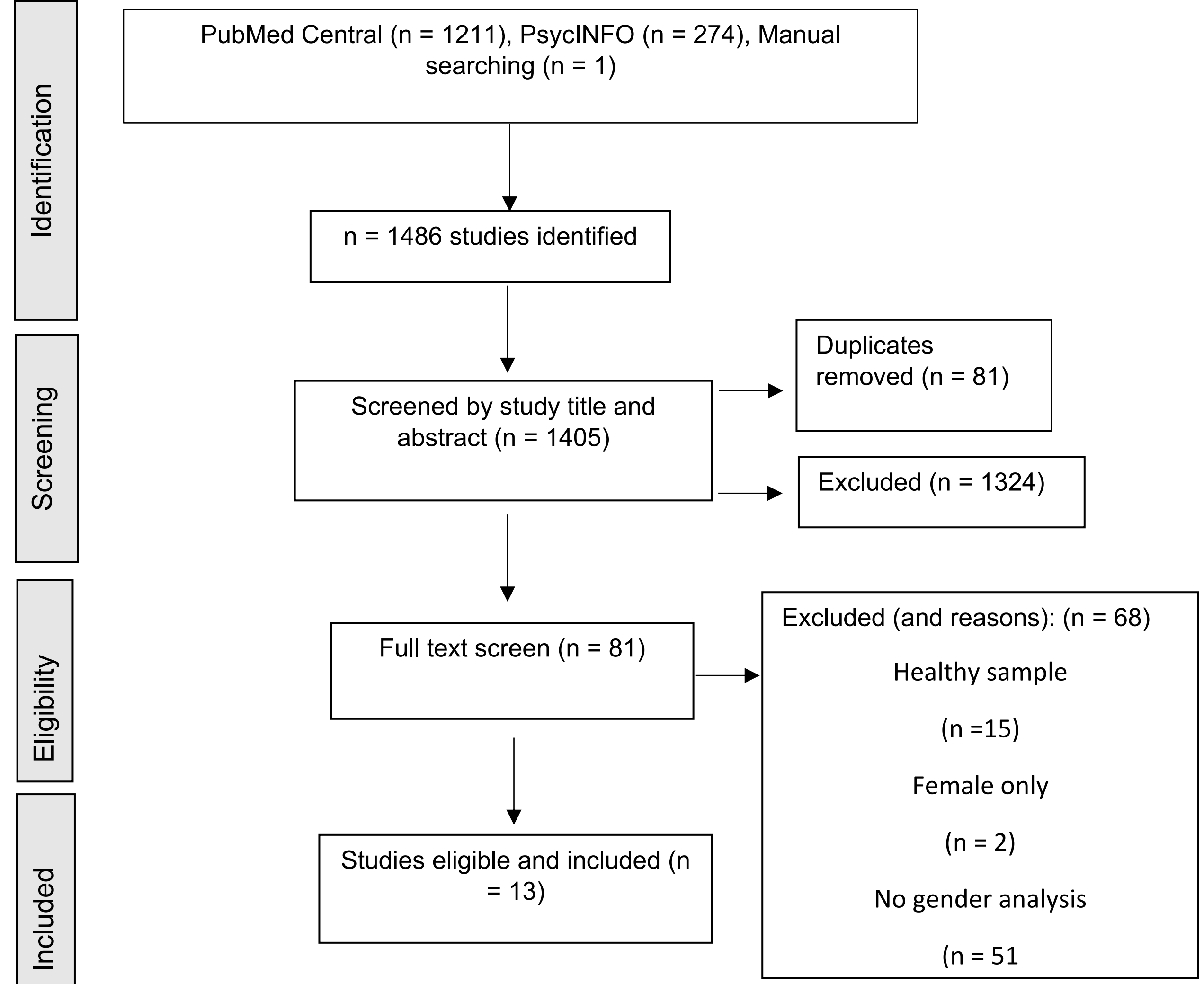
The mixed methods appraisal tool (MMAT) version 2018 (Hong et al. 2018) (see Appendix 1 for items) was used to appraise the quality of articles included in this review. As this review included a wide range of research methodologies, a tool that could be used to this breadth was necessary. While the MMAT user guide advises two independent reviewers are used for scoring, this wasn’t possible within the confines of this project. Furthermore, while it is discouraged to score articles numerically using the MMAT, a modified scoring system was adopted:

Each item was scored according to a traffic light system in which if it met the requirements of the item fully it was coded green, if it met the requirements of the item satisfactorily it was coded orange, and if it didn’t meet the requirements, it was coded red.

### *Data synthesis*

Due to heterogeneity and the diverse range of methodologies used in the studies included in the review, the articles were analysed using a narrative synthesis using Popay et al. (2006) as a guide. This approach enabled the use of both statistical commentary and research design and implementation issues relating to sex/gender in psychedelic research.

*Figure 1: PRISMA study flowchart*



## Results

The present study identified 13 studies which considered or explored the role of sex/gender in the use of PAT as an intervention for mental health or substance misuse difficulties. Of the 13 studies that met the inclusion criteria, this included 9 randomised controlled trials (RCT), 1 open-label trial, and 3 quantitative descriptive studies (one retrospective study, two pool analyses). The search yielded 51 studies that met the inclusion criteria of the search strategy. However, upon full screening didn't comment on sex/gender in design or analysis and as such were excluded.

A total of 12 papers were yielded from searches on PubMed and PsychInfo and a further record (Schenberg et al. 2014) was identified by other means i.e. manual searching of systematic review articles (Wheeler & Dyer 2020). Only studies relating to psilocybin, MDMA and ibogaine yielded results relevant to this review. *Figure 2* provides a summary of the studies included in the review.

*Figure 2: Study Summary Table*

| **Author /Date** | **Design** | **Participants** | **Intervention** | **Main findings** | **Gender/Sex related findings** |
|---|---|---|---|---|---|
| Ross et al. (2016) | RCT | 18 F, 11M | Psilocybin for cancer related anxiety | 83% of psilocybin group experienced anti-depressant response versus 14% of control.<br>58% of psilocybin group experienced clinically significant reduction in anxiety vs 14% of control. | No dichotomous factors (i.e. gender) significantly interacted with the primary outcome measures in between-group comparisons. |

| | | | | | |
|---|---|---|---|---|---|
| Carhart-Harris et al. (2018) | Open-label follow-up | 6 F, 14 M | Psilocybin for Treatment resistant depression | Marked reduction of depression 6 months after psilocybin dosing in open label study. | Limitation noted that final sample was male – indicating a high dropout rate for female participants. Noted that this limits extrapolation of finding to general public as women have higher rates of treatment resistant depression. Claimed to seek more representative samples in future studies. |
| Davis et al. (2020) | RCT | 16F, 11M | Psilocybin for Depression | Participants who received immediate psilocybin treatment showed improvement compared with those for whom treatment was delayed. | Participants were randomized using urn randomization (Stout et al. 1994), balancing for a number of factors including sex. Women participants agreed to being nonpregnant, being non-nursing, and agreeing to use contraception. |
| Goodwin et al. (2022) | RCT | 121F, 112M | Psilocybin for Treatment resistant depression | Greater benefits were enjoyed in relation to higher doses of psilocybin given. | A post hoc analysis of the primary end point that included sex showed results similar to those for the primary analysis - exact results weren't reported. |

| | | | | | |
|---|---|---|---|---|---|
| Mithoefer et al. (2011) | RCT | 17 F, 3 M | MDMA for PTSD | Significantly greater results recorded in MDMA group versus placebo | Unequal sample noted as a limitation – mention gender could have an effect on outcomes. |
| Ot'alora et al. (2018) | RCT | 19 F, 9 M | MDMA for PTSD | Significant reductions in PTSD symptoms. Remained below baseline at 12 month follow up. | Unequal gender balance noted as a limitation – 68% female |
| Mitchell et al. (2023) | RCT placebo controlled | 32F, 21M | MDMA for PTSD | MDMA-AT reduced PTSD symptoms and functional impairment in with moderate to severe PTSD. | Female sex assigned at birth was identified as having an association with positive outcomes irrespective of treatment condition (MDMA or control). |
| Brewerton et al. (2022) | RCT placebo controlled | 31 Male 58 Female.<br>31 Men, 56 Women, 2 Non-Binary | MDMA for PTSD/ eating disorder symptoms | Eating disorder symptoms were reduced in a population of individuals treated for PTSD. | Females showed a greater reduction in eating disorder symptomology following MDMA-AT than males. |

| | | | | | |
|---|---|---|---|---|---|
| Gorman et al. (2020) | Participant data were pooled from three Phase 2 clinical studies employing triple-blind crossover designs.<br><br>. | 31M, 31F | MDMA for PTSD/ Post traumatic growth | MDMA-AT therapy group benefited from greater post traumatic growth and a reduction in PTSD symptoms compared with control group. | Sex investigated as a covariate found not to be significant. |
| Wolfson et al. (2020) | RCT pilot study | 4M, 14F | MDMA for Anxiety/distress from life threatening illness. | MDMA group had greater mean reductions in distress however this didn't reach significance between groups. | Uneven sample (skewed in favour of females) reported as a limitation. |

| | | | | | |
|---|---|---|---|---|---|
| Oehen et al. (2013) | Double blind, placebo controlled RCT | 10F, 2M | MDMA for PTSD | Self-reported PTSD symptoms improvement. No significant reductions in CAPS scores. | Lack of statistical analysis between genders noted as a limitation, as was the skewed sample (in favour of females). |
| Jerome et al. (2020) | Pooled analysis of long term follow-up of 6 trials | 62F, 45M | MDMA for PTSD | CAPS scores continued to decrease following completion of treatment to long term follow up. Majority of the participants reported benefits. | Sex added stepwise to the base model to assess relationships between each variable and the primary outcome variable. However, the results of the analysis aren't reported. |
| Schenberg et al. (2014) | Retrospective | 8 F, 67 M | Ibogaine for Poly substance misuse | Retrospective study: 61% of sample of 75 previous alcohol, cannabis, cocaine and crack cocaine users treated with Ibogaine and psychotherapy reported prolonged abstinence. | No significant association was found between gender and the number of ibogaine sessions needed.<br><br>Significant association between gender and relapse after the first ibogaine session - men relapsed more frequently than<br>Women. 71% of men relapsed after first ibogaine session compared with 25% women. Those women engaged in one further ibogaine |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | session and were abstinent at the point of contact.<br><br>72% stated that they were abstinent, but 10 of those were currently undergoing other treatment interventions.<br>57% men were abstinent with no other treatments. |

### *Quality appraisal*

There were methodological strengths and limitations in the research included in this review (see *Appendix 2* for an appraisal table demonstrating this).

Most of the studies utilised a double-blind RCT methodology and aspects of these studies are laudable:

Most of the RCTs performed randomisation appropriately, clearly explaining the randomisation process adopted in detail either in the body of the study or in supplementary materials. There were limited exceptions in this regard; Mithoefer et al. (2011) and Oehen et al. (2012). These studies were the earliest conducted studies included in this review. Some studies used randomisation methods to ensure a balanced sex/gender ratio (Davis et al. 2020). The most common method of randomisation used was "web-based", accounting for four studies (Ot'alora et al. 2018; Mitchell et al. 2023; Wolfson et al. 2020).

Limitations concerning sampling were apparent across all methodologies. Small sample sizes were a feature of most of the studies, limiting statistical power and the capacity to identify therapeutic efficacy. Gender imbalance in samples was a common feature in studies, with 8/13 studies having unbalanced samples. MDMA studies were mostly skewed towards females while psilocybin and ibogaine were skewed in favour of males. Some studies acknowledged the imbalanced nature of their study as a limitation (Oehen et al. 2012; Carhart-Harris et al. 2017; Mithoefer et al. 2011; Ot'alora et al. 2018; Wolfson et al. 2020).

There was a relatively high dropout rate apparent across studies and conditions, however, the dropout rate was higher in the psychedelic condition than in the control conditions. In certain instances, this resulted in unequal sample sizes across groups. The high dropout rate may be due to the intense and challenging nature of psychedelic experiences; however, other factors should be taken into consideration. Ross et al. (2016), in a study investigating psilocybin and end-of-life anxiety, reported a 73% retention rate at follow-up, however reported that only one person withdrew from the study for reasons other than disease (cancer) progression. Ot'alora et al. (2018) described reasons for withdrawal as including withholding psychiatric diagnoses at screening in an attempt to evade exclusion criteria. Rates of adverse events in studies were generally low. This can be attributed to the careful screening of participants and their preparation for dosing. Most studies required the presence of two facilitators during the dosing stage of therapy, optimising risk monitoring and potentially containing adverse events.

To control expectancy effects, considerable efforts were made to ensure effective blinding in most studies and this was usually outlined in sufficient detail with some exceptions (Ross et al. 2016). While blinding efforts were a clear strength of the studies, blinding remains an issue in psychedelic research due to the strong subjective effects of the compounds and the accuracy to which conditions can be guessed by participants and assessors alike. To minimise the risk of this effect, some studies utilised an active placebo condition or comparator dose (Gorman et al. 2020; Jerome et al. 2020; Ot'alora et al. 2018; Oehen et al. 2013; Goodwin et al. 2022; Ross et al. 2016). Furthermore, independent raters and participants were blinded to the treatment condition until the conclusion of the intervention (Mithoefer et al. 2011; Ot'alora et al. 2018; Mitchell et al. 2023; Brewerton et al. 2022; Gorman et al. 2020; Oehen et al. 2013). Some studies surveyed investigators and participants to evaluate their efforts to guess the treatment condition and results indicated an ability to guess the treatment condition with a high degree of accuracy (Mithoefer et al. 2011; Ot'alora et al. 2018; Mitchell et al. 2023). This is problematic as there is evidence that psychedelics increase suggestibility (Carhart-Harris et al. 2015) and this could amplify expectancy effects.

More recent RCTs reported high levels of intervention adherence across conditions (Goodwin et al. 2022; Mitchell et al. 2023). However, particularly in earlier studies, levels of adherence to the participant's assigned intervention were complicated by the crossovers into open label conditions which were incorporated into many of the studies' designs (Ross et al. 2016; Davis et al. 2020; Mithoefer et al. 2011; Ot'alora et al. 2018; Wolfson et al. 2020). While such crossovers were generally included in the study protocol, there are limitations to this approach including excluding control group participants from long-term follow-up data collection. Perhaps due to time and funding constraints, crossovers often occurred shortly after primary outcomes were obtained. To include better long-term follow-up data to compare groups, crossover should be delayed to three months or longer. In one study, the protocol was amended to offer further dosing sessions to non-responders, which is a clear violation of treatment adherence (Oehen et al. 2012). A further consideration concerning treatment adherence is the lack of detail offered of the psychotherapeutic methods used in most studies, which could have a negative effect on the replicability and generalisability of findings. Manualised approaches to therapy could mitigate this effect.

The quality of measures used regarding outcomes was generally strong. Valid and reliable measures were generally adopted as means of measuring primary outcome data

across all study methodologies with some exceptions which were overly reliant on self-reported abstinence and as such were vulnerable to deception (Schenberg et al. 2014).

*Risk of publication bias*

This review identified a significant risk of publication bias concerning the research question. Notably, the search strategy yielded 51 results that underwent full screening but failed to meet the inclusion criteria, specifically in addressing gender within the study design or analysis. It is unclear from the close screening whether these studies did not consider gender in their design at all or simply did not report any differences in outcomes related to gender. While a thorough examination of the planned protocols of these studies might offer insights into this matter, such an investigation fell beyond the scope of this review. To mitigate against the further possibility of publication bias in this review, the author consulted the Dart.en database for unpublished relevant literature however, this didn't yield any results pertaining to the research question.

*Research design and implementation*

Many of the findings of this review focused on research design and sampling. The unbalanced nature of many of the samples included in this review is a cause for concern and a general limitation of research into PAT. Eight of the thirteen studies reviewed had an unbalanced sample with regard to sex/gender as defined by Rechlin et al. (2021). Only one study appeared to take steps to limit this phenomenon; Davis et al. (2021) described using an urn randomisation method which ensured balance between treatment groups on several factors including gender however reported no analysis of differences between these groups on the variable of gender.

Carhart-Harris et al. (2017) commented on the unbalanced sample as a limitation of their study in which the final sample was all male, noting that women experience a higher level of treatment-resistant depression than men and thus advised that the study isn't generalizable and that greater efforts would be made to recruit women for future studies. What is most noteworthy is the high dropout rate for women in this study, all six female participants, raising questions about barriers to accessibility and acceptability for women who wish to engage in psilocybin therapy trials. Some light may be shed on this issue by considering the strict inclusion criteria for women outlined in Davis et al. (2021), which required women to agree to be non-pregnant, non-nursing and using contraception to engage in the trial. Interestingly, such requirements may act as a barrier to women engaging in

psilocybin therapy research, the similar restrictions in MDMA therapy research don’t appear to influence female engagement, where women were dominant in all studies included in this review. In contrast to the psilocybin therapy trials, the lack of sex/gender balance in MDMA therapy research has been noted as a limitation in several studies which had a much higher proportion of females than males (Wolfson et al. 2020; Mithoefer et al. 2011; Ot’alora et al. 2018; Oehen et al. 2013). Ot’alora et al. (2018) note that the homogenous nature of the sample resulted in it being underpowered to conduct statistical analyses on gender and Oehen et al. (2013) note this as a limitation of the study. Brewerton et al. (2022) acknowledge that low sample sizes in male and non-binary groups may have been too small to detect the effects seen in females in reductions of eating-disordered behaviour.

In two studies, analyses were conducted using the variable of sex/gender however final results weren’t reported. Jerome et al. (2020), in a pooled analysis of six studies investigating MDMA for PTSD, reported adding sex as a covariate to be analysed however don’t report the results of this analysis. Goodwin et al. 2022, in a large RCT, reported that a post hoc analysis including sex as a variable showed results similar to those for the primary analysis, however, exact results weren’t reported.

### *Synthesis*

Of the 13 studies included in this review, only six studies in this review reported on analyses exploring differences in outcomes between sexes/genders. As such, there is insufficient evidence to draw firm conclusions about differences in outcomes.

Recently, a high-quality RCT by Mitchell et al. (2023) showed a positive association between being assigned female sex at birth and outcomes in both the MDMA-assisted therapy and placebo with therapy conditions. This analysis was reported to have been exploratory and not planned a priori. The authors postulate that these findings may require further study using exploratory methods of statistical analysis. However, this result was not found across all studies; Gorman et al. (2020) did not find significant differences in outcomes across genders when investigating sex as a covariate. That positive outcomes were consistent for females across conditions in Mitchell et al (2023), both of which included psychotherapy warrants further exploration and may raise interesting considerations for the suitability and acceptability of the psychotherapy aspect of the treatment for males, especially when viewed in the context of previous trial's samples being skewed towards females.

Brewerton et al. (2023) reported that women who scored highly in using the Eating Attitudes Test (EAT-26) outcome measure and engaged in MDMA-AT showed a greater reduction in the scale than men. It should be noted however that this sample was recruited for a PTSD trial and did not engage in a full clinical screen for eating disorders. As such findings may not be generalizable to eating disorders but indicate the need for consideration in future research.

This review didn't reveal differences in outcomes between sex/gender in psilocybin-assisted therapy studies. In an RCT investigating cancer-related distress in which those in the psilocybin group showed substantial reductions in depression and anxiety compared with a control group, Ross et al. (2016) examined the interaction of dichotomous factors including sex/gender with outcomes and found that there was no significant interaction. Furthermore, in a recent RCT for treatment-resistant depression, Goodwin et al. (2022) reported that a post hoc analysis of sex as a variable showed results similar to the primary analysis, although exact results weren't reported.

Concerning ibogaine, Schenenberg et al. (2014) reported that although there was no significant association between gender and the number of ibogaine sessions that were needed by participants in the treatment of substance misuse, there were marked differences in relapse

rates between men and women, with 71% of men relapsing after a first ibogaine session in comparison to 25% of women. The women who engaged in a further ibogaine session were all reported to be abstinent afterwards at the point of contact. The final analysis showed that 100% of women who engaged in the treatment achieved abstinence compared to 72% of men, 57% when excluding men who were currently undergoing other treatment interventions. While of interest, these results should be interpreted cautiously given the study's retrospective design and the unbalanced nature of the sample which had far fewer female participants than males.

## Discussion

There are currently no published reviews exploring sex/gender differences in PAT for mental health and substance misuse difficulties. The primary aim of this review was to review PAT studies that investigated and documented the potential influence of sex and gender on therapy outcomes. This question has not specifically been pursued in PAT research conducted thus far and, therefore, due to evidence being limited, it is not possible to provide clear conclusions as to whether sex and gender differences do influence outcomes in PAT. It hasn't been a primary objective of any study yet and most analyses have been secondary or incidental. This review highlights the need for this question to be pursued in future research.

Thus far, the quantitative literature fails to corroborate some of the insights apparent in qualitative studies, which indicate sex/gender is of importance in PAT (Danforth et al. 2018; Noorani et al. 2018; Watts et al. 2017). With regard to the first research question, whether outcomes differ between sex/gender in PAT studies, there were mixed results, with some consistencies apparent within individual compounds. Some studies indicate that differences appeared to be present (Schenberg et al. 2014; Brewerton et al. 2022; Mitchell et al. 2023) and other studies that conducted analyses failed to find statistically significant differences (Gorman et al. 2020; Goodwin et al. 2022; Ross et al. 2016). This review has garnered some tentative evidence that women benefit more from MDMA for PTSD than men (Brewerton et al. 2022; Mitchell et al. 2023), which would be consistent with previous research that women benefit more from PTSD therapy generally (Békés et al. 2016; Stefanovics et al. 2020; Gross et al. 2023). Furthermore, this review supports previous findings (Studerus et al. 2012; Garcia-Romeu et al. 2021) which failed to find sex/gender differences in relation to experiences of psilocybin.

It is imperative to note that sex/gender differences weren't the primary aim of analysis in these studies and that the findings were incidental and should be interpreted cautiously. As

such the reasons for differences or lack thereof in outcomes weren't elaborated in any study. Additionally, where statistical outcomes have been reported in this review, cautious interpretation of these findings is encouraged due to the skewed samples (male: female: TGD) and generally small sample sizes. Furthermore, due to the limited number of outcome differences reported and the lack of homogeneity in relation to mental health condition researched, intervention used and method of analysis no conclusions may be drawn.

A further question of this review was to assess whether research design and implementation hinder the exploration of gender differences in outcomes. This review yielded several important insights into this question. One key finding of this review is that 8 of the 13 studies meeting the inclusion criteria exhibited skewed samples. Unequal sample sizes in studies on psychedelic therapy introduce several challenges. This includes representation bias, where one gender may be overrepresented, limiting the study's generalizability and potentially overlooking minority gender experiences. This imbalance hampers the understanding of gender-specific responses, hindering the ability to draw meaningful conclusions about the therapy's impact. Additionally, skewed samples may fail to capture the diverse biological and psychological variability between men and women, crucial for understanding treatment outcomes. There's a risk of reinforcing gender stereotypes and ethical concerns arise if groups are under-represented. This imbalance also affects the tailoring of therapy approaches to underrepresented genders, limiting the development of gender-specific guidelines. Furthermore, biased information from skewed samples may influence policy and clinical decisions, potentially overlooking the diversity of responses and needs within an entire population.

Skewed samples were acknowledged as a limitation in some studies (Carhart-Harris et al. 2018; Mithoefer et al. 2011; Ot'alora et al. 2018; Wolfson et al. 2020; Oehen et al. 2013), but not others. While PAT research is in its early stages, making underpowered and skewed samples unsurprising, researchers must aim for balanced and representative samples to enhance the generalizability of findings and improve understanding of the benefits and risks of PAT across different genders and demographic groups. More recent RCTs with larger samples (Mitchell et al. 2023; Goodwin et al. 2022) offer hopeful signs of balanced sampling and analysis. Some recent studies of psychedelics have investigated the role of sex/gender more thoroughly or plan to do so. Vogt el al. (2023) investigated the acute effects of intravenous DMT in healthy participants. The sex of participants was compared and was found not to moderate the effects of the compound. Furthermore, Vogt et al. (2023) note the

equal representation of male and female participants as a strength of the study. Similarly, Straumann et al. (2023), in a double-blind, randomized, placebo-controlled, crossover design trial investigating the acute effects of LSD and MDMA co-administration noted the equal numbers of males and females as strength of the study, however, no analysis of differences between males and females was detailed in the paper. While some of these studies were excluded from this review due to their healthy samples and absence of therapeutic support in the protocol (Vogt el al. 2023; Straumann et al. 2023), they may serve as examples of balanced sampling to future studies in the PAT domain. Finally, in a protocol published for an upcoming RCT investigating psilocybin without psychedelic effects for treatment-resistant depression, Husain et al. (2023) outline plans to compare treatment effects by sex and gender, with results being published separately for males and females regardless of whether gender is a significant mediator.

The inclusion of transgender and gender-diverse individuals was also of interest in this review. Transgender people endure higher rates of PTSD than the general population and disproportionately higher rates of suicide (Brown and Jones, 2016). Notwithstanding this, the representation of these groups was low and may have been hidden by categorisation into sex binaries (male/female). Mitchell et al. (2021), in a study that didn't match the inclusion criteria of this review, reported in the demographics table "sex assigned at birth" and as a footnote, "Two participants included in the assigned female at birth MDMA group identified their gender as non-binary." This study positively highlights the importance of gender diversity in psychedelic research, setting an example for others to follow. However, the experiences of transgender and gender-diverse (TGD) individuals remain underexplored, and the small sample sizes limit the ability to effectively explore outcome differences.

The final research question related to the methodological quality of the studies that were included, which was generally high. Notwithstanding sampling which has already been discussed, most RCTs demonstrated performing randomisation appropriately. While there were relatively high dropout rates, this was generally accounted for by factors other than the PAT condition. Considerable efforts were made to ensure blinding however due to the strong, often unmistakeable subjective effects of psychedelics, this remains a challenge in psychedelic research generally however active placebo conditions were adopted by some studies to moderate this effect as much as possible. Collection of long-term follow-up data for participants has been difficult, due to the crossover into open-label conditions adopted by many studies.

Considering the substantial number of results yielded by the search strategy but subsequently excluded upon closer screening, it is imperative to acknowledge the potential susceptibility of this review to publication bias. Critiques have been raised regarding reporting practices in psychedelic science (Brennan, Kelman and Belser 2023; van Elk and Fried 2023). One manifestation of such bias is the "file drawer problem," wherein non-significant results are less likely to be published than significant findings (Easterbrook et al. 1991). Given that sex/gender differences were not the primary focus of investigation in these studies, non-significant results concerning gender may be more susceptible to exclusion. Additionally, the contentious nature of publishing sex/gender differences in psychological research, both historically and presently within Western culture, may introduce ideological bias among researchers, increasing the risk of omission of significant findings (Del Giudice 2023).

Overall, this review demonstrates that there is a lack of consideration of sex/gender in the PAT research literature which may be to the detriment of creating high quality research. This is consistent with psychological therapy research generally (Rechlin et al. 2021). It has long been mandated that both males and females are incorporated in the design of studies (Clayton and Collins 2014), however, these mandates aren't being used to their full potential, lacking any further measures to make the most of having a mixed sample, for example, ensuring a balanced sample and conducting subsequent analyses into sex as a covariate. This phenomenon isn't limited to PAT research, Rechlin et al. (2021) surveyed papers in six leading neuroscience and psychiatry journals over 10 years and concluded that while they noted a 30% increase in the percentage of papers including both sexes, only 19% of studies adopted a design that could be used for optimal discovery of possible sex differences and a mere 5% used sex as a discovery variable. The studies included in this review fell even below these low numbers. Heidari et al. (2016) proposes some guidelines that ameliorate this shortcoming in psychological science, for example, journals requesting that data be disaggregated by sex and gender and any differences or similarities explained by the authors. While more recent studies are promising, it is unfortunate that there has been a lack of emphasis in delineating sex/gender differences that could in turn help to optimise PAT and improve outcomes for men, women and gender-diverse individuals.

### *Strengths:*

1. It is the first review to investigate sex/gender-related findings in PAT.

2. The quality of the studies reviewed was generally strong. The majority of the studies took the form of placebo-controlled RCTs which were of a high quality.

***Limitations:***

1. PAT research is still in its infancy relative to the clinical research domain. Sex/gender differences weren't the principal focus of any of the studies included in this review, although efforts were made to summarise differences in outcomes in PAT, few studies ran such analyses. As such, it is impossible to draw any conclusions about any intervention's sex/gender differential effects.
2. There was considerable variability in research design across studies included in the review. The review included RCTs, non-RCTs, pooled analyses and a retrospective study. As such the level of methodological rigour applied across studies varied. Differences in study design could limit the generalisability of findings on sex/gender differences. The variability in methodology likely reflects the current stage of development of psychedelic research as an emerging area of clinical interest.
3. The current review was also by limited by the small sample sizes of the studies included. This limits statistical power even when analyses of gender are run. However, due to PAT being an area of emerging interest, this is likely to change. The unbalanced nature of samples – many didn't reach the 60% male-female ratio threshold outlined by Reichlin et al. (2021) makes analyses of differences between sex/gender difficult. Sex/gender differences should continue to be explored as sample sizes grow, with an emphasis being put on a balanced sex/gender ratio within samples. Furthermore, the sample demographics were largely homogenous (white, young, educated), limiting the generalisability of the findings to gender differences in other groups.
4. This review demonstrated a high risk of publication bias. It is possible that which weren't included in the review conducted analyses of sex/gender but didn't publish the results of the analysis.
5. Psychedelics are commonly used in other countries and there may be studies pertaining to the research question that weren't published in English.

***Recommendations:***

To make confident recommendations regarding clinical practice, research needs to develop further.

1. Future research should prioritise recruiting more balanced samples. Achieving balanced samples is crucial for advancing the field of PAT ethically and evidentially. Achieving balanced and representative samples is crucial for the broader applicability of study findings and a comprehensive understanding of the benefits and risks across different genders and demographics.
2. As research develops and more psychological presentations are investigated, sex/gender should be explored routinely in PAT studies to contribute to a more nuanced and comprehensive understanding of treatment outcomes. This would facilitate the development of more personalized and effective therapeutic interventions.
3. Exploratory methods of statistical analysis should be adopted to identify what differences, if any, exist between sex/gender in PAT outcomes. This could be a valuable strategy for generating hypotheses, identifying patterns, and gaining a deeper understanding of the complex relationships involved. These results should be complemented by confirmatory analyses in subsequent research to establish the robustness and generalizability of the observed effects.
4. Utilizing measures of acceptability in all treatment conditions and analysing differences between sexes/genders would improve understanding of treatment experiences and support the development of tailored interventions. This approach promotes client-centred therapy, considering the unique needs, preferences, and concerns of individuals, thereby improving therapeutic outcomes.
5. To identify whether selective reporting practices are prevalent, future reviews could focus on the protocols of studies to determine whether analyses of sex/gender are planned and/or take place but aren't published.

## Conclusion

The present review attempts to summarise the evidence for sex/gender differences in outcomes in PAT for mental health difficulties and substance misuse. It also attempted to summarise methodological issues that could impede conducting meaningful analyses of this question. As such, there remains a lack of evidence of sex/gender-influenced outcomes in PAT. This lack of clarity is in part due to research design and implementation however best practice along with mixed results in the evidence base indicate a need for further exploration of this topic. While several studies indicate evidence of differences, the vast majority of

studies have not explored the topic and further research on sex/gender differences in PAT is paramount.

## References


Angst, J., Gamma, A., Gastpar, M., Lépine, J.P., Mendlewicz, J. and Tylee, A., 2002. Gender differences in depression: Epidemiological findings from the European DEPRES I and II studies. *European archives of psychiatry and clinical neuroscience*, *252*, pp.201-209.

Addis, M.E. and Mahalik, J.R., 2003. Men, masculinity, and the contexts of help seeking. *American psychologist*, *58*(1), p.5.

Barnett, L., Muthukumaraswamy, S.D., Carhart-Harris, R.L. and Seth, A.K., 2020. Decreased directed functional connectivity in the psychedelic state. *NeuroImage*, *209*, p.116462.

Barrett, F.S., Bradstreet, M.P., Leoutsakos, J.M.S., Johnson, M.W. and Griffiths, R.R., 2016. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. *Journal of Psychopharmacology*, *30*(12), pp.1279-1295.

Békés, V., Beaulieu-Prévost, D., Guay, S., Belleville, G. and Marchand, A., 2016. Women with PTSD benefit more from psychotherapy than men. *Psychological Trauma: Theory, Research, Practice, and Policy*, *8*(6), p.720. https://doi.org/10.1037/tra0000122

Benitah, K., Siegel, A.N., Lipsitz, O., Rodrigues, N.B., Meshkat, S., Lee, Y., Mansur, R.B., Nasri, F., Lui, L.M., McIntyre, R.S. and Rosenblat, J.D., 2022. Sex differences in ketamine's therapeutic effects for mood disorders: A systematic review. *Psychiatry Research*, *312*, p.114579.

Bouso, J.C., Andión, Ó., Sarris, J.J., Scheidegger, M., Tófoli, L.F., Opaleye, E.S., Schubert, V. and Perkins, D., 2022. Adverse effects of ayahuasca: Results from the Global Ayahuasca Survey. *PLOS Global Public Health*, *2*(11), p.e0000438.

Brennan, W., Kelman, A.R. and Belser, A.B., 2023. A systematic review of reporting practices in psychedelic clinical trials: psychological support, therapy, and psychosocial interventions. *Psychedelic Medicine*, *1*(4), pp.218-229.

Brewerton, T.D., Wang, J.B., Lafrance, A., Pamplin, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A. and Doblin, R., 2022. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *Journal of Psychiatric Research*, *149*, pp.128-135.

Brown, G.R. and Jones, K.T., 2016. Mental health and medical health disparities in 5135 transgender veterans receiving healthcare in the Veterans Health Administration: A case–control study. *LGBT health*, *3*(2), pp.122-131.

Carbonaro, T.M., Barrett, F.S., Bradstreet, M.P., Johnson, M.W., MacLean, K.A., Jesse, R. and Griffiths, R.R., 2015. Survey study of challenging experiences after ingesting psilocybin mushrooms: Demographics and phenomenology. *Drug and Alcohol Dependence*, *100*(146), pp.e239-e240.

Carhart-Harris, R.L., Leech, R., Hellyer, P.J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D.R. and Nutt, D., 2014. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in human neuroscience*, *8*, p.20.

Carhart-Harris, R.L., Kaelen, M., Whalley, M.G., Bolstridge, M., Feilding, A. and Nutt, D.J., 2015. LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*, *232*, pp.785-794.

Carhart-Harris, R.L. and Goodwin, G.M., 2017. The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology*, *42*(11), pp.2105-2113.

Carhart-Harris, R.L., Bolstridge, M., Day, C.M., Rucker, J., Watts, R., Erritzoe, D.E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S. and Rickard, J.A., 2018. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology*, *235*, pp.399-408.

Cavarra, M., Falzone, A., Ramaekers, J.G., Kuypers, K.P. and Mento, C., 2022. Psychedelic-assisted psychotherapy—A systematic review of associated psychological interventions. *Frontiers in psychology*, *13*, p.887255.

Cavanaugh, C. and Abu Hussein, Y., 2020. Do journals instruct authors to address sex and gender in psychological science?. *Research integrity and peer review*, *5*, pp.1-2.

Chang, Q., Yip, P.S. and Chen, Y.Y., 2019. Gender inequality and suicide gender ratios in the world. *Journal of affective disorders*, *243*, pp.297-304.

Christiansen, D.M., McCarthy, M.M. and Seeman, M.V., 2022. Where sex meets gender: How sex and gender come together to cause sex differences in mental illness. *Frontiers in psychiatry*, *13*, p.856436.

Corrigan, K., Haran, M., McCandliss, C., McManus, R., Cleary, S., Trant, R., Kelly, Y., Ledden, K., Rush, G., O'Keane, V. and Kelly, J.R., 2022. Psychedelic perceptions: mental health service

user attitudes to psilocybin therapy. *Irish Journal of Medical Science (1971-)*, *191*(3), pp.1385-1397.

Danforth, A.L., Grob, C.S., Struble, C., Feduccia, A.A., Walker, N., Jerome, L., Klosinski, B. and Emerson, A., 2018. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology*, *235*(11), pp.3137-3148.

Davis, A.K., Barrett, F.S., May, D.G., Cosimano, M.P., Sepeda, N.D., Johnson, M.W., Finan, P.H. and Griffiths, R.R., 2021. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA psychiatry*, *78*(5), pp.481-489.

Davis, A.K., Agin-Liebes, G., España, M., Pilecki, B. and Luoma, J., 2022. Attitudes and beliefs about the therapeutic use of psychedelic drugs among psychologists in the United States. *Journal of psychoactive drugs*, *54*(4), pp.309-318. https://doi.org/10.1080/02791072.2021.1971343

Del Giudice, M., 2023. Ideological bias in the psychology of sex and gender. In *Ideological and Political Bias in Psychology: Nature, Scope, and Solutions* (pp. 743-778). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-031-29148-7_28

Easterbrook, P.J., Gopalan, R., Berlin, J.A. and Matthews, D.R., 1991. Publication bias in clinical research. *The Lancet*, *337*(8746), pp.867-872.

Eaton, N.R., Keyes, K.M., Krueger, R.F., Balsis, S., Skodol, A.E., Markon, K.E., Grant, B.F. and Hasin, D.S., 2012. An invariant dimensional liability model of gender differences in mental disorder prevalence: evidence from a national sample. *Journal of abnormal psychology*, *121*(1), p.282.

Erritzoe, D., Smith, J., Fisher, P.M., Carhart-Harris, R., Frokjaer, V.G. and Knudsen, G.M., 2019. Recreational use of psychedelics is associated with elevated personality trait openness: Exploration of associations with brain serotonin markers. *Journal of Psychopharmacology*, *33*(9), pp.1068-1075.

Franconi, F., Campesi, I., Colombo, D. and Antonini, P., 2019. Sex-gender variable: methodological recommendations for increasing scientific value of clinical studies. *Cells*, *8*(5), p.476.

Gahagan, J., Gray, K. and Whynacht, A., 2015. Sex and gender matter in health research: addressing health inequities in health research reporting. *International Journal for equity in health*, *14*, pp.1-4.

Garcia-Romeu, A., Barrett, F.S., Carbonaro, T.M., Johnson, M.W. and Griffiths, R.R., 2021. Optimal dosing for psilocybin pharmacotherapy: Considering weight-adjusted and fixed dosing approaches. *Journal of Psychopharmacology*, *35*(4), pp.353-361.

Gattuso, J.J., Perkins, D., Ruffell, S., Lawrence, A.J., Hoyer, D., Jacobson, L.H., Timmermann, C., Castle, D., Rossell, S.L., Downey, L.A. and Pagni, B.A., 2023. Default mode network modulation by psychedelics: a systematic review. *International Journal of Neuropsychopharmacology*, *26*(3), pp.155-188.

Gross, G.M., Spiller, T.R., Carretta, R., Sippel, L.M., Smith, N. and Harpaz-Rotem, I., 2023. Clinical outcomes of veterans affairs residential PTSD treatment for PTSD and depressive symptoms: 1-year follow-up outcomes and gender differences. *Psychological trauma: theory, research, practice, and policy*.

Gonzalez, J.M., Alegría, M., Prihoda, T.J., Copeland, L.A. and Zeber, J.E., 2011. How the relationship of attitudes toward mental health treatment and service use differs by age, gender, ethnicity/race and education. *Social psychiatry and psychiatric epidemiology*, *46*, pp.45-57.

Gorman, I., Belser, A.B., Jerome, L., Hennigan, C., Shechet, B., Hamilton, S., Yazar-Klosinski, B., Emerson, A. and Feduccia, A.A., 2020. Posttraumatic growth after MDMA-assisted psychotherapy for posttraumatic stress disorder. *Journal of traumatic stress*, *33*(2), pp.161-170.

Gogovor, A., Zomahoun, H.T.V., Ekanmian, G., Adisso, É.L., Deom Tardif, A., Khadhraoui, L., Rheault, N., Moher, D. and Légaré, F., 2021. Sex and gender considerations in reporting guidelines for health research: a systematic review. *Biology of sex Differences*, *12*, pp.1-11.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Arden, P.C., Baker, A., Bennett, J.C., Bird, C., Blom, R.E., Brennan, C., Brusch, D. and Burke, L., 2022. Single-dose psilocybin for a treatment-resistant episode of major depression. *New England Journal of Medicine*, *387*(18), pp.1637-1648.

Gukasyan, N. and Narayan, S.K., 2024. Menstrual changes and reversal of Amenorrhea induced by classic psychedelics: A case series. *Journal of psychoactive drugs*, *56*(1), pp.50-55.

Haijen, E.C., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R.E., Hampshire, A.D., Lorenz, R. and Carhart-Harris, R.L., 2018. Predicting responses to psychedelics: a prospective study. *Frontiers in pharmacology*, *9*, p.897.

Hartung, C.M. and Widiger, T.A., 1998. Gender differences in the diagnosis of mental disorders: Conclusions and controversies of the DSM–IV. *Psychological bulletin*, *123*(3), p.260.

Heidari, S., Babor, T.F., De Castro, P., Tort, S. and Curno, M., 2016. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Research integrity and peer review*, *1*, pp.1-9.

Hong, Q.N., Fàbregues, S., Bartlett, G., Boardman, F., Cargo, M., Dagenais, P., Gagnon, M.P., Griffiths, F., Nicolau, B., O'Cathain, A. and Rousseau, M.C., 2018. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Education for information*, *34*(4), pp.285-291.

Husain, M.I., Blumberger, D.M., Castle, D.J., Ledwos, N., Fellows, E., Jones, B.D., Ortiz, A., Kloiber, S., Wang, W., Rosenblat, J.D. and Mulsant, B.H., 2023. Psilocybin for treatment-resistant depression without psychedelic effects: study protocol for a 4-week, double-blind, proof-of-concept randomised controlled trial. *BJPsych open*, *9*(4), p.e134.

Hutten, N.R., Mason, N.L., Dolder, P.C. and Kuypers, K.P., 2019. Self-rated effectiveness of microdosing with psychedelics for mental and physical health problems among microdosers. *Frontiers in psychiatry*, *10*, p.672.

Jäncke, L., 2018. Sex/gender differences in cognition, neurophysiology, and neuroanatomy. *F1000Research*, *7*.

Jerome, L., Feduccia, A.A., Wang, J.B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M.C. and Doblin, R., 2020. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology*, *237*, pp.2485-2497.

Johansen, L., Liknaitzky, P., Nedeljkovic, M., Mastin-Purcell, L. and Murray, G., 2022. The psychological processes of classic psychedelics in the treatment of depression: a systematic review protocol. *Systematic Reviews*, *11*(1), p.85.

Johnson, M.W., Garcia-Romeu, A. and Griffiths, R.R., 2017. Long-term follow-up of psilocybin-facilitated smoking cessation. *The American journal of drug and alcohol abuse*, *43*(1), pp.55-60.

Kamboj, S.K., Walldén, Y.S., Falconer, C.J., Alotaibi, M.R., Blagbrough, I.S., Husbands, S.M. and Freeman, T.P., 2018. Additive effects of 3, 4-methylenedioxymethamphetamine (MDMA) and compassionate imagery on self-compassion in recreational users of ecstasy. *Mindfulness*, *9*, pp.1134-1145.

Kangaslampi, S., 2023. Association between mystical-type experiences under psychedelics and improvements in well-being or mental health–A comprehensive review of the evidence. *Journal of psychedelic studies*, *7*(1), pp.18-28.

Kessler, R.C., 2003. Epidemiology of women and depression. *Journal of affective disorders*, *74*(1), pp.5-13.

Khan, A., Brodhead, A.E., Kolts, R.L. and Brown, W.A., 2005. Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. *Journal of Psychiatric Research*, *39*(2), pp.145-150.

Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Ryan, C.E., Hess, A.L., Harrison, W. and Davis, S.M., 2000. Gender differences in chronic major and double depression. *Journal of Affective disorders*, *60*(1), pp.1-11.

Krebs, T.S. and Johansen, P.Ø., 2013. Over 30 million psychedelic users in the United States. *F1000Research*, *2*.

Liechti, M.E., Gamma, A. and Vollenweider, F.X., 2001. Gender differences in the subjective effects of MDMA. *Psychopharmacology*, *154*, pp.161-168.

Liddon, L., Kingerlee, R. and Barry, J.A., 2018. Gender differences in preferences for psychological treatment, coping strategies, and triggers to help-seeking. *British Journal of Clinical Psychology*, *57*(1), pp.42-58.

McManus, S., Bebbington, P., Jenkins, R. and Brugha, T., 2016. Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. A survey carried out for NHS Digital by NatCen Social Research and the Department of Health Sciences, University of Leicester.

Mitchell, J.M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G, M., Garas, W., Paleos, C., Gorman, I. and Nicholas, C., 2023. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Focus*, *21*(3), pp.315-328.

Mitchell, J.M., Ot'alora G, M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C.R., Quevedo, S., Balliett, B. and Hamilton, S., 2023. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Medicine*, *29*(10), pp.2473-2480.

Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L. and Doblin, R., 2011. The safety and efficacy of±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of psychopharmacology*, *25*(4), pp.439-452.

Morison, L., Trigeorgis, C. and John, M., 2014. Are mental health services inherently feminised?. *The Psychologist*. *27*(6), 414–416.

Nichols, D.E., 2022. Entactogens: how the name for a novel class of psychoactive agents originated. *Frontiers in psychiatry*, *13*, p.863088.

Noorani, T., Garcia-Romeu, A., Swift, T.C., Griffiths, R.R. and Johnson, M.W., 2018. Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. *Journal of Psychopharmacology*, *32*(7), pp.756-769.

Nour, M.M., Evans, L., Nutt, D. and Carhart-Harris, R.L., 2016. Ego-dissolution and psychedelics: validation of the ego-dissolution inventory (EDI). *Frontiers in human neuroscience*, *10*, p.269.

Oehen, P., Traber, R., Widmer, V. and Schnyder, U., 2013. A randomized, controlled pilot study of MDMA (±3, 4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of psychopharmacology*, *27*(1), pp.40-52.

Ogrodniczuk, J.S., 2006. Men, women, and their outcome in psychotherapy. *Psychotherapy research*, *16*(4), pp.453-462.

Ot'alora G, M., Grigsby, J., Poulter, B., Van Derveer III, J.W., Giron, S.G., Jerome, L., Feduccia, A.A., Hamilton, S., Yazar-Klosinski, B., Emerson, A. and Mithoefer, M.C., 2018. 3, 4-

Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. *Journal of Psychopharmacology*, *32*(12), pp.1295-1307.

Olff, M., Langeland, W., Draijer, N. and Gersons, B.P., 2007. Gender differences in posttraumatic stress disorder. *Psychological bulletin*, *133*(2), p.183.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E. and Chou, R., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*, *372*.

Palmer, M. and Maynard, O.M., 2022. Are you tripping comfortably? Investigating the relationship between harm reduction and the psychedelic experience. *Harm reduction journal*, *19*(1), p.81.

Pardo-Lozano, R., Farré, M., Yubero-Lahoz, S., O'Mathúna, B., Torrens, M., Mustata, C., Pérez-Mañá, C., Langohr, K., Cuyàs, E., Carbó, M.L. and de la Torre, R., 2012. Clinical pharmacology of 3, 4-methylenedioxymethamphetamine (MDMA,"ecstasy"): the influence of gender and genetics (CYP2D6, COMT, 5-HTT). *PloS one*, *7*(10), p.e47599.

Parker, G., Blanch, B. and Crawford, J., 2011. Does gender influence response to differing psychotherapies by those with unipolar depression?. *Journal of affective disorders*, *130*(1-2), pp.17-20.

Pilecki, B., Luoma, J.B., Bathje, G.J., Rhea, J. and Narloch, V.F., 2021. Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm Reduction Journal*, *18*(1), p.40.

Pinn, V.W., 2003. Sex and gender factors in medical studies: implications for health and clinical practice. *Jama*, *289*(4), pp.397-400.

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., Roen, K. and Duffy, S., 2006. Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme Version*, *1*(1), p.b92.

Rechlin, R.K., Splinter, T.F., Hodges, T.E., Albert, A.Y. and Galea, L.A., 2021. Harnessing the power of sex differences: What a difference ten years did not make. *BioRxiv*, pp.2021-06.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, K., Babb, J. and Su, Z., 2016. Rapid and sustained symptom reduction following

psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of psychopharmacology*, *30*(12), pp.1165-1180.

Ryali, S., Zhang, Y., de Los Angeles, C., Supekar, K. and Menon, V., 2024. Deep learning models reveal replicable, generalizable, and behaviorally relevant sex differences in human functional brain organization. *Proceedings of the National Academy of Sciences*, *121*(9), p.e2310012121.

Sagar-Ouriaghli, I., Godfrey, E., Bridge, L., Meade, L. and Brown, J.S., 2019. Improving mental health service utilization among men: a systematic review and synthesis of behavior change techniques within interventions targeting help-seeking. *American journal of men's health*, *13*(3), p.1557988319857009.

Sandison, R.A., Spencer, A.M. and Whitelaw, J.D.A., 1954. The therapeutic value of lysergic acid diethylamide in mental illness. *Journal of Mental Science*, *100*(419), pp.491-507.

Schenberg, E.E., de Castro Comis, M.A., Chaves, B.R. and da Silveira, D.X., 2014. Treating drug dependence with the aid of ibogaine: A retrospective study. *Journal of Psychopharmacology*, *28*(11), pp.993-1000.

Schenberg, E.E., 2018. Psychedelic-assisted psychotherapy: A paradigm shift in psychiatric research and development. *Frontiers in pharmacology*, *9*, p.733.

Stefanovics, E.A. and Rosenheck, R.A., 2020. Gender differences in outcomes following specialized intensive PTSD treatment in the Veterans Health Administration. *Psychological Trauma: Theory, Research, Practice, and Policy*, *12*(3), p.272.

Stout, R.L., Wirtz, P.W., Carbonari, J.P. and Del Boca, F.K., 1994. Ensuring balanced distribution of prognostic factors in treatment outcome research. *Journal of Studies on Alcohol, supplement*, (12), pp.70-75.

Strassman, R.J., Qualls, C.R. and Berg, L.M., 1996. Differential tolerance to biological and subjective effects of four closely spaced doses of N, N-dimethyltryptamine in humans. *Biological psychiatry*, *39*(9), pp.784-795.

Straumann, I., Ley, L., Holze, F., Becker, A.M., Klaiber, A., Wey, K., Duthaler, U., Varghese, N., Eckert, A. and Liechti, M.E., 2023. Acute effects of MDMA and LSD co-administration in a double-blind placebo-controlled study in healthy participants. *Neuropsychopharmacology*, *48*(13), pp.1840-1848.

Studerus, E., Gamma, A., Kometer, M. and Vollenweider, F.X., 2012. Prediction of psilocybin response in healthy volunteers. *PloS one*, *7*(2), p.e30800.

Tamres, L.K., Janicki, D. and Helgeson, V.S., 2002. Sex differences in coping behavior: A meta-analytic review and an examination of relative coping. *Personality and social psychology review*, *6*(1), pp.2-30.

Tibubos, A.N., Otten, D., Ernst, M. and Beutel, M.E., 2021. A systematic review on sex-and gender-sensitive research in public mental health during the first wave of the COVID-19 crisis. *Frontiers in psychiatry*, *12*, p.712492.

Valentine, S.E. and Shipherd, J.C., 2018. A systematic review of social stress and mental health among transgender and gender non-conforming people in the United States. *Clinical psychology review*, *66*, pp.24-38.

Van Eeden, A.E., Van Hoeken, D. and Hoek, H.W., 2021. Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Current opinion in psychiatry*, *34*(6), pp.515-524.

van Elk, M. and Fried, E.I., 2023. History repeating: guidelines to address common problems in psychedelic science. *Therapeutic Advances in Psychopharmacology*, *13*, p.20451253231198466.

Veisani, Y., Delpisheh, A. and Mohamadian, F., 2018. Prevalence and gender differences in psychiatric disorders and DSM-IV mental disorders: a population-based study. *Biomedical Research and Therapy*, *5*(1), pp.1975-1985.

Verheyden, S.L., Hadfield, J., Calin, T. and Curran, V.H., 2002. Sub-acute effects of MDMA (±3, 4-methylenedioxymethamphetamine," ecstasy") on mood: evidence of gender differences. *Psychopharmacology*, *161*, pp.23-31.

Vogt, S.B., Ley, L., Erne, L., Straumann, I., Becker, A.M., Klaiber, A., Holze, F., Vandersmissen, A., Mueller, L., Duthaler, U. and Rudin, D., 2023. Acute effects of intravenous DMT in a randomized placebo-controlled study in healthy participants. *Translational Psychiatry*, *13*(1), p.172.

Vorobyeva, N. and Kozlova, A.A., 2022. Three naturally-occurring Psychedelics and their significance in the treatment of mental health disorders. *Frontiers in Pharmacology*, *13*, p.927984.

Watts, R., Day, C., Krzanowski, J., Nutt, D. and Carhart-Harris, R., 2017. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *Journal of humanistic psychology*, *57*(5), pp.520-564.

Wheeler, S.W. and Dyer, N.L., 2020. A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice*, *7*(3), p.279.

Wolfson, P.E., Andries, J., Feduccia, A.A., Jerome, L., Wang, J.B., Williams, E., Carlin, S.C., Sola, E., Hamilton, S., Yazar-Klosinski, B. and Emerson, A., 2020. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Scientific reports*, *10*(1), p.20442.

Yousaf, O., Popat, A. and Hunter, M.S., 2015. An investigation of masculinity attitudes, gender, and attitudes toward psychological help-seeking. *Psychology of Men & Masculinity*, *16*(2), p.234.

Zucker, I. and Prendergast, B.J., 2020. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of sex differences*, *11*, pp.1-14.

# Appendix

## Appendix A: Journal Guidelines

https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=ujpd20#preparing-your-paper

Preparing Your Paper

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper.

A typical paper for this journal should be no more than 4,000 words for Original Research (Introduction, Methods, Results, Discussion) and for Review Articles, 4,500 words

Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Please use American spelling style consistently throughout your manuscript.

Please use double quotation marks, except where “a quotation is ‘within’ a quotation”.

Please note that long quotations should be indented without quotation marks.

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The main document should be double-spaced, with one-inch margins on all sides, and all pages should be numbered consecutively. Text should appear in 12-point

Times New Roman or other common 12-point font. Papers that report results of data collected from human participants must include a statement that written informed consent was obtained from participants. Please document and mention Institutional Review Board approval, where appropriate, in your manuscript.

## References

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## Checklist: What to Include

1. **Author details.** Please ensure all listed authors meet the Taylor & Francis authorship criteria. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
2. Should contain an unstructured abstract of 200 words. Read tips on writing your abstract.
3. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
4. Between 4 and 6 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.
5. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
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   This work was supported by the [Funding Agency] under Grant [number xxxx].
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   This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
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7. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
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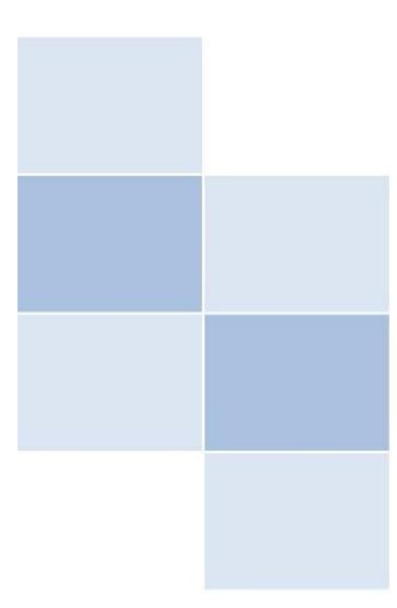
will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.

9. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
10. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our Submission of electronic artwork document.
11. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
12. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
13. **Units.** Please use SI units (non-italicized).

Appendix B: MMAT



# MIXED METHODS APPRAISAL TOOL (MMAT) VERSION 2018

## User guide

Prepared by

Quan Nha HONG[a], Pierre PLUYE[a], Sergi FÀBREGUES[b], Gillian BARTLETT[a], Felicity BOARDMAN[c], Margaret CARGO[d], Pierre DAGENAIS[e], Marie-Pierre GAGNON[f], Frances GRIFFITHS[c], Belinda NICOLAU[a], Alicia O'CATHAIN[g], Marie-Claude ROUSSEAU[h], & Isabelle VEDEL[a]

[a]McGill University, Montréal, Canada; [b]Universitat Oberta de Catalunya, Barcelona, Spain; [c]University of Warwick, Coventry, England; [d]University of Canberra, Canberra, Australia; [e]Université de Sherbrooke, Sherbrooke, Canada; [f]Université Laval, Québec, Canada; [g]University of Sheffield, Sheffield, England; [h]Institut Armand-Frappier Research Centre, Laval, Canada

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Last update: August 1st, 2018

**What is the MMAT?**

The MMAT is a critical appraisal tool that is designed for the appraisal stage of systematic mixed studies reviews, i.e., reviews that include qualitative, quantitative and mixed methods studies. It permits to appraise the methodological quality of five categories to studies: qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed methods studies.

**How was the MMAT developed?**

The MMAT was developed in 2006 (Pluye et al., 2009a) and was revised in 2011 (Pace et al., 2012). The present version 2018 was developed on the basis of findings from a literature review of critical appraisal tools, interviews with MMAT users, and an e-Delphi study with international experts (Hong, 2018). The MMAT developers are continuously seeking for improvement and testing of this tool. Users' feedback is always appreciated.

**What the MMAT can be used for?**

The MMAT can be used to appraise the quality of empirical studies, i.e., primary research based on experiment, observation or simulation (Abbott, 1998; Porta et al., 2014). It cannot be used for non-empirical papers such as review and theoretical papers. Also, the MMAT allows the appraisal of most common types of study methodologies and designs. However, some specific designs such as economic and diagnostic accuracy studies cannot be assessed with the MMAT. Other critical appraisal tools might be relevant for these designs.

**What are the requirements?**

Because critical appraisal is about judgment making, it is advised to have at least two reviewers independently involved in the appraisal process. Also, using the MMAT requires experience or training in these domains. For instance, MMAT users may be helped by a colleague with specific expertise when needed.

**How to use the MMAT?**

This document comprises two parts: checklist (Part I) and explanation of the criteria (Part II).

1. Respond to the two screening questions. Responding 'No' or 'Can't tell' to one or both questions might indicate that the paper is not an empirical study, and thus cannot be appraised using the MMAT. MMAT users might decide not to use these questions, especially if the selection criteria of their review are limited to empirical studies.
2. For each included study, choose the appropriate category of studies to appraise. Look at the description of the methods used in the included studies. If needed, use the algorithm at the end of this document.
3. Rate the criteria of the chosen category. For example, if the paper is a qualitative study, only rate the five criteria in the qualitative category. The 'Can't tell' response category means that the paper do not report appropriate information to answer 'Yes' or 'No', or that report unclear information related to the criterion. Rating 'Can't tell' could lead to look for companion papers, or contact authors to ask more information or clarification when needed. In Part II of this document, indicators are added for some criteria. The list is not exhaustive and not all indicators are necessary. You should agree among your team which ones are important to consider for your field and apply them uniformly across all included studies from the same category.

**How to score?**

It is discouraged to calculate an overall score from the ratings of each criterion. Instead, it is advised to provide a more detailed presentation of the ratings of each criterion to better inform the quality of the included studies. This may lead to perform a sensitivity analysis (i.e., to consider the quality of studies by contrasting their results). Excluding studies with low methodological quality is usually discouraged.

**How to cite this document?**

Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, Gagnon M-P, Griffiths F, Nicolau B, O'Cathain A, Rousseau M-C, Vedel I. Mixed Methods Appraisal Tool (MMAT), version 2018. Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada.

**Part I: Mixed Methods Appraisal Tool (MMAT), version 2018**

| Category of study designs | Methodological quality criteria | Responses | | | |
|---|---|---|---|---|---|
| | | Yes | No | Can't tell | Comments |
| Screening questions (for all types) | S1. Are there clear research questions? | | | | |
| | S2. Do the collected data allow to address the research questions? | | | | |
| | *Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.* | | | | |
| 1. Qualitative | 1.1. Is the qualitative approach appropriate to answer the research question? | | | | |
| | 1.2. Are the qualitative data collection methods adequate to address the research question? | | | | |
| | 1.3. Are the findings adequately derived from the data? | | | | |
| | 1.4. Is the interpretation of results sufficiently substantiated by data? | | | | |
| | 1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation? | | | | |
| 2. Quantitative randomized controlled trials | 2.1. Is randomization appropriately performed? | | | | |
| | 2.2. Are the groups comparable at baseline? | | | | |
| | 2.3. Are there complete outcome data? | | | | |
| | 2.4. Are outcome assessors blinded to the intervention provided? | | | | |
| | 2.5 Did the participants adhere to the assigned intervention? | | | | |
| 3. Quantitative non-randomized | 3.1. Are the participants representative of the target population? | | | | |
| | 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? | | | | |
| | 3.3. Are there complete outcome data? | | | | |
| | 3.4. Are the confounders accounted for in the design and analysis? | | | | |
| | 3.5. During the study period, is the intervention administered (or exposure occurred) as intended? | | | | |
| 4. Quantitative descriptive | 4.1. Is the sampling strategy relevant to address the research question? | | | | |
| | 4.2. Is the sample representative of the target population? | | | | |
| | 4.3. Are the measurements appropriate? | | | | |
| | 4.4. Is the risk of nonresponse bias low? | | | | |
| | 4.5. Is the statistical analysis appropriate to answer the research question? | | | | |
| 5. Mixed methods | 5.1. Is there an adequate rationale for using a mixed methods design to address the research question? | | | | |
| | 5.2. Are the different components of the study effectively integrated to answer the research question? | | | | |
| | 5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? | | | | |
| | 5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? | | | | |
| | 5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved? | | | | |

## Part II: Explanations

<table>
<tr><th>1. Qualitative studies</th><th>Methodological quality criteria</th></tr>
<tr><td rowspan="5">"Qualitative research is an approach for exploring and understanding the meaning individuals or groups ascribe to a social or human problem" (Creswell, 2013b, p. 3).<br><br>Common qualitative research approaches include (this list if not exhaustive):<br><br>Ethnography<br>The aim of the study is to describe and interpret the shared cultural behaviour of a group of individuals.<br><br>Phenomenology<br>The study focuses on the subjective experiences and interpretations of a phenomenon encountered by individuals.<br><br>Narrative research<br>The study analyzes life experiences of an individual or a group.<br><br>Grounded theory<br>Generation of theory from data in the process of conducting research (data collection occurs first).<br><br>Case study<br>In-depth exploration and/or explanation of issues intrinsic to a particular case. A case can be anything from a decision-making process, to a person, an organization, or a country.<br><br>Qualitative description<br>There is no specific methodology, but a qualitative data collection and analysis, e.g., in-depth interviews or focus groups, and hybrid thematic analysis (inductive and deductive).<br><br>Key references: Creswell (2013a); Sandelowski (2010); Schwandt (2015)</td><td>1.1. Is the qualitative approach appropriate to answer the research question?<br><br>Explanations<br>The qualitative approach used in a study (see non-exhaustive list on the left side of this table) should be appropriate for the research question and problem. For example, the use of a grounded theory approach should address the development of a theory and ethnography should study human cultures and societies.<br><br>This criterion was considered important to add in the MMAT since there is only one category of criteria for qualitative studies (compared to three for quantitative studies).</td></tr>
<tr><td>1.2. Are the qualitative data collection methods adequate to address the research question?<br><br>Explanations<br>This criterion is related to data collection method, including data sources (e.g., archives, documents), used to address the research question. To judge this criterion, consider whether the method of data collection (e.g., in depth interviews and/or group interviews, and/or observations) and the form of the data (e.g., tape recording, video material, diary, photo, and/or field notes) are adequate. Also, clear justifications are needed when data collection methods are modified during the study.</td></tr>
<tr><td>1.3. Are the findings adequately derived from the data?<br><br>Explanations<br>This criterion is related to the data analysis used. Several data analysis methods have been developed and their use depends on the research question and qualitative approach. For example, open, axial and selective coding is often associated with grounded theory, and within- and cross-case analysis is often seen in case study.</td></tr>
<tr><td>1.4. Is the interpretation of results sufficiently substantiated by data?<br><br>Explanations<br>The interpretation of results should be supported by the data collected. For example, the quotes provided to justify the themes should be adequate.</td></tr>
<tr><td>1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?<br><br>Explanations<br>There should be clear links between data sources, collection, analysis and interpretation.</td></tr>
</table>

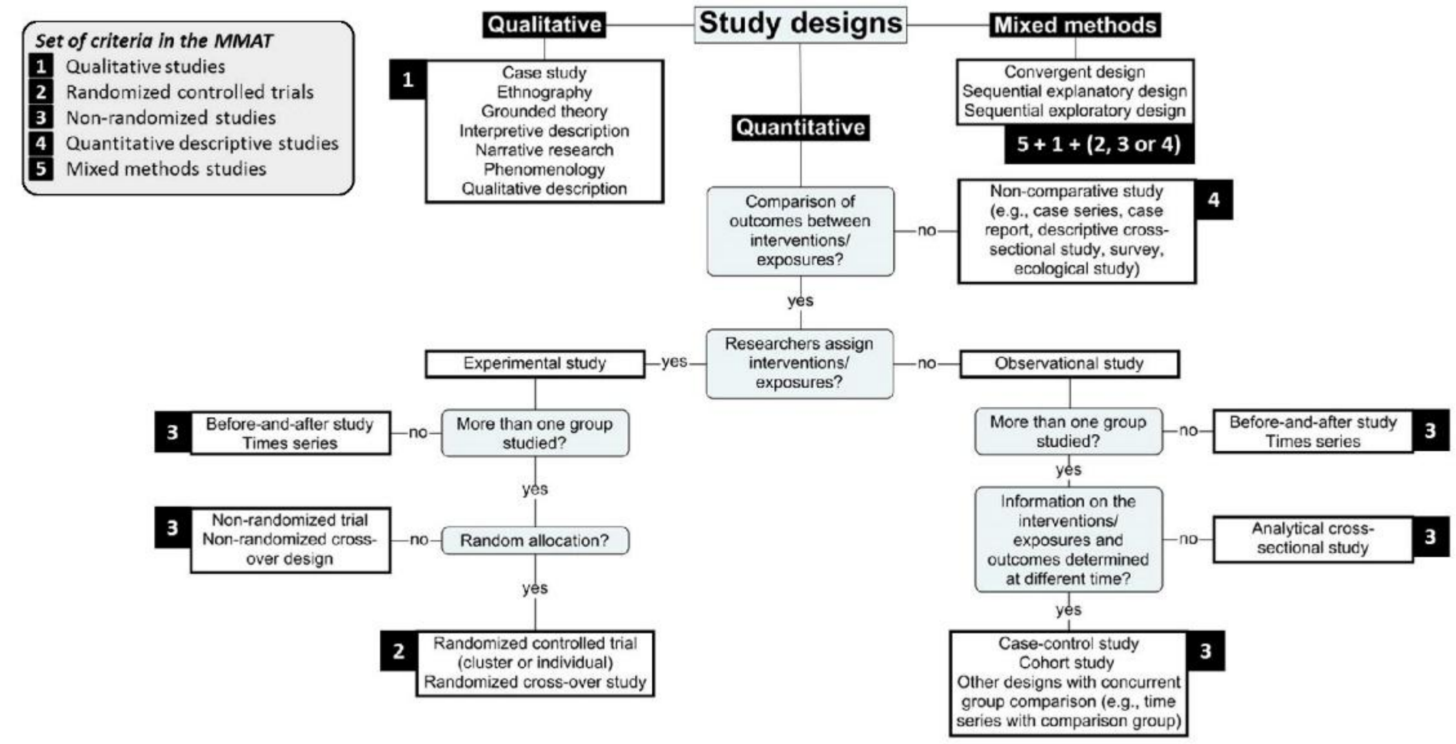
| 2. Quantitative randomized controlled trials | Methodological quality criteria |
|---|---|
| **Randomized controlled clinical trial**: A clinical study in which individual participants are allocated to intervention or control groups by randomization (intervention assigned by researchers).<br><br>Key references: Higgins and Green (2008); Higgins et al. (2016); Oxford Centre for Evidence-based Medicine (2016); Porta et al. (2014) | 2.1. Is randomization appropriately performed?<br><br>Explanations<br>In a randomized controlled trial, the allocation of a participant (or a data collection unit, e.g., a school) into the intervention or control group is based solely on chance. Researchers should describe how the randomization schedule was generated. A simple statement such as 'we randomly allocated' or 'using a randomized design' is insufficient to judge if randomization was appropriately performed. Also, assignment that is predictable such as using odd and even record numbers or dates is not appropriate. At minimum, a simple allocation (or unrestricted allocation) should be performed by following a predetermined plan/sequence. It is usually achieved by referring to a published list of random numbers, or to a list of random assignments generated by a computer. Also, restricted allocation can be performed such as blocked randomization (to ensure particular allocation ratios to the intervention groups), stratified randomization (randomization performed separately within strata), or minimization (to make small groups closely similar with respect to several characteristics). Another important characteristic to judge if randomization was appropriately performed is allocation concealment that protects assignment sequence until allocation. Researchers and participants should be unaware of the assignment sequence up to the point of allocation. Several strategies can be used to ensure allocation concealment such relying on a central randomization by a third party, or the use of sequentially numbered, opaque, sealed envelopes (Higgins et al., 2016). |
| | 2.2. Are the groups comparable at baseline?<br><br>Explanations<br>Baseline imbalance between groups suggests that there are problems with the randomization. Indicators from baseline imbalance include: "(1) unusually large differences between intervention group sizes; (2) a substantial excess in statistically significant differences in baseline characteristics than would be expected by chance alone; (3) imbalance in key prognostic factors (or baseline measures of outcome variables) that are unlikely to be due to chance; (4) excessive similarity in baseline characteristics that is not compatible with chance; (5) surprising absence of one or more key characteristics that would be expected to be reported" (Higgins et al., 2016, p. 10). |
| | 2.3. Are there complete outcome data?<br><br>Explanations<br>Almost all the participants contributed to almost all measures. There is no absolute and standard cut-off value for acceptable complete outcome data. Agree among your team what is considered complete outcome data in your field and apply this uniformly across all the included studies. For instance, in the literature, acceptable complete data value ranged from 80% (Thomas et al., 2004; Zaza et al., 2000) to 95% (Higgins et al., 2016). Similarly, different acceptable withdrawal/dropouts rates have been suggested: 5% (de Vet et al., 1997; MacLehose et al., 2000), 20% (Sindhu et al., 1997; Van Tulder et al., 2003) and 30% for a follow-up of more than one year (Viswanathan and Berkman, 2012). |
| | 2.4. Are outcome assessors blinded to the intervention provided?<br><br>Explanations<br>Outcome assessors should be unaware of who is receiving which interventions. The assessors can be the participants if using participant reported outcome (e.g., pain), the intervention provider (e.g., clinical exam), or other persons not involved in the intervention (Higgins et al., 2016). |
| | 2.5 Did the participants adhere to the assigned intervention?<br><br>Explanations<br>To judge this criterion, consider the proportion of participants who continued with their assigned intervention throughout follow-up. "Lack of adherence includes imperfect compliance, cessation of intervention, crossovers to the comparator intervention and switches to another active intervention." (Higgins et al., 2016, p. 25). |

<table>
<tr><th>3. Quantitative non-randomized studies</th><th>Methodological quality criteria</th></tr>
<tr><td rowspan="5">Non-randomized studies are defined as any quantitative studies estimating the effectiveness of an intervention or studying other exposures that do not use randomization to allocate units to comparison groups (Higgins and Green, 2008).<br><br>Common designs include (this list if not exhaustive):<br><br>Non-randomized controlled trials<br>The intervention is assigned by researchers, but there is no randomization, e.g., a pseudo-randomization. A non-random method of allocation is not reliable in producing alone similar groups.<br><br>Cohort study<br>Subsets of a defined population are assessed as exposed, not exposed, or exposed at different degrees to factors of interest. Participants are followed over time to determine if an outcome occurs (prospective longitudinal).<br><br>Case-control study<br>Cases, e.g., patients, associated with a certain outcome are selected, alongside a corresponding group of controls. Data is collected on whether cases and controls were exposed to the factor under study (retrospective).<br><br>Cross-sectional analytic study<br>At one particular time, the relationship between health-related characteristics (outcome) and other factors (intervention/exposure) is examined. E.g., the frequency of outcomes is compared in different population subgroups according to the presence/absence (or level) of the intervention/exposure.<br><br>Key references for non-randomized studies: Higgins and Green (2008); Porta et al. (2014); Sterne et al. (2016); Wells et al. (2000)</td>
<td>3.1. Are the participants representative of the target population?<br><br>Explanations<br>Indicators of representativeness include: clear description of the target population and of the sample (inclusion and exclusion criteria), reasons why certain eligible individuals chose not to participate, and any attempts to achieve a sample of participants that represents the target population.</td></tr>
<tr><td>3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?<br><br>Explanations<br>Indicators of appropriate measurements include: the variables are clearly defined and accurately measured; the measurements are justified and appropriate for answering the research question; the measurements reflect what they are supposed to measure; validated and reliability tested measures of the intervention/exposure and outcome of interest are used, or variables are measured using 'gold standard'.</td></tr>
<tr><td>3.3. Are there complete outcome data?<br><br>Explanations<br>Almost all the participants contributed to almost all measures. There is no absolute and standard cut-off value for acceptable complete outcome data. Agree among your team what is considered complete outcome data in your field (and based on the targeted journal) and apply this uniformly across all the included studies. For example, in the literature, acceptable complete data value ranged from 80% (Thomas et al., 2004; Zaza et al., 2000) to 95% (Higgins et al., 2016). Similarly, different acceptable withdrawal/dropouts rates have been suggested: 5% (de Vet et al., 1997; MacLehose et al., 2000), 20% (Sindhu et al., 1997; Van Tulder et al., 2003) and 30% for follow-up of more than one year (Viswanathan and Berkman, 2012).</td></tr>
<tr><td>3.4. Are the confounders accounted for in the design and analysis?<br><br>Explanations<br>Confounders are factors that predict both the outcome of interest and the intervention received/exposure at baseline. They can distort the interpretation of findings and need to be considered in the design and analysis of a non-randomized study. Confounding bias is low if there is no confounding expected, or appropriate methods to control for confounders are used (such as stratification, regression, matching, standardization, and inverse probability weighting).</td></tr>
<tr><td>3.5 During the study period, is the intervention administered (or exposure occurred) as intended?<br><br>Explanations<br>For intervention studies, consider whether the participants were treated in a way that is consistent with the planned intervention. Since the intervention is assigned by researchers, consider whether there was a presence of contamination (e.g., the control group may be indirectly exposed to the intervention) or whether unplanned co-interventions were present in one group (Sterne et al., 2016).<br><br>For observational studies, consider whether changes occurred in the exposure status among the participants. If yes, check if these changes are likely to influence the outcome of interest, were adjusted for, or whether unplanned co-exposures were present in one group (Morgan et al., 2017).</td></tr>
</table>

<table>
<tr><th>4. Quantitative descriptive studies</th><th>Methodological quality criteria</th></tr>
<tr><td rowspan="5">Quantitative descriptive studies are "concerned with and designed only to describe the existing distribution of variables without much regard to causal relationships or other hypotheses" (Porta et al., 2014, p. 72). They are used to monitoring the population, planning, and generating hypothesis (Grimes and Schulz, 2002).<br><br>Common designs include the following single-group studies (this list if not exhaustive):<br><br>Incidence or prevalence study without comparison group<br>In a defined population at one particular time, what is happening in a population, e.g., frequencies of factors (importance of problems), is described (portrayed).<br><br>Survey<br>"Research method by which information is gathered by asking people questions on a specific topic and the data collection procedure is standardized and well defined." (Bennett et al., 2011, p. 3).<br><br>Case series<br>A collection of individuals with similar characteristics are used to describe an outcome.<br><br>Case report<br>An individual or a group with a unique/unusual outcome is described in detail.<br><br>Key references: Critical Appraisal Skills Programme (2017); Draugalis et al. (2008)</td><td>4.1. Is the sampling strategy relevant to address the research question?<br><br>Explanations<br>Sampling strategy refers to the way the sample was selected. There are two main categories of sampling strategies: probability sampling (involve random selection) and non-probability sampling. Depending on the research question, probability sampling might be preferable. Non-probability sampling does not provide equal chance of being selected. To judge this criterion, consider whether the source of sample is relevant to the target population; a clear justification of the sample frame used is provided; or the sampling procedure is adequate.</td></tr>
<tr><td>4.2. Is the sample representative of the target population?<br><br>Explanations<br>There should be a match between respondents and the target population. Indicators of representativeness include: clear description of the target population and of the sample (such as respective sizes and inclusion and exclusion criteria), reasons why certain eligible individuals chose not to participate, and any attempts to achieve a sample of participants that represents the target population.</td></tr>
<tr><td>4.3. Are the measurements appropriate?<br><br>Explanations<br>Indicators of appropriate measurements include: the variables are clearly defined and accurately measured, the measurements are justified and appropriate for answering the research question; the measurements reflect what they are supposed to measure; validated and reliability tested measures of the outcome of interest are used, variables are measured using 'gold standard', or questionnaires are pre-tested prior to data collection.</td></tr>
<tr><td>4.4. Is the risk of nonresponse bias low?<br><br>Explanations<br>Nonresponse bias consists of "an error of nonobservation reflecting an unsuccessful attempt to obtain the desired information from an eligible unit." (Federal Committee on Statistical Methodology, 2001, p. 6). To judge this criterion, consider whether the respondents and non-respondents are different on the variable of interest. This information might not always be reported in a paper. Some indicators of low nonresponse bias can be considered such as a low nonresponse rate, reasons for nonresponse (e.g., noncontacts vs. refusals), and statistical compensation for nonresponse (e.g., imputation).<br><br>The nonresponse bias is might not be pertinent for case series and case report. This criterion could be adapted. For instance, complete data on the cases might be important to consider in these designs.</td></tr>
<tr><td>4.5. Is the statistical analysis appropriate to answer the research question?<br><br>Explanations<br>The statistical analyses used should be clearly stated and justified in order to judge if they are appropriate for the design and research question, and if any problems with data analysis limited the interpretation of the results.</td></tr>
</table>

<table>
<tr><th>5. Mixed methods studies</th><th>Methodological quality criteria</th></tr>
<tr><td rowspan="5">Mixed methods (MM) research involves combining qualitative (QUAL) and quantitative (QUAN) methods. In this tool, to be considered MM, studies have to meet the following criteria (Creswell and Plano Clark, 2017): (a) at least one QUAL method and one QUAN method are combined; (b) each method is used rigorously in accordance to the generally accepted criteria in the area (or tradition) of research invoked; and (c) the combination of the methods is carried out at the minimum through a MM design (defined a priori, or emerging) and the integration of the QUAL and QUAN phases, results, and data.<br><br>Common designs include (this list if not exhaustive):<br><br>Convergent design<br>The QUAL and QUAN components are usually (but not necessarily) concomitant. The purpose is to examine the same phenomenon by interpreting QUAL and QUAN results (bringing data analysis together at the interpretation stage), or by integrating QUAL and QUAN datasets (e.g., data on same cases), or by transforming data (e.g., quantization of qualitative data).<br><br>Sequential explanatory design<br>Results of the phase 1 - QUAN component inform the phase 2 - QUAL component. The purpose is to explain QUAN results using QUAL findings. E.g., the QUAN results guide the selection of QUAL data sources and data collection, and the QUAL findings contribute to the interpretation of QUAN results.<br><br>Sequential exploratory design<br>Results of the phase 1 - QUAL component inform the phase 2 - QUAN component. The purpose is to explore, develop and test an instrument (or taxonomy), or a conceptual framework (or theoretical model). E.g., the QUAL findings inform the QUAN data collection, and the QUAN results allow a statistical generalization of the QUAL findings.<br><br>Key references: Creswell et al. (2011); Creswell and Plano Clark, (2017); O'Cathain (2010)</td><td>5.1. Is there an adequate rationale for using a mixed methods design to address the research question?<br><br>Explanations<br>The reasons for conducting a mixed methods study should be clearly explained. Several reasons can be invoked such as to enhance or build upon qualitative findings with quantitative results and vice versa; to provide a comprehensive and complete understanding of a phenomenon or to develop and test instruments (Bryman, 2006).</td></tr>
<tr><td>5.2. Are the different components of the study effectively integrated to answer the research question?<br><br>Explanations<br>Integration is a core component of mixed methods research and is defined as the “explicit interrelating of the quantitative and qualitative component in a mixed methods study” (Plano Clark and Ivankova, 2015, p. 40). Look for information on how qualitative and quantitative phases, results, and data were integrated (Pluye et al., 2018). For instance, how data gathered by both research methods was brought together to form a complete picture (e.g., joint displays) and when integration occurred (e.g., during the data collection-analysis or/and during the interpretation of qualitative and quantitative results).</td></tr>
<tr><td>5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?<br><br>Explanations<br>This criterion is related to meta-inference, which is defined as the overall interpretations derived from integrating qualitative and quantitative findings (Teddlie and Tashakkori, 2009). Meta-inference occurs during the interpretation of the findings from the integration of the qualitative and quantitative components, and shows the added value of conducting a mixed methods study rather than having two separate studies.</td></tr>
<tr><td>5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?<br><br>Explanations<br>When integrating the findings from the qualitative and quantitative components, divergences and inconsistencies (also called conflicts, contradictions, discordances, discrepancies, and dissonances) can be found. It is not sufficient to only report the divergences; they need to be explained. Different strategies to address the divergences have been suggested such as reconciliation, initiation, bracketing and exclusion (Pluye et al., 2009b). Rate this criterion ‘Yes’ if there is no divergence.</td></tr>
<tr><td>5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?<br><br>Explanations<br>The quality of the qualitative and quantitative components should be individually appraised to ensure that no important threats to trustworthiness are present. To appraise 5.5, use criteria for the qualitative component (1.1 to 1.5), and the appropriate criteria for the quantitative component (2.1 to 2.5, or 3.1 to 3.5, or 4.1 to 4.5). The quality of both components should be high for the mixed methods study to be considered of good quality. The premise is that the overall quality of a mixed methods study cannot exceed the quality of its weakest component. For example, if the quantitative component is rated high quality and the qualitative component is rated low quality, the overall rating for this criterion will be of low quality.</td></tr>
</table>

**Algorithm for selecting the study categories to rate in the MMAT***




*Adapted from National Institute for Health Care Excellence. (2012). *Methods for the development of nice public health guidance*. London: National Institute for Health and Care Excellence; and Scottish Intercollegiate Guidelines Network. (2017). *Algorithm for classifying study design for questions of effectiveness*. Retrieved December 1, 2017, from http://www.sign.ac.uk/assets/study_design.pdf. 8

## Appendix C: Appraisal Table

*Randomised controlled trials*

| Study | 2.1 Is randomisation appropriately performed? | 2.2 Are the groups comparable at baseline? | 2.3 Are there complete outcome data? | 2.4 Are outcome assessors blinded to the intervention provided? | 2.5 Did the participants adhere to the assigned intervention? |
|---|---|---|---|---|---|
| Brewerton | Orange<br><br>Not explained in detail – part of another study focused on PTSD. Incidental data of ED were collected. | Orange<br><br>Imbalanced gender skew in favour of females. | Green<br><br>91% (80% Thomas et al., 2014). 8% participants withdrew. | Orange<br><br>Not explained in detail - part of another study focused on PTSD. | Orange<br><br>Not clear. |
| Ross et al. (2016) | Green<br><br>Detailed procedure included in supplementary materials.<br><br>Both groups completed PAT at separate intervals. | Green<br><br>Small sample sizes with some discrepancies on demographic variables - no stratified according to demographic variables. Can be explained by chance alone. | Green<br><br>73% participants retained at follow up (80% Thomas et al., 2014). However, only 1 person withdrew for reasons other than disease progression. | Orange<br><br>Don't know. Outlined in supplementary material. | Orange<br><br>Both groups completed PAT at separate intervals are part of open label arm. Reduces long term follow up potential. |

| Davis et al. 2020 | Green<br><br>Both groups completed PAT at separate intervals.<br><br>Urn randomisation used, balancing for a number of factors including sex. | Green<br><br>Small sample sizes with some discrepancies on demographic variables - no stratified according to demographic variables. Can be explained by chance alone. | Green<br><br>No primary outcome data missing. | Green<br><br>Participants and raters blinded. | Orange<br><br>Both groups completed PAT at separate intervals are part of open label arm. Reduces long term follow up potential |
|---|---|---|---|---|---|
| Goodwin et al. 2022 | Green<br><br>1:1:1 and stratified according to country and previous experience with psilocybin. | Green | Green<br><br>Similar rates of withdrawal across the three treatment conditions however 90% of sample was maintained. | Green<br><br>All assessors were blinded to treatment condition. | Green<br><br>All analyses including per protocol indicated high level of compliance. |
| Mithoefer et al. 2011 | Red<br><br>Not detailed in paper. | Orange<br><br>Control condition had 60% size of the experimental | Orange<br><br>A third session offered to experimental group. Omitted from | Green<br><br>Participants blinded until three weeks after second session. | Orange<br><br>Some cross over to open label arm of trial. Limits long term |

| | | | | | |
|---|---|---|---|---|---|
| | | as per protocol. | analysis but revision to protocol. | Study utilised an independent randomisation monitor.<br><br>Independent rater, subjects and investigators all blinded.<br><br>Blinding conditions were evaluated and almost always correctly guessed.<br><br>Acknowledged in limitations that blinding was compromised by strong subjective effects of the drug and | follow up data. |
| Ot'alora et al. 2018 | Green<br><br>"Web based system" of randomisation blinded to site staff, study | Green<br><br><br>Yes. | Green<br><br>10% drop out rate. This included psychiatric diagnoses | Green<br><br>Independent rater blinded until follow up interview completed. | Orange<br><br>Crossovers to open label trial occurred after completing |

| | | | | | |
|---|---|---|---|---|---|
| | monitors and statistical analysts. | | withheld during screening. | Site staff, study monitors and statistical analysts were blinded to condition.<br><br>Different blinded independent assessors used for follow up assessment to therapy sessions.<br><br>Dose response design utilised to enhance blinding. Therapists and participants were able to guess condition most of the time. | arm of trial. Limits long term follow up data. |
| Mitchell et al. 2023 | Green<br><br>Web randomisation system used. | Orange<br><br>Some gender imbalances across conditions. | Orange<br><br>10% drop out rate. | Green<br><br>Blind indep assessors to general study design, study visit, treatment assignment, | Green |

| | | | | | |
|---|---|---|---|---|---|
| | | | | number of treatments received and any safety data.<br><br>Blinding survey indicated most guessed correct condition. | |
| Mitchell et al. 2021 | Green<br><br>Web randomisation used and named. Centralised randomisation schedule developed by independent third party. | Orange<br><br>Some gender imbalances across conditions. | Green<br><br>9% drop out rate.<br><br>One participant didn't complete some outcome data however completed primary outcome assessment. This was included and didn't significantly alter the final results. | Green<br><br>Inactive placebo used.<br><br>Independent rater used as as primary assessor. Didn't see the same participant and blinded to study design, visit number, treatment assignment, and all data collected by therapy team. | Green |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Participant's instructed to withhold their guesses about treatment condition from assessors. | |
| Wolfson et al. 2020 | Green<br><br>Web based – unique container numbers. Maintained by independent parties. | Orange<br><br>Gender imbalance in sample. | Green<br><br>No drop outs after randomisation. | Orange<br><br>Blinding maintained until conclusion of trial – then cross over. | Orange<br><br>Open label crossover. Placebo group crossed over into open label arm after trial concluded (one month after final session). Limits long term follow up data. |
| Oehen et al. 2012 | Orange<br><br>Not detailed. | Orange<br><br>Small sample.<br><br>Gender imbalance in the sample. Noted as a limitation.<br><br>Greater numbers in | Green<br><br>14% drop out rate. One AE. | Green<br><br>Active placebo used.<br><br>Investigator was blinded to the condition – guessed mostly correctly. Subjects were also blind to | Red<br><br>Protocol amended to offer two further full dose sessions to those in the full dose group who didn't respond. Rationale for |

| | | active dose group – purposive – assess safety and efficacy.<br><br>Lack of balance noted as a limitation. | | the condition – guessed correctly approx. 60%.<br><br>Blinded independent rater used to admindster outcome measures. | this is subjective and based on whether improvement is evident – risk of bias.<br><br>Open label crossover for active placebo group. |
|---|---|---|---|---|---|

*Quantitative non-Randomised Control Trials:*

| Study | Are the participants' representative of the target population? | Are measurements appropriate regarding both the outcome and intervention (or exposure)? | Are there complete outcome data? | Are the confounders accounted for in the design and analysis? | During the study period, is the intervention administered (or exposure occurred) as intended? |
|---|---|---|---|---|---|
| Carhart-Harris 2017<br><br>6 month follow up | Orange<br><br>Women under represented in sample compared to depression prevalence in the population. Noted as a limitation. | Green<br><br>Safety – side effects self reported.<br><br>Depression self-reported through multiple valid/reliable measurements as well as clinician | Orange<br><br>19/20 participants completed all measures.<br><br>However later notes that final eight | Green<br><br>Lack of a control condition is continuously acknowledged as a limitation. | Green. |

| | | | | | |
|---|---|---|---|---|---|
| | Final eight participants all male. | administered scales. Secondary measures used to compared with other studies. | participants were male. | | |
| Brown & Alper (2018) | Orange<br><br>Limited sample. Females under represented | Red<br><br>Validity/reliability of scales used not commented on.<br><br>Attempted to independently verify substance use self-reports. Not clear what strategy used if this wasn't completed. | Orange<br><br>Imputation methods clearly explained – pre-treatment baseline used for missing post treatment values. This was the case for participants in residential treatment during the study – not accounting for the possibility that substance use could have worsened since | Red<br><br>Potential confounding variable of post ibogaine treatments not fully accounted for. | Green. |

| | | | | | |
|---|---|---|---|---|---|
| | | | ibogaine therapy. | | |

Quantitative descriptive:

| **Study** | **Is the sampling strategy relevant to address the research question?** | **Is the sample representative of the target population?** | **Are the measurements appropriate?** | **Is the risk of nonresponse bias low?** | **Is the statistical analysis appropriate to answer the research question?** |
|---|---|---|---|---|---|
| Jerome et al. 2020 | Green<br><br>All studies collected data relevant to the research question. | Green<br><br>All participants have been screened to meet criteria for PTSD using validated methods | Green<br><br>CAPS is the gold standard measure of PTSD, completed by blinded interviewers. | Green<br><br>High response rate to long term follow up. Reported seven individuals who reported harms from the trial. | Green<br><br>Clearly stated and justified. |
| Gorman et al. 2020 | Orange<br><br>All studies collected data relevant to the research question.<br><br>Some variations in study design, | Orange<br><br>Small, homogenous sample.<br><br>All participants have been screened to meet criteria | Orange<br><br>Post traumatic growth measure (PGI) relied on self-report only however has been test as valid and reliable. | Orange<br><br>Unclear | Green<br><br>Clearly stated and justified. |

|  | doses of MDMA and sample sizes. | for PTSD using validated methods |  |  |  |
|---|---|---|---|---|---|
| Schenberg et al. 2014 | Orange<br><br>Very limited sample to choose from. However retrospective nature of data collection could be avoided? | Green.<br><br>Drug dependent individuals. Clear description of the inclusion criteria for the intervention. | Red.<br><br>Measurements were self-reported duration of abstinence and easily falsified. Excluded brief “lapses” into drug use. Reliable and valid outcome measures not used. | Red<br><br>No, data on self-reported abstinence collected from “close relatives” as well patients. | Orange<br><br>Clearly stated but not justified. |

# Paper Two: Empirical Paper

***"They could be in the raptures of hell…"***

**Exploring Therapist Perceptions of Distress in Psychedelic-Assisted Therapy:**

**A Reflexive Thematic Analysis**

**Word Count:**

**7972**

***This paper has been written in accordance with submission guidelines for The Journal of Psychoactive Drugs (Appendix A). Please note, there have been slight deviations from the guidelines in this version to ensure adherence to thesis requirements.***

## Abstract

Psychedelic-assisted therapy (PAT) has shown promising preliminary results for mental health and substance misuse conditions but it carries the risk of heightened distress for participants. To enhance clinical practice, a deeper understanding of distress in PAT is essential. This study recruited 12 experienced PAT therapists worldwide via social media. Semi-structured interviews were used to explore perspectives on distress. Reflexive Thematic Analysis (RTA) identified three primary themes: "Making Sense of Distress," "Therapist as the Safe Base," and "Navigating Distress," each with sub-themes that clarify their significance and impact. Findings reveal that distress during PAT can be intensified and includes some unique characteristics compared to routine psychotherapy. Distress can be experienced as part of a meaningful process in PAT. Sometimes, distress can be an internal process, making it challenging for therapists to detect. A trusting relationship with participants is crucial to navigating distressing experiences. This study explores therapists' decision-making processes regarding offering direct support to participants experiencing distress and outlines strategies to manage distress. The importance of making meaning of distress is emphasised. Broader clinical implications include recommendations for developing PAT training programs and ethical considerations of informed consent. These findings contribute to a deeper understanding of participant distress in PAT, underscoring the need for enhanced therapist preparation and support.

KEYWORDS: Psychedelic-assisted therapy, distress, challenging experiences, therapists, therapeutic relationship

## Introduction

### *Background*

The use of psychedelic compounds in the context of indigenous sacramental and healing practices traces its origins to antiquity, spanning millennia (Schultes 1979). Psychedelic science in mental health care originated in the 1950s with the discovery of LSD. When combined with psychotherapy, substances like psilocybin, LSD, and mescaline showed significant symptom reductions and improved quality of life (Phelps 2017). However, political upheaval in the 1960s led to the outlawing and stigmatization of psychedelics in psychological research. After a hiatus, quality research resumed in the 1990s with studies on DMT (Strassman 1994). Recent studies using psilocybin have shown promising results in smoking cessation, anxiety in advanced illness, obsessive-compulsive disorder, and efficacy comparable to conventional antidepressants for treatment-resistant depression. Studies using

MDMA have shown comparably promising results in the treatment of post-traumatic stress disorder (Wheeler and Dyer 2020; Cavarra et al. 2022).

While legal access to PAT is increasing, with some countries permitting PAT in private healthcare and retreat settings, globally PAT is mainly administered through controlled clinical research. Current psychedelic-assisted therapy (PAT) protocols are developing and draw from a wide variety of psychotherapeutic orientations including cognitive behavioural therapy, existential psychotherapy, psychodynamic therapy, motivational interviewing, acceptance and commitment therapy and perceptual control theory (Brennan and Belser 2022). While psychotherapeutic orientation and number of sessions offered varies by provider, the structure of therapy is typically the same. There are three distinct phases to the treatment (Chisamore et al. 2024):

1. Screening and preparation of participants. Typically includes education about the psychedelic experience, establishing goals and developing rapport.
2. Dosing i.e. administration of the psychedelic compound under supervision.
3. Integration. The participant and therapist meet to discuss insights gained during treatment.

### *Distress in PAT*

Psychedelics can be psychologically agitative (Marrocu et al. 2024); participants can endure meaning high levels of distress while in an altered state of consciousness, intensifying emotions and altering the way that stimuli are perceived. This phenomenon is well documented historically. Indeed, the possibility is captured in the original coining of the term psychedelic when Humphry Osmond wrote to Aldous Huxley in 1957: *"To fathom Hell… or soar angelic/Just take a pinch of psychedelic"* (Tanne 2004). In guidelines written for human hallucinogen research, Johnson Richards and Griffiths (2008) describe several types of distress including sensory (e.g illusions), somatic (over attention to physiological processes), 'personal psychological' (uncomfortable insights about one's life) and metaphysical (e.g. troubling thoughts/feelings about evil forces).

Psychedelics potentially carry the risk of lasting distress. Naturalistic studies investigating recreational use of psychedelics reported that 2.6% of people who used psychedelics needed professional healthcare support following a distressing experience (Simonsson et al. 2023). Similarly, Carbonaro et al. (2016) reported lasting psychological difficulties in 7.6% of respondents to a survey of negative recreational experiences.

While distressing experiences are thought to be more likely and more harmful in recreational settings, they have been documented in clinically controlled environments and have been described as a risk factor in long-term negative psychological responses to psychedelics including risk of re-traumatisation (Bremler et al. 2023; Breeksema et al. 2022). In a recent meta-analysis of the adverse effects of therapeutic doses of psilocybin, the incidence of anxiety ranged from 4% to 26% and paranoia was reported in three studies (Yerunabdi et al. 2024). In a study using a high dose of psilocybin on healthy volunteers, approximately 40% of participants experienced moderate to severe anxiety, panic or distress (Griffiths et al. 2006). Davis et al (2020) reported 67% of participants identified a therapeutic psilocybin session as being among their top five most psychologically demanding experiences, with 30% ranking it as the most psychologically challenging experience of their life. In a review of adverse experiences in clinical research, Breeksema et al. (2022) described qualitative accounts of “occasionally terrifying, frightening and confusing experiences.” It is also reflected in the qualitative accounts of participants:

*That whole experience just felt for me like a fever nightmare* (Nielson et al. 2018).

While distressing experiences that remain unresolved and unprocessed may result in enduring negative outcomes, many users and participants report distressing experiences to be meaningful and/or therapeutically beneficial when contained appropriately. For example, emotional breakthrough has been identified as predictive of positive outcomes in PAT and is typically characterised, in part, by a struggle with difficult psychological states (Bremler et al. 2023; Roseman et al. 2019; Haijen et al. 2018). Herein lies the difficulty of assessing acute distress within the context of PAT; many such experiences are retrospectively reported to be beneficial (Avisar, 2024; Breeksema et al. 2023).

Distressing psychedelic experiences can be moderated by optimizing "set and setting." "Set" refers to the individual's psychological state or ‘mindset’, including intentions and goals. "Setting" involves the physical environment during dosing, and also the therapeutic environment, including the number of preparatory sessions, therapist involvement, therapeutic alliance quality and aftercare duration. (Leary, Litwin and Metzner 1963; Phelps 2017).

The terminology used to describe distressing experiences in PAT varies. "Challenging experience" was coined to describe difficult psychological experiences in recreational settings (Carbonaro et al. 2016) however it has been adopted in clinical research (Bremler et

al. 2023). Sometimes, in clinical research, distressing experiences are dubbed "adverse experiences" (Breeksema et al. 2022) however this term also captures phenomena of a physiological nature that are common during psychedelic dosing e.g. nausea and headache. Consequently , adverse events in PAT have been criticised as being poorly defined, and as such, underreported in research (Breeksema et al. 2022).

### *Role of the Therapist*

Many PAT protocols emphasise the utility of individuals staying with and/or moving towards distress as the appropriate response (Gorman et al. 2021; Watts et al. 2017). This underlines the importance of skilled therapists with adequate training preparing participants and guiding them through distress (Mithoefer et al 2013; Phelps 2017). Phelps (2017) identifies the ability to work with unexpected and difficult experiences in induced alternate states as a key skill to be developed during PAT therapy training and emphasises the importance of drawing on a range of complementary techniques in order to manage such eventualities. Roseman et al. (2019) noted the importance of a strong therapeutic alliance in allowing a participant to navigate a distressing psychedelic experience, offering the following reasons: the trust the patient has in the therapist will increase the trust in letting go and enhance the therapeutic process. The therapeutic alliance can reignite a sense of human connection and belonging in those who have suffered from some sort of alienation and/or trauma.

The influence of the therapeutic relationship in PAT has been studied quantitatively. Murphy et al. (2022) and Levin et al. (2024) demonstrated that the quality of the therapeutic alliance in PAT predicted depression scores at follow-up. Levin et al. (2024) identified a need for research to explore therapist characteristics that maximise the therapeutic alliance. Qualitative accounts from participants reflect the crucial role of the therapeutic relationship in navigating distressing experiences (Belser et al. 2017). Previous qualitative research with PAT therapists has focused on the personal use of psychedelics (Neilsen and Guss 2018), underground (non-legal) settings (Brennan et al. 2021) and integration therapists (Earlywine et al. 2022). To date, little is known about therapist's experiences of delivering PAT and any accompanying perspectives on aspects of the intervention.

### *Rationale*

PAT research programmes are expanding and PAT is being offered to people experiencing a broader range of mental health issues.

Regulation of psychedelics is fast changing around the world, making the use of PAT legal and far more accessible. There will be an urgent need for clinicians competent in this

intervention, and as such, there is a need to continue recognising, managing and appropriately integrating experiences of distress. Furthermore, there is a need to understand how therapists make sense of the distress they encounter and the interventions they make.

Current research has been critiqued for not reporting on adverse experiences adequately (Bremler et al. 2023; Colcott et al. 2023), which may indicate a lack of shared understanding of the phenomenon of distress. Previous reviews have encouraged the use of qualitative research in this area to add nuance to the meaning of distressing experiences (Breeksema et al. 2022). Although the topic has been discussed by therapists in the field (Phelps 2017; Richards 2015; Johnson, Richards and Griffiths 2008), no qualitative studies have specifically examined participant distress in PAT from the perspective of experienced therapists. Such research could provide a deeper, more sophisticated understanding of distress in PAT and its management.

### *Aims*

Distress in PAT encompasses a diverse range of psychologically difficult experiences that may also be therapeutically beneficial. The current research aims to generate a deeper understanding of adverse distressing experiences and those that may be of benefit. It also aims to generate a greater understanding of the role of the therapist in helping participants to manage distressing psychedelic experiences. Potential implications include; the unique features of distress in PAT, therapist responses to distress, maintaining therapeutic rapport, integrating the experience, ethical/safety considerations and training/supervision considerations.

### *Research Question*

How do psychedelic-assisted psychotherapists perceive distressing experiences in participants during PAT?

## Methods

### *Design*

An explorative, qualitative study of therapist's perceptions of distress in PAT.

It is acknowledged that the term "distress" was used instead of more recent terminology such as "challenging experiences" or "adverse experiences." Due to the subtleties outlined, a lack of clarity prevails over the terminology to describe distress in PAT (Breeksema et al. 2022). As such, the author used the broadest terminology available to maximise the inductive nature of the study while focusing the research on the experience of the participant therapists.

The study utilized a semi-structured interview schedule to guide data collection. Semi-structured interviews were selected for their flexibility in focusing on specific topics while allowing researchers to effectively probe participants' responses (Kajornboon 2005).

Open questions were developed based on gaps in the literature and discussion with the researcher's supervisors to maximise meaningful content. To facilitate a deeper discussion of the topic, participants were invited to share specific instances of encountering distress in PAT. Divergent information was discussed further when pertinent to the research question.

topics included participant demographics (such as educational background and experience in PAT), views on the nature and characteristics of distress in PAT, perceived causes and personal experiences of distress, interventions employed, cues for when to intervene, as well as considerations related to training, ethics, and safety.

### *Methodology*

Qualitative research facilitates a detailed exploration of the intricacies of participants' internal experiences along with the opportunity to document responses to these experiences. The researcher aimed to develop deep, explorative data on therapists' perceptions of participant distress in PAT. Reflexive Thematic Analysis (RTA) was selected to analyse the dataset to facilitate the identification of similarities, differences and patterns in the data (Braun and Clarke 2021).

The selection of Reflexive Thematic Analysis (RTA) for this study was intentional, as it allows for a thoughtful and reflective analysis of the data. This approach enables the researcher to draw on personal insights related to the topic, while identifying meaningful patterns that align with the study's objectives (Braun and Clarke 2019). Alternative methodologies, such as Interpretative Phenomenological Analysis, were considered due to the relevance of the lived experiences of psychedelic therapists. However, it was anticipated that the data would reveal a broad range of relevant themes, including patterns in perception and sense-making that could apply to a wider group of therapists. Given the exploratory nature of the research question and the expectation of diverse themes related to distress in psychedelic therapy, RTA was deemed more appropriate due to its flexibility in exploring both lived experience and the processes of meaning-making.

RTA was selected over codebook thematic analysis which necessitates multiple coders and uses a structured codebook approach to analysis. The researcher selected RTA due

to its greater flexibility and scope to make use of the researcher's self-reflexivity during analysis (Braun and Clarke 2021), encouraging researchers to reflect on how individual biases and beliefs shape the research process and encouraging the use of these insights (Braun and Clarke 2022).

### *Epistemological Positioning and Reflexivity*

This analysis was informed by the critical realist philosophical positioning of the researcher. Critical realism combines a 'realist' ontological position with a 'subjectivist' epistemological position. Critical realism provides a framework for understanding the complexity of the world by acknowledging both the existence of objective reality (objectivist ontology) and the subjective nature of our knowledge (subjectivist epistemology). It assumes the existence of an objective reality however acknowledges that this is interpreted differently by individual socially constructed meaning. As such there is an acknowledgement that the researcher's meaning-making processes could influence the research. Therefore, it is important to reflect on aspects of the researcher's influencing factors. Hence the researcher writes in the first person.

I am an Irish male in his early 30's. Historically, I have experimented with a variety of psychedelic compounds in a recreational manner, including MDMA, psilocybin and LSD. Some of the experiences felt highly meaningful and instilled in me a belief in the power of psychedelics to facilitate meaning and positive change in one's life. While studying psychology I have maintained an interest in emerging evidence of PAT for a variety of mental health presentations and monitored this research excitedly. My enthusiasm is tempered by working with people with severe problems affecting their mental health in a variety of settings and the contributing factor of substance misuse. As such I am wary of the potential risks of this intervention. I am mindful too that I have a lasting interest in relational psychodynamic theory and that I may be vulnerable to biasing insights that speak to this orientation.

### *Rigour*

To maintain academic rigour, the researcher documented their thoughts and feelings in a reflexive journal, updating their reflections after re-reading and immersing themselves in the data (See Appendix B). Research supervision, along with peer supervision workshops, provided valuable spaces for discussing insights and reflections. The researcher endeavoured to provide a transparent analysis of the data, selecting quotations from all participants. The

researcher referred to Braun and Clarke's (2022) 15-point checklist for good reflexive TA throughout the process.

### ***Participants***

#### *Sample Size*

A sample size of 12 participants was recruited for the study, following Braun and Clarke's (2022) broad recommendation for 10-20 participants for doctoral RTA studies. The concept of data saturation has been described as "deeply problematic" and vague (Braun and Clarke 2022) and the use of statistical models has also been criticised (Braun and Clarke 2021). As such, Malterud et al.'s (2016) concept of "information power" was used. The researcher repeatedly reflected on the depth of the information collected and whether it sufficiently matched the objectives of the study. After careful and continuous review, 12 participants were deemed to have provided satisfactory data of sufficient depth.

#### *Inclusion and Exclusion Criteria*

To effectively explore therapist's perspectives of distress in PAT, instead of the broader question of therapists as a whole, recruitment focused on individuals who were legally accredited to deliver psychotherapy in their locality and had significant experience delivering PAT using the classic psychedelics (psilocybin, LSD, DMT and mescaline) or MDMA in a legal setting. After consultation with the researcher's secondary supervisor, who has experience of designing PAT therapist training programmes, in order to maximise recruitment, significant experience was defined as having facilitated at least three sessions of PAT in a legal setting such as a clinical trial or retreat. Furthermore, participants were required to have encountered client distress while administering PAT.

Although both MDMA and serotonergic hallucinogens have distinct pharmacological characteristics, they are frequently grouped together as "psychedelics" and applied within similar therapeutic settings, with many therapists trained to administer psilocybin and MDMA-assisted therapy. Both carry the risk of amplified distress (Breeksema et al. 2022).

#### *Sampling*

Online recruitment took place from April to June 2024. Potential participants were identified on LinkedIn and contacted directly via private message. Some participants were emailed using details from their LinkedIn profile page. Further participants were recruited via snowball sampling. Alongside the invitation to participate, participants were provided with an information sheet (Appendix C) and consent form (Appendix D) and offered the opportunity to ask questions.

### ***Procedure***

An interview appointment was arranged at the participant's convenience. All interviews were conducted remotely using MS Teams (Classic). The participants were invited to complete the consent form themselves however were given the option to complete the form verbally at the interview appointment. To ensure clarity regarding their consent, the consent process was recorded, capturing the participant's explicit agreement or disagreement with each consent item (yes/no). This recording served as a crucial safeguard, offering clarification in case any questions arise regarding the participant's provision of fully informed consent. The researcher, as a procedural step, marked the consent form on behalf of the participant. The researcher stored a copy of the completed consent form and sent a copy to the individual participant. Participants were then asked a series of demographic questions to identify their level of experience with PAT, their professional accreditation and the country where they work as PAT therapists. The interviewer was guided by an interview schedule (Appendix E) during this process however was flexible regarding the questions asked, preferring to be guided by the flow of the conversation.

The interviews were transcribed automatically using Microsoft Teams. Transcriptions were checked by the researcher following the interview. Verbatim transcripts were provided to participants for their review before proceeding with the analysis, allowing them the opportunity to suggest changes or omissions (Amankwaa 2016). This step was taken to ensure trustworthiness and transparency in the research process. Any identifying information was removed from the transcripts. Non-verbal observations of interest were added to the transcript e.g. laughter or hesitations.

Interviews took place over approximately one hour. The researcher ensured confidentiality by conducting the online interviews from a private study in their home.

### Data Analysis

The data was analysed inductively, focusing on generating themes directly from the content of the data, rather than fitting the data into pre-existing theoretical frameworks, facilitating a flexible approach to the research question.

Braun and Clarke's (2022) six stages of RTA were used to guide the analysis of the transcripts.

1. Familiarisation with the data.
2. Initial coding
3. Generating initial themes

4. Reviewing themes
5. Defining and naming themes
6. Report writing

Each interview was watched twice while checking the transcriptions for accuracy and making notes in a reflexivity journal to ensure familiarity.

Initial codes were generated using the comment function on Microsoft Word (see Appendix F). Transcripts and codes were then transferred to NVivo 14, a qualitative data software programme and more detailed coding took place at a semantic and latent level (see Appendix G, H and I). Overlapping codes were consolidated, distinct codes were further developed, and codes with insufficient frequency were discarded. Patterns within the data were identified through this organisation and codes were then arranged into themes and subthemes by combining related codes to establish broader patterns of meaning (See Appendix J). The themes were reviewed, refined and reorganised in a continual process to ensure they pertained to the aims of the study and were coherent (See Appendix K). Patton's (2014) dual criteria for judging categories were applied to the process to ensure internal homogeneity within themes and external heterogeneity between themes. Throughout the report writing process, themes, subthemes and codes were further defined, reviewed and discarded.

### *Ethics*

The Staffordshire University Research Ethics panel granted approval for the project (see Appendix L). An information sheet detailing confidentiality, the right to withdraw from the study and anonymity was given to all participants to read before obtaining written/verbal consent for their participation. Following the interview, participants were sent a debrief sheet which included directions to support should they experience distress related to the interview process (Appendix M). To ensure confidentiality and anonymity, participants were assigned a pseudonym and any other identifying information was excluded or amended during transcription. No incentives to participate were offered.

## Results

### *Participants*

Twelve participants were recruited from the UK, Netherlands, USA, Australia and Switzerland. Participants legally delivered PAT in clinical trial settings, privately or in retreats. Seven were clinical psychologists, three were psychotherapists and two were psychiatrists. The approximate number of PAT sessions they had delivered varied between 10 and 700. The compounds that were used included; psilocybin, MDMA, LSD and DMT.

*Table 1: Participants*

| Pseudonym | Professional Accreditation |
|---|---|
| Sean | Psychotherapist |
| James | Clinical Psychologist |
| Joseph | Clinical Psychologist |
| Arjuna | Clinical Psychologist |
| Kate | Psychotherapist |
| Timothy | Psychiatrist |
| Ava | Psychotherapist |
| Richard | Psychiatrist |
| Maria | Clinical Psychologist |
| Hugo | Clinical Psychologist |
| Gemma | Clinical Psychologist |
| Chris | Clinical Psychologist |

### *Findings*

*Table 2: Themes and subthemes*

| Themes | Subthemes |
|---|---|
| *Making Sense of Distress* | The Amplified Nature of Distress |
| | Difficulties Assessing Distress |
| | Normalising Distress as a Meaningful Process |
| *Therapist as the Safe Base* | Building Connection |
| | Holding Participants through Distress |

| | |
|---|---|
| *Navigating Distress* | Preparing for the Ineffable |
| | Balancing Autonomy with Support |
| | Finding Meaning in Distress |

***Theme One: Making Sense of Distress***

This theme illustrates some of the unique features of distress in PAT and the meaning that is ascribed to it by therapists. *Amplified Nature of Distress* describes the vivid nature of distress, what can be seen and the presentations of distress that are encountered by therapists that are peculiar to PAT. *Difficulties Assessing Distress* highlights the challenges of assessing a phenomenon which may be a highly internal process or appear inconsistent with participants' experience. *Normalising Distress as a Meaningful Process* describes the views therapists have of distress as a process that may be helpful.

***Amplified Nature of Distress in PAT***

Therapists described the phenomenon of psychedelics intensifying psychological phenomena and increasing their significance. Sometimes, this referred to ordinary psychological processes getting magnified, for example, emotions and thought patterns. Participants were described as experiencing heightened negative emotions "*We see people expressing stronger emotions than they might otherwise normally do… whether that's grief and crying… anxiety or fear… Anger… Frustration"* (Chris). "Looping" was a term repeated by therapists which describes acute rumination "*if you had a client being like "I hate myself. I hate myself. I hate myself."* (Gemma).

Therapists also described a variety of forms of distress that can be described as an altered perception of reality. *"You've got other people who go through the most distressing things you could imagine. They could be in the raptures of hell. They could feel horrific. They could feel that they're dying. They could feel that they're losing touch with their body. They could feel that… They are something they feared they were and get lost in this terror…"* (James). Similarly, therapists described paranoia, participants becoming distressed by delusional or persecutory thoughts *"The woman became convinced with drug onset that her family had been killed that morning in a horrific accident."* (Arjuna).

Other forms of distress included challenging biographical material, including vividly re-experiencing traumatic events. "*Two people I'm thinking of who just really kind of dove back into re-experiencing some of their traumas, say a sexual assault that they had dissociated from. And then during the session are then able to, you know, remember both the emotions and the physical sensations of that."* (Timothy). Sometimes, distress was described as a panic or trauma response. "*Beginning to hyperventilate. Crying, screaming, agitated movement. Kind of dissociated process. Eyes wide open. You know, staring right through or beyond me..."* (Arjuna).

***Difficulties Assessing Distress***

Assessing distress in PAT was described as complex. Therapists were surprised and, sometimes, troubled by how routine visible indicators of distress (e.g. crying) may not be obvious in PAT due to the possibility of distress being an entirely internal phenomenon which may not appear physiologically. Some therapists shared anecdotes of participants showing no signs of visible distress or appearing calm during dosing but retrospectively reporting extreme distress. *"No verbal response at all and we were monitoring blood pressures as well. His pressure was normal range, no deviation, no shift in movement, no shift in colour. He kept the eye shades on throughout, his respiration was normal. No kind of agitated process. No verbal process, nothing. The next day, when we talked about the experience, he said it was absolutely, utterly terrifying"* (Arjuna). Conversely, therapists also described participants appearing to be highly distressed but later reporting that they weren't *"when she came out of it, she just felt like she'd had a real release and that it was a good experience"* (Kate).

***Normalising Distress as a Meaningful Process***

Therapists normalised the occurrence of distress, drawing parallels with routine psychotherapy. "*There is no therapy without distress"* (James). Therapists reflected that distress in PAT was expected *"not an outlier"* (Richard). Therapists reported that participants experienced distress differently, and described it mostly as meaningful. Distress was sometimes conceptualised as an "unfolding process" whereby distress was experienced by participants as a necessary route towards healing: *"This is difficult but it's what I need to do"* (Hugo).

Therapists offered views about the value of participants confronting or staying with distress to transcend it as a crucial part of the PAT experience.

*"Although people might be shaken by the experience, they've also survived, transcended, recognised their own resilience, gone more deeply beyond the death of the conceptual self or their great fears, whatever they may be. They've survived it all and there's something very meaningful about that deep experience being held so that what people will sometimes say… They don't experience fear or anxiety in nearly the same way, because they've conquered the self, or they've conquered their own fear." (*Arjuna)

While therapists were careful not to overstate the risks of participants becoming distressed in PAT, they also acknowledged a risk of harm from distress if it isn't attended to appropriately. *"It's all very well shaking the snow globe, but it's really how it lands that matters. How it lands within the psyche of the person, how they make sense of it and how they're held through it determines whether it could be traumatic or therapeutic"* (Kate).

***Theme Two: Therapist as the Safe Base***

This theme illustrates therapists' perception of their role as being a "safe base" grounded in reality and underpinned by trust for participants to return to for care when exploring an altered state of consciousness. *Building Connection* describes the importance that therapists place on establishing a robust therapeutic relationship. *Holding Participants through Distress* describes the role of the therapist in creating a space where the patient feels safe, understood, and nurtured through distress.

***Building Connection***

Therapists described the importance of a trusting relationship in PAT: *"They need to trust your ability to… hold them in their most difficult and vulnerable psychological state"* (Sean). Therapists described their ability to offer support effectively as being contingent on a foundation of connection *"One of the things that really has struck me in the early days of this work… Is how the subtle interventions we use for quite heightened distress, they wouldn't work if we didn't have a therapeutic relationship before…"* (Gemma).

Therapists identified challenges to building a trusting connection such as the core difficulty that many people have in trusting others *"reality is that many patients have exactly this issue that it's difficult to trust."* (Ava). Other challenges included the constraints of the research environment *"The preparation sessions are pretty stacked… Something we've tried to do in our trial is trying to remind ourselves… Some of those details, if we don't get to them*

*all… It's not the end of the world... The most important thing is we're building that trust and responding in a way that communicates trust"* (Chris).

***Holding Participants through Distress***

Therapists emphasised the importance of therapeutic presence in responding to distress and communicating this to participants. *"You're not alone. I'm with you. I'm here. I've got your back. You're safe."* (Chris). Therapists described the necessity of tolerating high levels of distress to facilitate PAT effectively. "*Nothing more important in PAT than to be in an environment where you can be distressed and that is welcomed, no one's panicking. Every part of them is welcome and that we are there… that we can handle all the distress and all the things that might happen."* (James).

Therapists described the importance of maintaining a calm presence. "*A relaxed sitter is a good sitter. I think that's one of the most important things that you have the capacity to hold and be still within yourself..."* (Ava). Therapists described the challenge of maintaining a sense of concentration and attunement to participants during long dosing sessions. "*The times where they have gone sideways for me is when I'm preoccupied."* (Arjuna).

Furthermore, there was a sense of some therapists feeling challenged in their role by the acuity of the distress they encountered, feeling "*thrown in the deep end"* (Kate). They attributed this to a lack of experiential training. Also, the complexity of issues experienced by people they were working with, who may be predisposed to experiencing higher levels of distress as a result of their presentation, was challenging.

*"We can only give these medicines to the most treatment-resistant people… So it's only legal for people that have tried everything else… These are our first psychedelic clients."* (Gemma).

***Theme Three: Navigating Distress***

This theme reflects the therapist's perceptions of guiding participants through distress in PAT, some of the perceived challenges of doing so and some of the self-reflection that is required. *Preparing for the Ineffable* describes the process of preparing participants for the possibility of distress. *Balancing Autonomy and Support* highlights the complexity of therapists allowing participants to experience the entire catalogue of phenomena that may include transient distress while also providing sufficient care and guidance. *Finding meaning*

*in Distress* highlights the of role therapists helping participants to make meaning of distress in the therapy that follows psychedelic dosing.

***Preparing for the Ineffable***

Therapists described how preparing participants for the potential to experience distress and the need to move towards and stay with distressing content is crucial. "*You're really prepping them and cheerleading them to go towards what's difficult"* (James).

Therapists highlighted the challenges of preparing for psychedelic experiences which may be unpredictable and ineffable. *"How do we prepare someone for an experience that's indescribable? An ineffable experience or ego death? We can talk about things that might help, but even those are difficult to describe."* (Maria). Similarly, therapists shared difficulties within the informed consent process. *"They're consenting to the total unknown… We give them different examples of experiences that they might have, but they don't know and we don't know what will come up. So I think it's just really preparing them for… The unknown…Potentially something really intense…"* (Gemma).

Therapists described contracting their response to distress clearly with participants. Responses included the agreed use of therapeutic touch and a reminder to use existing skills such as breathing techniques.

***Balancing Autonomy with Support***

Therapists described the tension between adopting a generally favoured non-directive approach to PAT with needing to move towards a more directive supporting role when necessary. There was a perspective that the non-directive stance was needed to avoid interrupting important internal processes. However, some therapists expressed discomfort with an overreliance on this position and identified a risk of neglecting to intervene when needed. "*There's a conundrum, which is for a psychedelic therapist to not be too lax and not taking the right steps or having the right amount of concern to work with or address the distress that is arising"* (Hugo). Therapists described ongoing self-reflection as a key component of their decisions on whether or not to offer interactive support, especially reflecting on their need to "rescue" participants. *"When we see someone in distress, we can feel that and the question I always ask myself first is it my distress that I'm wanting help with? Or is it their distress?"* (Maria).

Therapists identified cues for directive support which included panic, paranoia, trauma responses and risk to safety. Duration of distress was also seen as an important metric in deciding whether to intervene. Some therapists described measuring the duration of distress intuitively. *"15-20 minutes… As a general rule of thumb… If it doesn't feel like they're moving on to something that I might be a little bit more active in how I'm responding."* (Chris).

Types of therapist-led interventions included grounding strategies, such as supporting somatic awareness by engaging in dialogue to verbally direct participants' attention to internal experiences. "*Just bringing someone's awareness to, "OK, what is it that you're noticing in your body? Where are you noticing it? Can you describe it? What happens if you take some breaths in and out and just think of your breath as moving a little bit of air around that part of the body."* (Timothy). Also, the use of therapeutic touch "*it may be that people need nervous system regulation and that can be done through touch."* (Sean). Other grounding techniques were also described which directed participants' attention away from distressing internal experiences. "*We created the option of like creating a wrapped up towel to put at their feet to sort of ground ... so it would be like a simple technique to… physiologically tell the nervous system. 'Hey, you're OK.'"* (Kate).

***Finding Meaning in Distress***

Therapists stressed the importance of helping participants make meaning of distressing experiences. "*I think some of the hardest trips aren't the ones necessarily that are the most painful in terms of intensity, but that don't make sense to the client."* (Chris). The meaning-making process was flexible, dependant on the unique psychedelic experience of the participant. Therapists saw themselves as having an important role in meaning-making in the integration sessions that follow a psychedelic experience. "*So we help people find meaning in suffering… Then help them frame it as a process that you know that you may have gone through a very difficult part… but often perhaps it was necessary and important…"* (Sean). Therapists expressed an ethical desire to be flexible towards providing further support than is included in standard protocols when needed and for participants to be offered adequate support to process distress. "*So there are quite a lot of psychedelic integration groups now that exist. If someone has a particularly challenging experience, we'll probably get the sponsor to pay for a bit more integration to help them move through it."* (Kate)

## Discussion

The purpose of this study was to explore how therapists perceive participant distress in PAT. Most therapists normalised distress as a necessary part of healing, not just in PAT but in therapy in general, they described a variety of forms of distress that were intense and would be highly unusual in other forms of psychotherapy. While therapists described distressing experiences as having the potential to be highly meaningful, they also acknowledged the potential risk of harm to participants. Therapists described difficulties in assessing distress, which may be hidden. Therapists described an important role in forming a robust therapeutic alliance with participants, in order for them to be able to effectively guide participants through distressing experiences. Three major themes were identified: "Making Sense of Distress," "Therapist as the Safe Base," and "Navigating Distress."

Within the "Making sense of Distress" theme, therapists described how they evaluated distress in PAT. This theme supports the existing theory of psychedelics as "non-specific amplifiers" which can intensify mental phenomena such as distress (Grof 1994; Gorman et al. 2021). Therapists reported high levels of distress, including terror but viewed these experiences as potentially meaningful and beneficial. Therapists shared anecdotes from participants who reported terrifying experiences during sessions yet reported emerging stronger from these experiences and with profound insights. Some therapists described participants reporting feeling that these difficult experiences were crucially necessary. Consequently, therapists viewed distress as a process not to be interrupted without careful consideration of its potential value to the participant. This study supports previous research highlighting the difficulty of accurately measuring beneficial phenomena that could be simultaneously categorised as an adverse event in clinical research (Breeksema 2022). Similarly, Murphy et al. (2023) highlight the possibility of symptoms worsening in the short term after accessing challenging biographical material but ultimately facilitating meaningful connection to the self and others over time. This highlights the lack of clarity on how the concept of distress is communicated within a Western cultural context i.e. PAT research (Robinson et al. 2024).

A significant finding was the challenging position therapists found themselves in when assessing participants for distress. Therapists recounted instances where participants exhibited little or no outward signs of distress, including physiological measures such as blood pressure but later reported terrifying experiences; a phenomenon that appeared to be limited to classic psychedelics. This discrepancy highlights the limitations of relying solely

on observable indicators to identify distress, a phenomenon not well-documented in existing literature. These findings underscore the need for future research and enhanced training for therapists to better prepare them for the unpredictable and sometimes undetectable nature of distress in PAT, perhaps with a greater emphasis on experiential training.

Therapists emphasised the importance of maintaining a trusting relationship characterised by a calm, consistent and caring presence through long dosing sessions that may include heightened expressions of distress. This was conceptualised as the 'safe base' from which participants could explore an altered state of consciousness. These findings support existing research on the link between the therapeutic relationship and quality of experience (Murphy et al. 2022; Levin et al. 2024). Establishing a consistent, trustworthy relationship was a central concern of the therapists, reflecting Phelps' (2017) competency of 'Trust Enhancement.' This also reflects the characteristics of psychedelic carers in non-clinical settings outlined by Thal, Engel and Bright (2022). These findings highlight challenges to fulfilling this competency, with therapists feeling constrained by systemic factors such as treatment protocols that sometimes hindered the establishment of necessary therapeutic rapport due to short preparation phases and practical requirements such as psychometric measures. Furthermore, therapists were mindful of the barriers to trust common in certain mental health conditions i.e. trauma presentations. Insights from this study highlight the importance of not rushing the screening or preparation phases of treatment to ensure the intervention is therapeutic and distress can be safely experienced. These findings support suggestions that the routine three sessions of preparation outlined in many protocols may be insufficient for some participants, emphasising the need for more extensive preparation that explicitly prioritises establishing the therapeutic relationship over other requirements (Levin et al. 2022).

"Navigating Distress" highlights the tension therapists felt between traditionally non-directive approaches in PAT and the need for more interactive support when distress was perceived. There was a sense of uncertainty regarding when directive support was needed and this appeared to be context-specific. Reflecting on impulses to rescue participants and avoiding being overly reactive were identified as important considerations for therapists, highlighting the importance of therapeutic presence or 'doing by non-doing' (Phelps 2017). Intensified psychodynamic factors in PAT, for example, transference and countertransference, may be relevant to this process. Phelps (2017) identifies self-awareness as a crucial competency of PAT therapists, emphasising the need for therapists to reflect on

activations of countertransference and the importance of enacting roles in response to unconscious material that emerges during sessions, for example, the need to rescue participants. Relatedly, Grof (1980) recommends building awareness of impulses to act impressively towards participants. These insights emphasize the role of clinical supervision, personal therapy and other efforts to build self-awareness.

Therapists identified several cues for engaging with distressed participants. While lasting harm or negative outcomes caused by distress were reportedly rare, therapists maintained an awareness of the risk that distress could become traumatising. Therapists described employing a range of complementary techniques, another competency highlighted by Phelps (2017). Grounding techniques were used to lower participants' levels of arousal, including somatic awareness and the use of therapeutic touch. This insight highlights the need for therapists to be proficient at helping to regulate distressed participants when interactive support is warranted. Duration of distress was identified as a cue for supportive intervention however this factor remained undefined, with therapists describing using intuition or arbitrary metrics of time to determine their decision to support participants.

This study emphasises the importance of thoroughly preparing participants for the possibility of distress, with difficulties identified in obtaining informed consent. Therapists described the difficulty of communicating the transformative and often ineffable nature of psychedelic experiences, which may have highly distressing moments. This has been identified as a dilemma by Jacobs (2023), who described the process of informed consent as it is typically conceived in medical ethics as not possible in PAT. Others (Viliger 2024) have argued that it is possible and have pointed towards enhanced informed consent procedures by sharing examples of other participants' transformative experiences, which for the purposes of this study, could include examples of intensely distressing psychedelic experiences. This study highlights the necessity of further clarifying informed consent procedures in PAT.

Finally, this study highlights the crucial role of careful integration of distressing experiences in PAT, supporting previous literature and current practice (Grof 1994; Johnson, Richards and Griffiths 2008; Phelps 2017).

### *Strengths*

Therapists' perceptions of distress in PAT is a previously unexplored topic. This research articulates the complexity with which distress is viewed by therapists within PAT research and clinical practice, highlighting the possibility that highly distressing experiences can be

both transformative and therapeutic or traumatising and harmful. The study also highlighted a lack of clarity in therapists' understanding of when interactive intervention may be needed and identified a potential vulnerability of therapists feeling the need to rescue participants. Furthermore, the study highlights the possibly under-reported phenomenon of distress not being apparent to therapists that may even evade physiological measurement apparatus. This study demonstrates the need for distress to be central to training psychedelic therapists and highlights the role of experiential training on this topic where possible.

As outlined by Braun and Clarke (2022), the insights generated by this research are reflexively shaped by the researcher's own experiences. The researcher's personal experience delivering and participating in psychotherapy as well as having personal experiences of altered states of consciousness from psychedelics allowed him to connect deeply with the research topic.

### *Limitations*

The conception of the "Safe Base" theme and subtheme "Holding distress" is guided by the researcher's orientation towards psychodynamic principles (Bowlby 1969; Winnicott 1963). As such, the role of the therapist is specific to a Western cultural context and could be viewed differently in other cultures and traditions associated with the use of psychedelics e.g. indigenous, Shamanism.

A general limitation of qualitative research is that it examines the perceptions of a relatively small sample of a population. Breeksema et al. (2022) identified that therapist observations can be subject to ambiguity since they may be influenced by their subjective perceptions and interpretations.

The researcher was mindful of the limited number of therapists administering PAT and deliberately selected a broad inclusion criteria to satisfy recruitment efforts however it is possible that this came at the expense of some depth within the data and limited generalisability. There was considerable variance within the sample concerning the compounds used in PAT. Therapists listed psilocybin, DMT, LSD and MDMA as compounds used. While psilocybin, DMT and LSD are "classic" serotonergic psychedelics and are generally thought to have a similar mechanism of action, MDMA is pharmacologically distinct and operates differently. While all the listed compounds are administered in a similar therapeutic setting and are associated with expressions of distress, there are idiosyncrasies regarding the expression of distress that may not have been captured within the analysis. As

such, future research may focus on therapist's perceptions of participant distress within the context of specific compounds. The research may also have been influenced by the heterogeneity of therapist characteristics in the sample. Perceptions of participant distress varied according to the level of experience of the therapist, with more experienced therapists appearing more comfortable with distress arising within the context of PAT than therapists with relatively less experience with the intervention.

Similarly, the clinical presentations and settings that therapists' facilitated PAT were varied. Presentations included depression, anxiety, anxiety related to a health condition, PTSD and healthy populations. Some therapists attributed the distress exhibited to the clinical presentation as much as the compound used. Furthermore, the settings in which therapists administered PAT varied between clinical trials, private healthcare settings and retreats. Some therapists predominately operated within a group therapy setting with multiple facilitators. There was a variety of geographical locations where PAT was being facilitated. These are variables that could limit the transferability of these findings and future research could benefit from narrowing the inclusion criteria accordingly, focusing on distress associated with specific compounds, clinical presentations and clinical settings. This may be particularly useful as the use of PAT proliferates and potential sample sizes of therapists grow.

While all participant therapists' reflections informed data analysis and efforts were made to include quotes from all participant therapists, less quotes were used for some therapists. This may have been influenced by some of the sample not being native English speakers.

### *Future Research*

Further qualitative investigation into distress in PAT would be useful, focusing on participant experiences of this phenomenon. This study highlights the phenomenon of hidden distress in PAT, which may be under-reported in the literature. Four of the therapist participants in this study described such experiences, indicating that this phenomenon may be under-reported. Future research could focus on the phenomenology of hidden distress or develop assessment methods to detect it more accurately.

Duration of distress was a key consideration concerning making decisions whether to offer interactive support, with therapists describing waiting to see whether distress resolves

itself independently before intervening unless there was a risk to the participant's safety. Further research is needed to investigate the link between duration of distress and outcomes.

Future research may also investigate whether more experienced PAT therapists perceive distress differently to less experienced or newly qualified therapists and explore the reasons and consequences of this difference.

## Conclusion

This research aimed to explore the question: *How do psychedelic-assisted psychotherapists perceive distressing experiences in participants during PAT?* Using RTA, three themes were identified; "Making Sense of Distress," "Therapist as the Safe Base," and "Navigating Distress."

Distress was viewed as potentially part of a meaningful healing process however; it was also viewed as potentially harmful. Assessing distress is complex due to the possibility that it may not be apparent by standard methods of observation and may be part of a beneficial process. Therapists described the crucial role of the therapeutic relationship in creating a sense of safety. Therapists described ethical considerations relating to the informed consent process. There is a lack of clarity regarding when to offer directive support to distressed participants, complicated by therapists being vulnerable to trying to rescue participants from elevated distress. Grounding techniques were described as common interventions by therapists when needed. Therapists emphasised the need to support participants to make meaning of distressing experiences.

### *Clinical Implications*

- Therapists should be prepared to encounter high levels of distress when administering PAT.
- Heightened distress may not be associated with negative outcomes in PAT.
- Therapists should be aware that distress may not be visibly apparent in participants.
- Training programmes should emphasise the complex nature of distress in PAT and appropriate responses to it, prioritising the self-awareness of therapists.
- Establishing a strong therapeutic relationship should be prioritised with preparation sessions added as required.

- Therapists and researchers should be mindful of potential gaps in the informed consent process in PAT, Therapists should consider offering examples of distressing experiences.
- Therapists should clearly contract with clients what actions to take in response to distress and should be skilled in a variety of grounding techniques.
- Participants should be supported to make meaning of distressing experiences and further integration sessions should be offered when required.

## References


Amankwaa, L., 2016. Creating protocols for trustworthiness in qualitative research. *Journal of cultural diversity*, *23*(3).

Avissar, N., 2024. Psychedelics and Risk Assessment: Examining Self Factors through Qualitative Research. *The Journal of Psychedelic Psychiatry*, 6(1).

Barrett, F.S., Bradstreet, M.P., Leoutsakos, J.M.S., Johnson, M.W. and Griffiths, R.R., 2016. The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. *Journal of Psychopharmacology*, *30*(12), pp.1279-1295.

Belser, A.B., Agin-Liebes, G., Swift, T.C., Terrana, S., Devenot, N., Friedman, H.L., Guss, J., Bossis, A. and Ross, S., 2017. Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomenological analysis. *Journal of Humanistic Psychology*, *57*(4), pp.354-388.

Birmingham, P. and Wilkinson, D., 2003. *Using research instruments: A guide for researchers*. Routledge.

Bowlby, J., 1969. *Attachment and loss* (No. 79). Random House.

Braun, V. and Clarke, V., 2006. Using thematic analysis in psychology. *Qualitative research in psychology*, *3*(2), pp.77-101.

Braun, V. and Clarke, V., 2019. Reflecting on reflexive thematic analysis. *Qualitative research in sport, exercise and health*, *11*(4), pp.589-597.

Braun, V. and Clarke, V., 2021. To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample-size rationales. *Qualitative research in sport, exercise and health*, *13*(2), pp.201-216.

Braun, V. and Clarke, V., 2021. One size fits all? What counts as quality practice in (reflexive) thematic analysis? *Qualitative research in psychology*, *18*(3), pp.328-352.

Braun, V. and Clarke, V., 2022. Conceptual and design thinking for thematic analysis. *Qualitative psychology*, *9*(1), p.3.

Braun, V., & Clarke, V., 2022. *Thematic Analysis: a practical guide.* Sage Publications Ltd.

Breeksema, J.J., Kuin, B.W., Kamphuis, J., van den Brink, W., Vermetten, E. and Schoevers, R.A., 2022. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review. *Journal of Psychopharmacology*, *36*(10), pp.1100-1117.

Bremler, R., Katati, N., Shergill, P., Erritzoe, D. and Carhart-Harris, R.L., 2023. Case analysis of long-term negative psychological responses to psychedelics. *Scientific Reports*, *13*(1), p.15998.

Brennan, W., Jackson, M.A., MacLean, K. and Ponterotto, J.G., 2021. A qualitative exploration of relational ethical challenges and practices in psychedelic healing. *Journal of Humanistic Psychology*, p.00221678211045265.

Brennan, W. and Belser, A.B., 2022. Models of psychedelic-assisted psychotherapy: A contemporary assessment and an introduction to EMBARK, a transdiagnostic, trans-drug model. *Frontiers in psychology*, *13*, p.866018.

Carbonaro, T.M., Bradstreet, M.P., Barrett, F.S., MacLean, K.A., Jesse, R., Johnson, M.W. and Griffiths, R.R., 2016. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of psychopharmacology*, *30*(12), pp.1268-1278.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D. and Nutt, D.J., 2021. Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine*, *384*(15), pp.1402-1411.

Cavarra, M., Falzone, A., Ramaekers, J.G., Kuypers, K.P. and Mento, C., 2022. Psychedelic-assisted psychotherapy—A systematic review of associated psychological interventions. *Frontiers in psychology*, *13*, p.887255.

Chisamore, N., Johnson, D., Chen, M.J., Offman, H., Chen-Li, D., Kaczmarek, E.S., Doyle, Z., McIntyre, R.S. and Rosenblat, J.D., 2024. Protocols and practices in psilocybin assisted psychotherapy for depression: a systematic review. *Journal of psychiatric research*.

Cohen, Z.D. and DeRubeis, R.J., 2018. Treatment selection in depression. *Annual Review of Clinical Psychology*, *14*(1), pp.209-236.

Colcott, J., Guerin, A.A., Carter, O., Meikle, S. and Bedi, G., 2024. Side-effects of MDMA-assisted psychotherapy: a systematic review and meta-analysis. *Neuropsychopharmacology*, pp.1-19.

Davis, A.K., Barrett, F.S., May, D.G., Cosimano, M.P., Sepeda, N.D., Johnson, M.W., Finan, P.H. and Griffiths, R.R., 2021. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA psychiatry*, *78*(5), pp.481-489.

Earleywine, M., Low, F., Lau, C. and De Leo, J., 2022. Integration in psychedelic-assisted treatments: Recurring themes in current providers' definitions, challenges, and concerns. *Journal of Humanistic Psychology*, p.00221678221085800.

Emerson, A., Ponté, L., Jerome, L. and Doblin, R., 2014. History and future of the Multidisciplinary Association for Psychedelic Studies (MAPS). *Journal of psychoactive drugs*, *46*(1), pp.27-36.

Gorman, I., Nielson, E.M., Molinar, A., Cassidy, K. and Sabbagh, J., 2021. Psychedelic harm reduction and integration: A transtheoretical model for clinical practice. *Frontiers in psychology*, *12*, p.645246.

Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P. and Klinedinst, M.A., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology*, *30*(12), pp.1181-1197.

Griffiths, R.R., Richards, W.A., McCann, U. and Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, *187*, pp.268-283.

Grof, S. 1994. *LSD Psychotherapy*. 2nd ed. Alameda, CA: Hunter House.

Haijen, E.C., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R.E., Hampshire, A.D., Lorenz, R. and Carhart-Harris, R.L., 2018. Predicting responses to psychedelics: a prospective study. *Frontiers in pharmacology*, *9*, p.897.

Jacobs, E., 2023. Transformative experience and informed consent to psychedelic-assisted psychotherapy. *Frontiers in Psychology*, *14*, p.1108333.

Jesse, R. and Griffiths, R.R., 2014. Psilocybin research at Johns Hopkins: A 2014 report. *Seeking the sacred with psychoactive substances: Chemical paths to spirituality and to god*, *2*, pp.29-43.

Johnson, M.W., Richards, W.A. and Griffiths, R.R., 2008. Human hallucinogen research: guidelines for safety. *Journal of psychopharmacology*, *22*(6), pp.603-620.

Johnson, M.W., Garcia-Romeu, A., Cosimano, M.P. and Griffiths, R.R., 2014. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *Journal of psychopharmacology*, *28*(11), pp.983-992.

Kajornboon, A.B., 2005. Using interviews as research instruments. *E-journal for Research Teachers*, *2*(1), pp.1-9.

Leary, T., Litwin, G.H. and Metzner, R., 1963. Reactions to psilocybjn administered in a supportive environment. *The Journal of nervous and mental disease*, *137*(6), pp.561-573.

Lennard, H. and Hewitt, M., 1960. The study of communication processes under LSD. *The use of LSD in psychotherapy*, pp.199-240.

Levin, A.W., Lancelotta, R., Sepeda, N.D., Gukasyan, N., Nayak, S., Wagener, T.L., Barrett, F.S., Griffiths, R.R. and Davis, A.K., 2024. The therapeutic alliance between study participants and intervention facilitators is associated with acute effects and clinical outcomes in a psilocybin-assisted therapy trial for major depressive disorder. *PloS one*, *19*(3), p.e0300501.

Marrocu, A., Kettner, H., Weiss, B., Zeifman, R.J., Erritzoe, D. and Carhart-Harris, R.L., 2024. Psychiatric risks for worsened mental health after psychedelic use. *Journal of Psychopharmacology*, *38*(3), pp.225-235.

Malterud, K., Siersma, V.D. and Guassora, A.D., 2016. Sample size in qualitative interview studies: guided by information power. *Qualitative health research*, *26*(13), pp.1753-1760.

Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Martin, S.F., Yazar-Klosinski, B., Michel, Y., Brewerton, T.D. and Doblin, R., 2013. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *Journal of psychopharmacology*, *27*(1), pp.28-39.

Murphy, R., Kettner, H., Zeifman, R., Giribaldi, B., Kartner, L., Martell, J., Read, T., Murphy-Beiner, A., Baker-Jones, M., Nutt, D. and Erritzoe, D., 2022. Therapeutic alliance and rapport modulate responses to psilocybin assisted therapy for depression. *Frontiers in Pharmacology*, *12*, p.788155.

Nielson, E.M. and Guss, J., 2018. The influence of therapists' first-hand experience with psychedelics on psychedelic-assisted psychotherapy research and therapist training. *Journal of Psychedelic Studies*, *2*(2), pp.64-73.

Nielson, E.M., May, D.G., Forcehimes, A.A. and Bogenschutz, M.P., 2018. The psychedelic debriefing in alcohol dependence treatment: illustrating key change phenomena through qualitative content analysis of clinical sessions. *Frontiers in pharmacology*, *9*, p.132.

Patton, M.Q., 2014. *Qualitative research & evaluation methods: Integrating theory and practice*. Sage publications.

Pahnke, W.N. and Richards, W.A., 1966. Implications of LSD and experimental mysticism. *Journal of Religion and Health*, *5*(3), pp.175-208. doi:10.1080/02791072.1970.10471366

Phelps, J., 2017. Developing guidelines and competencies for the training of psychedelic therapists. *Journal of Humanistic Psychology*, *57*(5), pp.450-487.

Richards, W.A., 2015. *Sacred knowledge: Psychedelics and religious experiences*. Columbia University Press.

Roseman, L., Haijen, E., Idialu-Ikato, K., Kaelen, M., Watts, R. and Carhart-Harris, R. 2019. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. *Journal of psychopharmacology*, *33*(9), pp.1076-1087.

Robinson, O.C., Evans, J., Luke, D., McAlpine, R., Sahely, A., Fisher, A., Sundeman, S., Ketzitzidou Argyri, E., Murphy-Beiner, A., Michelle, K. and Prideaux, E., 2024. Coming back together: a qualitative survey study of coping and support strategies used by people to cope with extended difficulties after the use of psychedelic drugs. *Frontiers in Psychology*, *15*, p.1369715.

Robinson, O.C., Evans, J., Luke, D., McAlpine, R., Sahely, A., Fisher, A., Sundeman, S., Ketzitzidou Argyri, E., Murphy-Beiner, A., Michelle, K. and Prideaux, E., 2024. Coming back together: a qualitative survey study of coping and support strategies used by people to cope with extended difficulties after the use of psychedelic drugs. *Frontiers in Psychology*, *15*, p.1369715. doi:10.1177/0269881116675512

Schultes, R. E. 1979. *The plants of the gods: Origins of hallucinogenic use*. New

York, NY: McGraw-Hill.

Shireen, H., Siemers, N., Dor-Ziderman, Y., Knäuper, B. and Moodley, R., 2022. Treating others as we treat ourselves: A qualitative study of the influence of psychotherapists' mindfulness meditation practice on their psychotherapeutic work. *Current Psychology*, pp.1-15.

Simonsson, O., Hendricks, P.S., Chambers, R., Osika, W. and Goldberg, S.B., 2023. Prevalence and associations of challenging, difficult or distressing experiences using classic psychedelics. *Journal of Affective Disorders*, *326*, pp.105-110.

Smith, W.R. and Sisti, D., 2021. Ethics and ego dissolution: the case of psilocybin. *Journal of medical ethics*, *47*(12), pp.807-814.

Strassman, R. 2002. Sitting for sessions: Dharma and DMT research. In C. Grob (Ed.), *Hallucinogens: A reader* (pp. 113-121).

Strassman, R.J., 1995. Hallucinogenic drugs in psychiatric research and treatment perspectives and prospects. *The Journal of nervous and mental disease*, *183*(3), pp.127-138.

Strassman, R.J. and Qualls, C.R., 1994. Dose-response study of N, N-dimethyltryptamine in humans: I. Neuroendocrine, autonomic, and cardiovascular effects. *Archives of general psychiatry*, *51*(2), pp.85-97.

Tanne, J.H., 2004. Humphry Osmond. *BMJ: British Medical Journal*, *328*(7441), p.713.

Thal, S., Engel, L.B. and Bright, S.J., 2022. Presence, trust, and empathy: preferred characteristics of psychedelic carers. *Journal of Humanistic Psychology*, p.00221678221081380.

Villiger, D., 2024. Giving consent to the ineffable. *Neuroethics*, *17*(1), p.11.

Watts, R., Day, C., Krzanowski, J., Nutt, D. and Carhart-Harris, R., 2017. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *Journal of humanistic psychology*, *57*(5), pp.520-564.

Wheeler, S.W. and Dyer, N.L., 2020. A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice*, *7*(3), p.279.

Winnicott, D.W., 1963. From dependence towards independence in the development of the individual. *The maturational processes and the facilitating environment*, *1985*, pp.83-92.

Yerubandi, A., Thomas, J.E., Bhuiya, N.M.A., Harrington, C., Zapata, L.V. and Caballero, J., 2024. Acute adverse effects of therapeutic doses of psilocybin: A systematic review and meta-analysis. *JAMA Network Open*, *7*(4), pp.e245960-e245960.

# Appendix

## Appendix A: Journal Guidelines

https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=ujpd20#preparing-your-paper

### Preparing Your Paper

#### Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

#### Word Limits

Please include a word count for your paper.

A typical paper for this journal should be no more than 4,000 words for Original Research (Introduction, Methods, Results, Discussion) and for Review Articles, 4,500 words

#### Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Please use American spelling style consistently throughout your manuscript.

Please use double quotation marks, except where "a quotation is 'within' a quotation".

Please note that long quotations should be indented without quotation marks.

#### Formatting and Templates

Papers may be submitted in Word or LaTeX formats. Please do not submit your paper as a PDF. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s).

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References

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14. **Author details.** Please ensure all listed authors meet the Taylor & Francis authorship criteria. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
15. Should contain an unstructured abstract of 200 words. Read tips on writing your abstract.
16. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
17. Between 4 and 6 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.
18. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
    *For single agency grants*
    This work was supported by the [Funding Agency] under Grant [number xxxx].
    *For multiple agency grants*
    This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
19. **Disclosure statement.** This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing

interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare*. Further guidance on what is a conflict of interest and how to disclose it.

20. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
21. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
22. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
23. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our Submission of electronic artwork document.
24. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
25. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
26. **Units.** Please use SI units (non-italicized).

## Appendix B: Reflexive Journal Entry

**Interview 4 – "Joseph"**

**24/04/2024**

Only met for to sign off the consent form today. Ended up chatting amicable for about half an hour so I felt like I got to know him a bit which was nice. He was really friendly and eager to participate – again, could very much see the value in the project which instilled further confidence. Spoke about the project in general – he seemed to think I had identified a very important gap in the literature. I shared with him my concern that the research question may be poorly defined, that I should've gone with the term "challenging experiences" however he made the very good point that "distress" is more accessible to clinicians outside of the psychedelic sphere.

# Appendix C – Participant information sheet

**Participant Information Sheet (PIS)**

**Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis**

You are being invited to take part in a research study investigating therapist's perceptions of client distress in psychedelic assisted therapy. This research is being conducted in collaboration with Staffordshire University's Clinical Psychology Doctorate (ClinPsyD) for the purposes of completing a research thesis as part of the primary investigators academic training. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

## About the research

- **Who will conduct the research?**

The primary investigator for this research project is Conor Coman, Clinical Psychology Trainee at the Staffordshire University. This research is affiliated with the school of Health, Sciences and Wellbeing at Staffordshire University.

- **What is the purpose of the research?**

Psychedelic-assisted therapy is experiencing a resurgence of interest in the scientific, clinical and public realms. Clinical trials are indicating positive outcomes positive outcomes for a range of difficulties including; smoking cessation, health-related anxiety in palliative care, substance misuse and treatment resistant depression. To date, there is a dearth of research exploring therapist's perceptions of participant distress in psychedelic assisted therapy.

In this study, we hope to create a greater understanding of the unique characteristics of distress in psychedelic therapy, its implications for the treatment and the skills needed to contain it. To date, no attempt has been made to research this topic qualitatively from the point of view of therapists experienced in this modality. Therefore, this study could represent a novel and significant contribution to the knowledge base that may influence the rapidly changing way in which psychedelic-assisted therapy is delivered to patients.

You have been invited to take part in this research because you have been identified as a professional who works therapeutically with patients using psychedelic assisted therapy.

- **Am I suitable to take part?**

For you to participate in this study, we ask that you hold a qualification in a form of recognised psychotherapy accredited by an official professional organisation, for example, the British Psychological

Society, British Association for Counselling and Psychotherapy, British Association for Counselling or international equivalent e.g. American Psychological Association, Canadian Psychological Association or Australian Counselling Association. Furthermore, we ask that you have facilitated at least three psychedelic assisted therapy sessions in a legal setting, for example a clinical trial or have legally facilitated psychedelic assisted therapy within a geographical area in which has been legalised. This is so we can ensure that you hold the relevant skills to adequately reflect on the process of delivering psychedelic assisted therapy safely and have the necessary experience to reflect on participant distress within this context.

- **Will the outcomes of the research be published?**

We intend to publish the results in peer-reviewed journals and present the results at scientific conferences. Participants will not be provided with an individual summary of their results. However, we will provide participants with a summary of the overall study findings if they would like this.

If you would like to be informed about the outcome of this research, an opportunity will be presented to you as part of our thank you email at the end of the study. Participants email addresses will be stored separately from data collected for purposes of the project.

## What would my involvement be?

- **What would I be asked to do if I took part?**

If you decide to take part, you will first speak to a researcher either by phone or Microsoft Teams according to your preference. The researcher will address any inquiries you may have regarding the research. Once you feel adequately informed, you will be invited to complete a consent form, either through a telephone call or on Microsoft Teams, based on your preference. The consent process will be recorded to ensure documentation of your agreement (yes/no) for each consent item, and you will receive a copy of the consent form.

Following the consent process, a scheduled one-hour interview over Microsoft Teams will be arranged, and the session will be recorded. The interview will begin with basic inquiries about yourself and your experience of delivering psychedelic therapy. Subsequently, the focus will shift to your perceptions of participant distress within psychedelic therapy. The interview's verbatim transcription will be provided for your review, allowing you the opportunity to suggest changes or omissions before the researcher proceeds with the analysis.

- **Will I be compensated for taking part?**

There are no direct benefits of taking part, but the information gained will help create a greater understanding of distress which may ultimately inform professional practice. This could lead to more

effective therapeutic assessment and intervention and better patient outcomes, particularly as many healthcare organisations are moving rapidly to implement psychedelic assisted therapy.

- **What happens if I do not want to take part or if I change my mind?**

It is up to you to decide whether or not to take part. Should you decide that you do not wish to take part, simply do not follow the link provided to the first questionnaire, or if you would prefer, you can respond to the email sent by the research team to directly inform them of your decision.

If you do decide to take part you are advised to keep a record of this information sheet and you will be directed to Qualtrics via a link within an email from the research team, where you will complete and sign a consent form.

If you decide to take part, you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been written up as we will not be able to identify your specific data. This does not affect your data protection rights. If you decide not to take part, you do not need to do anything further.

## Data Protection and Confidentiality

- **What information will you collect about me?**

As part of this research project, we will ask you to provide information that could identify you, called "personal identifiable information". Specifically, we will ask to collect:

Essential

- Your email address
- Your job title and accrediting organisation.
- The number of psychedelic assisted therapy sessions that you have facilitated. .

Optional

- Your name
- The country or region in which you facilitate psychedelic assisted therapy
- List the types of classical psychedelics (psilocybin, LSD, DMT, mescaline, MDMA) that you have used in legal therapeutic settings.

If you opt to participate in the study, a pseudonym will be assigned to protect the confidentiality of your information. You have the choice to select your own pseudonym; however, if you prefer not to decide, one will be assigned to you. In the event that you choose to have a pseudonym assigned, you will be informed of the selection and have the option to change it if desired. All pseudonyms will be securely stored in password-protected encrypted files, kept separately from the research data. The researcher will take responsibility for ensuring the secure storage of this pseudonym list.

The recordings will undergo transcription, converting spoken content into text on a computer. Any identifying information, including your name, will be removed to ensure anonymity. The transcribed information will be analyzed, and the original recordings will be deleted. Direct quotes from the anonymized transcripts may be included in the final report and utilized in scientific publications. To maintain anonymity, your pseudonym, rather than your real name, will be used in all references to the data.

- **Under what legal basis are you collecting this information?**

We are collecting and storing this personal identifiable information in accordance with UK data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reason is that it is "a public interest task" and "a process necessary for research purposes".

- **What are my rights in relation to the information you will collect about me?**

You have a number of rights under data protection law regarding your personal information. For example, you can request a copy of the information we hold about you. If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult our Privacy Notice for Research.

- **Will my participation in the study be confidential and my personal identifiable information be protected?**

Your data will be processed in accordance with the General Data Protection Regulation 2016 (GDPR).

The data controller for this project will be Staffordshire University. The university will process your personal data for the purpose of the research outlined above. The legal basis for processing your personal data for research purposes under the GDPR is a 'task in the public interest'. You can provide your consent for the use of your personal data in this study by completing the consent form that has been provided to you.

You have the right to access information held about you. Your right of access can be exercised in accordance with the GDPR. You also have other rights including rights of correction, erasure, objection, and data portability. Questions, comments and requests about your personal data can also be sent to the Staffordshire University Data Protection Officer. If you wish to lodge a complaint with the Information Commissioner's Office, please visit *www.ico.org.uk*.

Please also note that individuals from The Staffordshire University or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

The duty of confidentiality is not absolute in law and may, in exceptional circumstances, or overridden by more compelling duties such as the duty to protect individuals from harm or alerting authorities to evidence of legal activities (BPS Practice Guidelines, 2017).

## What if I have a complaint?

It is unlikely that anything would go wrong, but if you have a concern about any aspect of the study, you should contact one of the researchers who will do their best to answer your questions (see below for details).

**If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact the chair of the Staffordshire university ethics committee at:**

**ethics@staffs.ac.uk**

You also have a right to complain to the Information Commissioner's Office about complaints relating to your personal identifiable information Tel 0303 123 1113

## What if I experience distress from participating?

Due to the nature of the project, this is considered an unlikely event. Please contact your local healthcare provider.

## What do I do now?

If you have any queries about the study or if you are interested in taking part then please contact the primary researcher**. If you wish to participate in the project or know more about the study, please contact the lead researcher, Conor Coman whose contact details can be seen below.**

## Contact details:

**Conor Coman - Clinical Psychologist in Doctorate Training.**

**C026151l@student.staffs.ac.uk**

**+44 7384 273532**

**Dr Gary Lee – Clinical Psychologist and research supervisor**

**gary.lee@staffs.ac.uk**

**Thank you for taking the time to read this information sheet.**

## Appendix D – Consent Form

**Participant Consent Form**

**Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis**

Please **initial** box (OR researcher to tick for remote consent)

1. I confirm that I have reviewed the information sheet dated 28.01.2024, Version 1.0, for the study mentioned above. I have had the opportunity to ask any questions I had, and the researcher has satisfactorily addressed all my concerns. ☐

2. I understand that it is my choice to participate or not, and I am free to leave the study at any time without having to explain why. My rights won't be affected if I decide to withdraw. ☐

3. I consent to researchers continuing to use the information I provided if I withdraw or am withdrawn from the study for any reason, unless I contact them within 14 days of the interview. ☐

5. I acknowledge that all information will be confidential, accessible only to the study team as necessary. My personal data will be retained for 10 years, but I will only be identifiable by a pseudonym. I understand that confidentiality may be compromised in cases of risk to others, myself, or if criminal disclosures occur. ☐

6. I consent to participate in an interview discussing perceptions of participant distress in psychedelic therapy, and I agree to have the interview recorded. I understand that the recording will be transcribed, with any personal information removed. Additionally, I consent to the use of anonymized quotations from the interviews for sharing research findings through journal articles, conference presentations, and internal publications. ☐

7. I confirm that I am a qualified therapist and may legally deliver psychotherapy in my locality. ☐

8. I confirm that I have facilitated at least three sessions of psychedelic assisted therapy using a classic psychedelic or MDMA in a legal setting. ☐

9. I confirm that I have encountered participant distress while administering psychedelic assisted therapy. ☐

10. I agree to take part in the above study. ☐

Name of Participant Date Signature

(OR *provided electronically by the researcher, on behalf of the participant for remote consent)*

**Participant pseudonym:**

I have explained the study to the participant and have answered the participant's questions honestly and fully

Name of Researcher Date Signature

Original for researcher file and 1 copy for participant

Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis – Consent Form – v 1.0 28.01.2024

## Appendix E – Interview schedule

**Interview Topic Schedule**

**Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis**

**Consent will be verbally confirmed using the Participant Consent Form, which will be audio recorded before the interview begins**

**Introduction:**

Hi my name is Conor.

Thank you for participating in this research project investigating therapist perceptions of participant distress in psychedelic assisted therapy.

Your participation is invaluable as it will provide us with information to support future research in this area.

Today, I'm interested in hearing your thoughts about distress in psychedelic therapy. There are no right or wrong answers, so feel free to share openly. Our conversation is being recorded to ensure we don't miss any of your valuable insights. The interview should take no longer than 60 minutes.

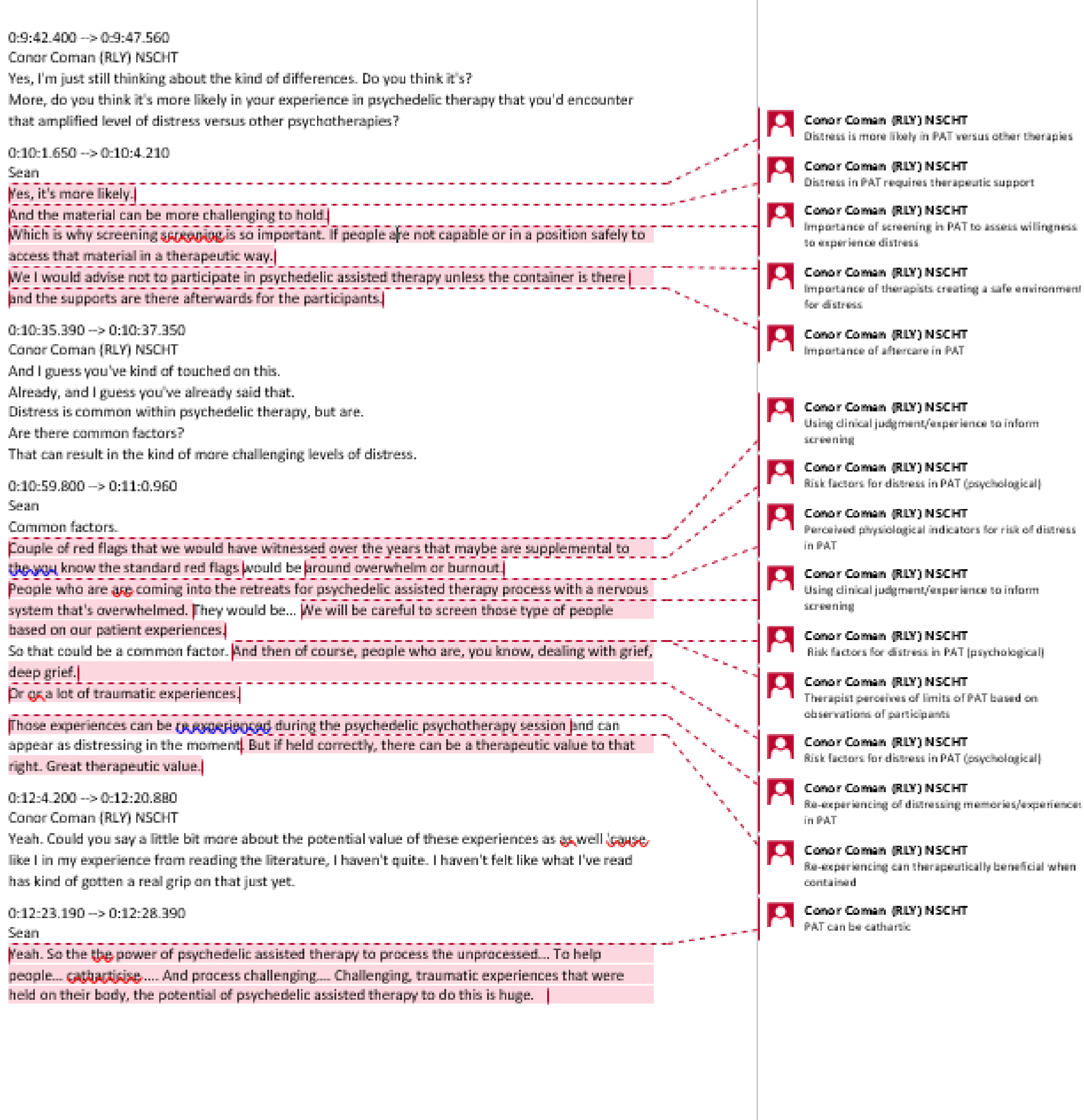
When discussing distress in psychedelic therapy, it's important to recognize that therapy inherently involves some level of risk and potential harm. Therefore, we want you to feel at ease expressing your opinions without worrying about judgment. Rest assured that anything you share during the interview will be kept confidential. However, if you disclose something indicating significant or deliberate harm, we would need to address it further in accordance with ethical guidelines. If we ever had to breach confidentiality and notify relevant authorities, we would try to discuss this with you beforehand.

Do you have any questions for me before we begin the interview?

| |
|---|
| What is your professional background/accreditation? |
| What country/countries have you practiced psychedelic therapy in? |
| What context was the therapy delivered e.g. clinical trial? Retreat? |
| Approximately how many sessions of psychedelic assisted therapy have you facilitated? |
| What psychedelic compounds have you used in therapy? |
| What are your views of participant distress in psychedelic assisted therapy? |
| What in your view are the differences between client distress in PAT versus other therapies? |
| Can you describe some of the characteristics of the distress you have seen in psychedelic-assisted therapy? |

| In your experience, are there any common factors that can result in participant distress? |
|---|
| Can you tell me about a specific experience of participant distress in psychedelic therapy? |
| How has this experience or any other experiences influenced your approach to psychedelic-assisted therapy? |
| Are there any changes or adjustments you've made to your practice based on these experiences? |
| Can you discuss any specific interventions or techniques you find effective in addressing distress? |
| What previous professional experiences have proven useful in containing distress in psychedelic assisted therapy? |
| What training did you receive on how to contain distress in PAT? Did this feel sufficient? What, if anything was missing? |
| Can you tell your views in relation to whether participant distress in psychedelic therapy could lead to positive outcomes? |
| Can you tell me about your views of risk in relation to participant distress in psychedelic therapy? |
| What ethical questions does distress in PAT pose to therapists? |
| Can you discuss any situations that have posed ethical dilemmas with regards containing distress? |
| What strategies do you employ during integration when a participant has experienced distress during dosing in psychedelic assisted therapy? |
| How do you perceive the role of the therapeutic relationship in managing or mitigating distress in psychedelic-assisted therapy? |
| What insights or lessons have you gained from your experiences in managing client distress during psychedelic sessions? |
| Has your perception/view of distress in PAT changed over time? |
| Can you describe your approach to follow-up care and ongoing support for clients who have experienced distress during psychedelic-assisted therapy? |
| What advice would you give to other therapists about managing participant distress in psychedelic assisted therapy? |

# Appendix F – Coding example, Microsoft Word



0:9:42.400 --> 0:9:47.560
Conor Coman (RLY) NSCHT
Yes, I'm just still thinking about the kind of differences. Do you think it's?
More, do you think it's more likely in your experience in psychedelic therapy that you'd encounter that amplified level of distress versus other psychotherapies?

0:10:1.650 --> 0:10:4.210
Sean
Yes, it's more likely.
And the material can be more challenging to hold.
Which is why screening screening is so important. If people are not capable or in a position safely to access that material in a therapeutic way.
We I would advise not to participate in psychedelic assisted therapy unless the container is there and the supports are there afterwards for the participants.

0:10:35.390 --> 0:10:37.350
Conor Coman (RLY) NSCHT
And I guess you've kind of touched on this.
Already, and I guess you've already said that.
Distress is common within psychedelic therapy, but are.
Are there common factors?
That can result in the kind of more challenging levels of distress.

0:10:59.800 --> 0:11:0.960
Sean
Common factors.
Couple of red flags that we would have witnessed over the years that maybe are supplemental to the you know the standard red flags would be around overwhelm or burnout.
People who are are coming into the retreats for psychedelic assisted therapy process with a nervous system that's overwhelmed. They would be... We will be careful to screen those type of people based on our patient experiences.
So that could be a common factor. And then of course, people who are, you know, dealing with grief, deep grief.
Or or a lot of traumatic experiences.

Those experiences can be re experienced during the psychedelic psychotherapy session and can appear as distressing in the moment. But if held correctly, there can be a therapeutic value to that right. Great therapeutic value.

0:12:4.200 --> 0:12:20.880
Conor Coman (RLY) NSCHT
Yeah. Could you say a little bit more about the potential value of these experiences as as well 'cause like I in my experience from reading the literature, I haven't quite. I haven't felt like what I've read has kind of gotten a real grip on that just yet.

0:12:23.190 --> 0:12:28.390
Sean
Yeah. So the the power of psychedelic assisted therapy to process the unprocessed... To help people... cathartisise..... And process challenging.... Challenging, traumatic experiences that were held on their body, the potential of psychedelic assisted therapy to do this is huge.

Comments:

Conor Coman (RLY) NSCHT
Distress is more likely in PAT versus other therapies

Conor Coman (RLY) NSCHT
Distress in PAT requires therapeutic support

Conor Coman (RLY) NSCHT
Importance of screening in PAT to assess willingness to experience distress

Conor Coman (RLY) NSCHT
Importance of therapists creating a safe environment for distress

Conor Coman (RLY) NSCHT
Importance of aftercare in PAT

Conor Coman (RLY) NSCHT
Using clinical judgment/experience to inform screening

Conor Coman (RLY) NSCHT
Risk factors for distress in PAT (psychological)

Conor Coman (RLY) NSCHT
Perceived physiological indicators for risk of distress in PAT

Conor Coman (RLY) NSCHT
Using clinical judgment/experience to inform screening

Conor Coman (RLY) NSCHT
Risk factors for distress in PAT (psychological)

Conor Coman (RLY) NSCHT
Therapist perceives of limits of PAT based on observations of participants

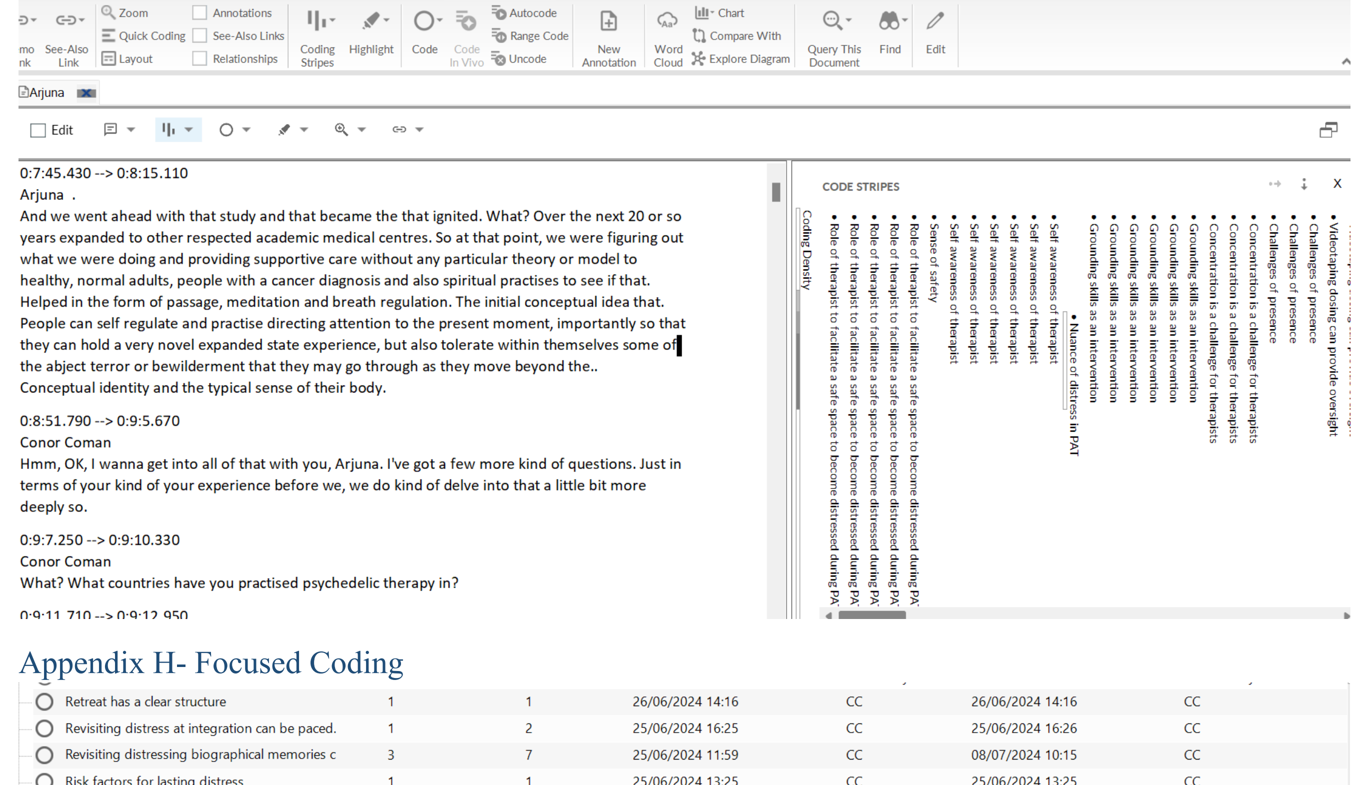
Conor Coman (RLY) NSCHT
Risk factors for distress in PAT (psychological)

Conor Coman (RLY) NSCHT
Re-experiencing of distressing memories/experiences in PAT

Conor Coman (RLY) NSCHT
Re-experiencing can therapeutically beneficial when contained

Conor Coman (RLY) NSCHT
PAT can be cathartic

# Appendix G – Coding using NVivo




# Appendix H- Focused Coding

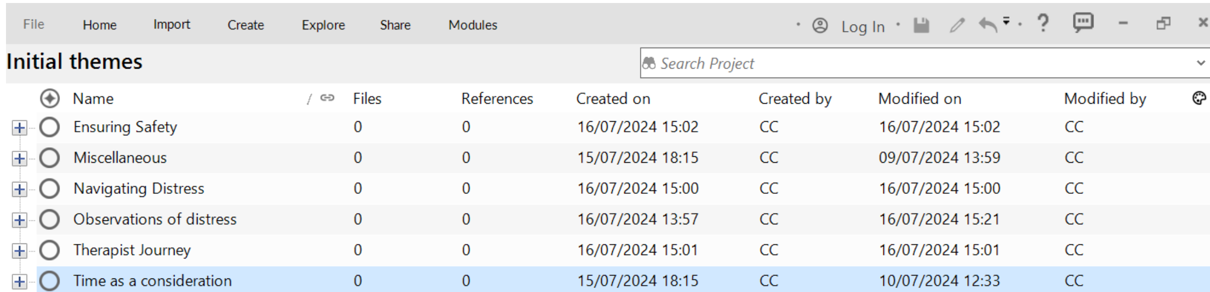
| | | | | | | |
|---|---|---|---|---|---|---|
| Retreat has a clear structure | 1 | 1 | 26/06/2024 14:16 | CC | 26/06/2024 14:16 | CC |
| Revisiting distress at integration can be paced. | 1 | 2 | 25/06/2024 16:25 | CC | 25/06/2024 16:26 | CC |
| Revisiting distressing biographical memories c | 3 | 7 | 25/06/2024 11:59 | CC | 08/07/2024 10:15 | CC |
| Risk factors for lasting distress | 1 | 1 | 25/06/2024 13:25 | CC | 25/06/2024 13:25 | CC |
| Risk of disclosure hangover in PAT | 1 | 2 | 01/07/2024 12:27 | CC | 01/07/2024 14:11 | CC |
| Risk of distress being re-traumatising for partic | 4 | 4 | 26/06/2024 14:55 | CC | 04/07/2024 16:29 | CC |
| Risk of distress being traumatising for participa | 2 | 2 | 25/06/2024 12:27 | CC | 26/06/2024 15:10 | CC |
| Risk of individuals excluded at screening gettin | 1 | 1 | 01/07/2024 13:15 | CC | 01/07/2024 13:15 | CC |
| Risk of interupting process by intervening in d | 4 | 9 | 01/07/2024 10:31 | CC | 05/07/2024 14:52 | CC |
| Risk of misinterpreting the client's verbal cues. | 1 | 3 | 04/07/2024 16:30 | CC | 05/07/2024 15:11 | CC |
| risk of not using touch when needed | 3 | 5 | 01/07/2024 13:54 | CC | 04/07/2024 14:01 | CC |
| Risk of over acceptance of distress in PAT | 1 | 3 | 25/06/2024 09:54 | CC | 25/06/2024 12:37 | CC |
| Risk of physical injury | 2 | 2 | 26/06/2024 12:04 | CC | 02/07/2024 15:50 | CC |
| Risk of physical injury a cue for intervention for | 3 | 3 | 25/06/2024 15:42 | CC | 08/07/2024 09:39 | CC |
| Risk of prolonged difficulties | 1 | 1 | 25/06/2024 11:18 | CC | 25/06/2024 11:18 | CC |
| Risk of psychedelics in non-clinical settings | 1 | 1 | 25/06/2024 11:55 | CC | 25/06/2024 11:55 | CC |
| Risk of under reporting distress | 1 | 1 | 25/06/2024 12:38 | CC | 25/06/2024 12:38 | CC |
| Risk of using touch | 2 | 2 | 01/07/2024 13:52 | CC | 03/07/2024 15:41 | CC |
| Risk should be under control before PAT | 1 | 1 | 03/07/2024 11:18 | CC | 03/07/2024 11:18 | CC |
| Risk that the participant feels they have let the | 1 | 1 | 03/07/2024 15:50 | CC | 03/07/2024 15:50 | CC |

# Appendix I – Coding example

| Sample text | Sematic coding | Latent codes |
|---|---|---|
| "And maybe I'll go one step further, which is why I was really interested in speaking to you, which is like. Then then there's also a following conundrum, which is. For for a psychedelic therapist to not be too lax about the distress and just sort of saying, "well, this is part of the process." And not and not taking the right steps or having the right amount of | Interest in Addressing Distress<br><br>Therapeutic Dilemma of Responding to distress<br><br>Importance of Appropriate Response | Balancing Act in between directive/non directive intervention<br><br>Reflects a sense of professional responsibility in managing client distress effectively.<br><br>Indicates a critical examination of current practices in |

| concern to work with or address the distress that is arising.” | | psychedelic therapy and a desire to refine them. |
|---|---|---|

# Appendix J - Initial themes



File Home Import Create Explore Share Modules

**Initial themes**

| Name | Files | References | Created on | Created by | Modified on | Modified by |
|---|---|---|---|---|---|---|
| Ensuring Safety | 0 | 0 | 16/07/2024 15:02 | CC | 16/07/2024 15:02 | CC |
| Miscellaneous | 0 | 0 | 15/07/2024 18:15 | CC | 09/07/2024 13:59 | CC |
| Navigating Distress | 0 | 0 | 16/07/2024 15:00 | CC | 16/07/2024 15:00 | CC |
| Observations of distress | 0 | 0 | 16/07/2024 13:57 | CC | 16/07/2024 15:21 | CC |
| Therapist Journey | 0 | 0 | 16/07/2024 15:01 | CC | 16/07/2024 15:01 | CC |
| Time as a consideration | 0 | 0 | 15/07/2024 18:15 | CC | 10/07/2024 12:33 | CC |

# Appendix K - Developed Themes

**Themes 2nd iteration**

| Name | Files | References | Created on | Created by | Modified on | Modified by |
|---|---|---|---|---|---|---|
| Ensuring Safety | 0 | 0 | 21/07/2024 09:21 | CC | 16/07/2024 15:02 | CC |
| Identifying Distress | 0 | 0 | 21/07/2024 13:52 | CC | 22/07/2024 11:58 | CC |
| Making sense of Distress | 0 | 0 | 21/07/2024 12:00 | CC | 21/07/2024 12:00 | CC |
| Miscellaneous | 0 | 0 | 21/07/2024 09:21 | CC | 09/07/2024 13:59 | CC |
| Navigating Distress | 0 | 0 | 21/07/2024 09:21 | CC | 16/07/2024 15:00 | CC |
| Therapist as a Container | 0 | 0 | 21/07/2024 13:46 | CC | 22/07/2024 08:48 | CC |
| Therapist Journey | 0 | 0 | 21/07/2024 09:21 | CC | 16/07/2024 15:01 | CC |

# Appendix L– Ethical Approval

**School of Health, Education, Policing and Sciences**

ETHICAL APPROVAL FEEDBACK

| Researcher name: | Conor Coman |
|---|---|
| Title of Study: | Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis. |
| Status of approval: | Approved |

Thank you for addressing the committee's comments. Your research proposal has now been approved by the Ethics Panel and you may commence the implementation phase of your study. You should note that any divergence from the approved procedures and research method will invalidate any insurance and liability cover from the University. You should, therefore, notify the Panel of any significant divergence from this approved proposal. This approval is only valid for as long as you are registered as a student at the University.

You should arrange to meet with your supervisor for support during the process of completing your study and writing your dissertation.

When your study is complete, please send the ethics committee an end of study report. A template can be found on the ethics BlackBoard site.

**Signed:** **Date: 04.03.2024**

Dr Jade Elliott

Ethics Co-ordinator
Psychology
School of Health, Science and Wellbeing

## Appendix M – Debrief Sheet

**Therapist perceptions of participant distress in psychedelic assisted therapy: A reflexive thematic analysis**

**Debrief Sheet**

Thank you for taking part in a research study investigating therapist's perceptions of client distress in psychedelic assisted therapy. This research is being conducted in collaboration with Staffordshire University's Clinical Psychology Doctorate (ClinPsyD) for the purposes of completing a research thesis as part of the primary investigators academic training.

Psychedelic-assisted therapy is experiencing a resurgence of interest in the scientific, clinical and public realms. Clinical trials are indicating positive outcomes positive outcomes for a range of difficulties including; smoking cessation, health-related anxiety in palliative care, substance misuse and treatment resistant depression. To date, there is a dearth of research exploring therapist's perceptions of participant distress in psychedelic assisted therapy.

In this study, we hope to create a greater understanding of the unique characteristics of distress in psychedelic therapy, its implications for the treatment and the skills needed to contain it. To date, no attempt has been made to research this topic qualitatively from the point of view of therapists experienced in this modality. Therefore, this study could represent a novel and significant contribution to the knowledge base that may influence the rapidly changing way in which psychedelic-assisted therapy is delivered to patients.

➢ **What happens if I change my mind about my participation in the study?**

You are still free to withdraw from this study without giving a reason and without detriment to yourself. If you wish to withdraw, please contact the lead researcher using the contact details listed below. It will not be possible to remove your data from the project once it has been written up as we will not be able to identify your specific data. Write up will take place within 14 days of the interview, after which it will not be possible to delete your data. This does not affect your data protection rights.

### What if I have a complaint?

➢ **Contact details for complaints**

If you have a concern about any aspect of the study, you should contact one of the researchers who will do their best to answer your questions (see below for details).

**If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact the chair of the Staffordshire university ethics committee at:**

**ethics@staffs.ac.uk**

You also have a right to complain to the Information Commissioner's Office about complaints relating to your personal identifiable information Tel 0303 123 1113

## What if I experience distress from participating?

Due to the nature of the project, this is considered an unlikely event. Please contact your local healthcare provider.

## Contact details:

**Conor Coman - Clinical Psychologist in Doctorate Training.**

**C026151l@student.staffs.ac.uk**

**Dr Gary Lee – Clinical Psychologist and research supervisor**

**gary.lee@staffs.ac.uk**

**Paper Three: Executive Summary**

***"They could be in the raptures of hell…"***

**Exploring therapist perceptions of distress in psychedelic assisted therapy:**

**A Reflexive Thematic Analysis**

Word Count: 2438

*This paper is aimed at psychotherapists who have experience delivering psychedelic assisted therapy or have an interest in it. It will be offered to the therapists who participated in this research project. It is not intended for publication.*

## Introduction

This report summarises a qualitative research study exploring the perceptions of therapists of the distress that participants can experience during psychedelic-assisted therapy (PAT). It is a condensed and accessible summary of a longer, more detailed report. It is aimed at professionals who may have an interest in this research, for example, psychologists and psychotherapists who have experience delivering PAT or have an interest in doing so.

### *Background*

PAT refers to psychotherapy that is supplemented by the use of psychedelics to create an altered state of consciousness. In this study, the term psychedelic refers to classic psychedelics, for example, psilocybin and LSD. It also includes MDMA, which operates differently but is administered in similar settings. PAT is an emerging treatment for a variety of presentations including; treatment resistant depression, post-traumatic stress disorder, anxiety in advanced illness, obsessive-compulsive disorder and smoking cessation (Wheeler and Dyer, 2020; Cavarra et al. 2022).

A characteristic of PAT is the potential for participants to experience elevated levels of distress (Bremler et al. 2023; Breeksema et al. 2022). Such distress can include but isn't limited to anxiety, paranoia, frightening hallucinations, delusions, uncomfortable insights, and troubling thoughts/feelings of a metaphysical nature (Johnson, Richards and Griffiths 2008). Distress during a psychedelic experience is associated with lasting psychological harm (Johnson, Richards and Griffiths 2008; Carbonaro et al. 2016). However, some participants describe experiences that include distress as therapeutically beneficial (Breeksema et al. 2023).

### *What does this Mean in Practice?*

The concept of "set and setting" is used to describe the internal and external environment in PAT (Leary et al. 1963). "Set" refers to the mindset of the individual taking the psychedelic. "Setting" refers to the physical, social and relational setting in which the in the individual takes the psychedelic. It is thought that an optimal set and setting is associated with positive outcomes and may moderate distress (Phelps 2017).

Therapists are thought to have a crucial role in optimising both set, by preparing participants adequately for the experience and setting, by creating a safe environment for participants to experience an altered state of consciousness. Generally, it is recommended that participants stay with or move towards distress in PAT, a process which requires skilled therapeutic support (Tai et al. 2021; Gorman et al. 2021; Watts et al. 2017). Furthermore, for

distress to be made sense of as a meaningful experience, therapist support may be necessary (Grof 1994; Johnson, Richards and Griffiths 2008).

### *Why was this Research Undertaken?*

- Current research has been criticised for under-reporting adverse experiences in PAT (Bremler et al. 2023; Colcott et al. 2023). This may be due to a lack of clarity over whether distress is an adverse experience.
- How therapists perceive participant distress in PAT hasn't previously been explored, despite evidence that it is a common phenomenon.
- Distress in PAT may be associated with both positive and negative outcomes, it is important to develop a better understanding of its nuances from the perspective of experts.
- As PAT becomes more available around the world, an understanding of distress may inform how it is thought about and managed by therapists.

### *Aims of the Research*

- To explore how participant distress is perceived by therapists in PAT.
- Understand therapists' perception of their role in supporting participants who become distressed.

## Method

### *Approach*

Due to the exploratory nature of the research, a qualitative method was used. Reflexive thematic analysis (Braun and Clarke 2022) was used to analyse the interview transcripts. This is a method of analysing interviews to find patterns. It follows six stages:

1. Familiarisation with the dataset.
2. Coding.
3. Generating initial themes.
4. Developing and reviewing themes.
5. Defining, refining and naming themes.
6. Writing the report.

Reflexive Thematic Analysis values reflecting on how the researcher's experiences and opinions can influence the research. In this instance, the researcher has experience in taking psychedelics recreationally and in delivering psychotherapy.

### *Participants*

To be included in the study, therapists had to meet the following criteria:

- Legally accredited to deliver psychotherapy in their locality.
- Experience facilitating at least three sessions of PAT.
- Encountered client distress during PAT.

*The Sample*

- Twelve participants
- Seven clinical psychologists, three psychotherapists and two psychiatrists.
- Recruited primarily via social media (LinkedIn).
- Located in the UK, Netherlands, Switzerland, USA and Australia.
- Had facilitated between 10 and 700 sessions of PAT.
- Psychedelic compounds used included psilocybin, MDMA, LSD and DMT.
- PAT was facilitated in a variety of legal contexts; clinical trials, privately and retreats.

### *Data Collection*

- Interested participants were asked to review an information sheet to ensure they were eligible for the study.
- If eligible, an interview was arranged at their convenience on Microsoft Teams and lasted approximately 60 minutes. This was recorded and transcribed.
- Before the interview began, after being offered the chance to ask any questions, the interviewer and participants completed and signed a consent form.
- Some demographic information was collected, including the participant's level of experience.
- The interview explored the participant's perception of distress in PAT, drawing on their experiences encountering this phenomenon.
- The interview was semi-structured, meaning the researcher used a set of questions to guide the interview but was flexible in following the flow of the conversation.

## Findings

The qualitative analysis of the data resulted in three themes and eight subthemes which reflected therapists' perceptions of participant distress in PAT. These are shown in the table below and then explained in more detail with quotes selected to illustrate them.

| Themes | Subthemes |
|---|---|
| *Making Sense of Distress* | The Amplified Nature of Distress |
| | Difficulties Assessing Distress |
| | Normalising Distress as a Meaningful Process |
| *Therapist as the Safe Base* | Building Connection |
| | Holding Participants through Distress |
| *Navigating Distress* | Preparing for the Ineffable |
| | Balancing Autonomy with Support |
| | Finding Meaning in Distress |

**Theme One: Making Sense of Distress**

Therapists described some of the unique characteristics of distress in PAT and how they understand its role within the treatment.

**Amplified Nature of Distress**

Therapists described how participants can experience high levels of distress in PAT. Sometimes, this related to experiencing regular psychological phenomena such as emotions and thought patterns. Sometimes, therapists described distress as related to an altered perception of reality, which could be terrifying and involve paranoid thoughts.

> *"You've got other people who go through the most distressing things you could imagine. They could be in the raptures of hell. They could feel horrific. They could feel that they're dying. They could feel that they're losing touch with their body. They could feel that... They are something they feared they were and get lost in this terror..."*
>
> James

Therapists also described participants encountering distressing memories very vividly. This was described as sometimes triggering a PTSD response.

> "*Two people I'm thinking of who just really kind of dove back into re-experiencing some of their traumas, say a sexual assault that they had dissociated from. And then during the session are then able to, you know, remember both the emotions and the physical sensations of that.*"
>
> Timothy

**Difficulties Assessing Distress**

Some therapists described difficulties assessing distress. In particular, they described some participants appearing calm and not showing signs of distress even on physiological measurements but later reporting terrifying experiences.

> *"No verbal response at all and we were monitoring blood pressures as well. His pressure was normal range, no deviation, no shift in movement, no shift in colour. He kept the eye shades on throughout, his respiration was normal. No kind of agitated process. No verbal process, nothing. The next day, when we talked about the experience, he said it was absolutely, utterly terrifying"*
>
> Arjuna

### Normalising Distress as a Meaningful Process

Therapists normalised the phenomenon of distress in PAT, describing it as a process expected in any psychotherapy. They were careful not to over-emphasise the risk of distress in PAT however they also accepted that there was a risk of harm if not managed carefully.

> *"It's all very well shaking the snow globe, but it's really how it lands that matters. How does it land within the psyche of the person, how they make sense of it and how they're held through it determines whether it could be traumatic or therapeutic"*
>
> Kate

Therapists reported some participants feeling that the distress they experienced was a necessary part of the healing process and were therefore better able to tolerate it. They described participants feeling strengthened by their experience of encountering and overcoming difficult experiences.

> *"Although people might be shaken by the experience, they've also survived, transcended, recognised their own resilience, gone more deeply beyond the death of the conceptual self or their great fears, whatever they may be. They've survived it all and there's something very meaningful about that deep experience being held so that what people will sometimes say… They don't experience fear or anxiety in nearly the same way, because they've conquered the self, or they've conquered their own fear."*
>
> Arjuna

### Theme two: Therapist as the Safe Base

Therapists viewed their role as a "safe base" within the PAT process, providing a reliable and trustworthy space for patients to return to when exploring altered states of consciousness which might include distressing experiences.

### Building Connection

Therapists emphasised the importance of establishing a strong, trusting relationship with participants.

> *"They need to trust your ability to… hold them in their most difficult and vulnerable psychological state"*
>
> Sean

Therapists identified several important challenges to overcome to facilitate a strong connection with participants, including how many participants have difficulty trusting others generally and this may be a factor in their needing therapy in the first place. Another obstacle to building the necessary trust with participants was identified as some of the practicalities outlined in research and therapy protocols e.g. psychometric measures and questionnaires.

**Holding Participants through Distress**

Therapists described their role in creating a sense of safety for participants to be able to experience an altered state of consciousness that may include distress.

> *"You're not alone. I'm with you. I'm here. I've got your back. You're safe."*
>
> Chris

They emphasised the importance of regulating their own emotions during long sessions when high levels of distress occurred in PAT. Therapists described a challenge to this requirement in feeling unprepared by training or "thrown into the deep end" with regards to the levels of distress they encountered in PAT.

**Theme three: Navigating Distress**

Therapists shared their experiences of guiding participants through distress in PAT and the challenges of doing this.

**Preparing for the Ineffable**

Therapists described preparing participants for the challenge of moving towards or staying with distressing psychedelic experiences. They described feeling the limits of language during this process due to the indescribable nature of some psychedelic experiences. This concern also extended to gaining informed consent for PAT.

> *"How do we prepare someone for… An experience that's indescribable? An ineffable experience or ego death? We can talk about things that might help, but even those it's difficult to describe."*
>
> Maria

Therapists described clearly contracting their responses to participants in the event they became distressed, including the use of touch and a reminder to use existing coping skills such as breathing techniques.

**Balancing Autonomy with Support**

Therapists described feeling the tension of adopting a traditionally favoured non-directive approach with providing support to distressed participants when necessary. Self-reflection was described as a key factor when deciding whether to offer more direct support, especially considering an impulse to "rescue" participants.

> *"When we see someone in distress, we can feel that and the question I always ask myself first is it my distress that I'm wanting help with? Or is it their distress?"*
>
> Maria

Therapists described how the duration of distress may indicate the need for direct support however they differed in how they measured the necessary duration, often describing this as an intuitive process. Other cues included panic, paranoia, trauma responses and risk to safety. Therapists described using a variety of grounding techniques to support participants when necessary.

**Finding Meaning in Distress**

Therapists reflected on the crucial role of finding meaning in suffering when participants encounter distress during PAT.

> *"I think some of the hardest trips aren't the ones necessarily that are the most painful in terms of intensity, but that don't make sense to the client."*
>
> Chris

Therapists reflected on the important role of therapists in facilitating this process and the need to provide further support when indicated.

## Summary and Conclusions

- This study aimed to explore how therapists perceive participant distress in PAT.
- The analysis produced three main themes: **Making sense of distress, Therapist as the Safe Base** and **Navigating Distress**.
- These findings reflected therapists' nuanced views of distress in PAT.
- Therapists reported that high levels of distress can occur in PAT.
- Distress can be associated with harm and negative outcomes however also can be part of a beneficial and therapeutic experience.

- Distress in PAT can be difficult to assess due to the potential for it to be a highly internal experience without visible indicators.
- Therapists were careful about intervening in distress without thinking about the value it might have for the participant.
- It is crucially important in PAT to establish a trusting relationship between therapist and participant.
- The ineffable nature of psychedelic experiences complicates the process of preparing participants for distressing experiences and getting informed consent.
- Self-reflection is a key consideration when deciding whether to provide direct support for distress.
- Complementary techniques such as grounding practices are helpful tools in managing distress that is at risk of becoming harmful to the participant.
- A key role of therapists is to help participants find meaning in distressing experiences.

### *Limitations*

- This study focused on the subjective experiences of a small number of therapists. Distress might be thought about differently by others.
- The therapists in the sample used a wide variety of psychedelic compounds, clinical presentations and settings. These variables could have different effects concerning distress.

## What Now?

### *Clinical Implications*

- Therapists should be prepared to encounter high levels of distress when administering PAT.
- Training programmes should emphasise the complex nature of distress in PAT and appropriate responses to it, prioritising the self-awareness of therapists.
- Therapists should be aware that distress may not be visibly apparent in participants.
- Establishing a strong therapeutic relationship should be prioritised.
- Therapists and researchers should be mindful of potential gaps in the informed consent process in PAT and this should be reviewed regularly.
- Therapists should be skilled in grounding techniques to support participants when necessary.

- Participants should be supported to make meaning of distressing experiences and further integration sessions should be offered when required.

### *Areas for Future Research*

- Further qualitative research focusing on distress from the perspective of participants.
- Research focusing on the phenomenon of distress that isn't visible by standard methods of observation.
- Research focusing on the link between duration of distress and lasting harm.

## References


Braun, V., & Clarke, V., 2022. *Thematic Analysis: a practical guide.* Sage Publications Ltd.

Breeksema, J.J., Kuin, B.W., Kamphuis, J., van den Brink, W., Vermetten, E. and Schoevers, R.A., 2022. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review. *Journal of Psychopharmacology*, *36*(10), pp.1100-1117.

Bremler, R., Katati, N., Shergill, P., Erritzoe, D. and Carhart-Harris, R.L., 2023. Case analysis of long-term negative psychological responses to psychedelics. *Scientific Reports*, *13*(1), p.15998.

Carbonaro, T.M., Bradstreet, M.P., Barrett, F.S., MacLean, K.A., Jesse, R., Johnson, M.W. and Griffiths, R.R., 2016. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of psychopharmacology*, *30*(12), pp.1268-1278.

Cavarra, M., Falzone, A., Ramaekers, J.G., Kuypers, K.P. and Mento, C., 2022. Psychedelic-assisted psychotherapy—A systematic review of associated psychological interventions. *Frontiers in psychology*, *13*, p.887255.

Colcott, J., Guerin, A.A., Carter, O., Meikle, S. and Bedi, G., 2024. Side-effects of MDMA-assisted psychotherapy: a systematic review and meta-analysis. *Neuropsychopharmacology*, pp.1-19.

Gorman, I., Nielson, E.M., Molinar, A., Cassidy, K. and Sabbagh, J., 2021. Psychedelic harm reduction and integration: A transtheoretical model for clinical practice. *Frontiers in psychology*, *12*, p.645246.

Grof, S. 1994. *LSD Psychotherapy*. 2nd ed. Alameda, CA: Hunter House.

Johnson, M.W., Richards, W.A. and Griffiths, R.R., 2008. Human hallucinogen research: guidelines for safety. *Journal of psychopharmacology*, *22*(6), pp.603-620.

Leary, T., Litwin, G.H. and Metzner, R., 1963. Reactions to psilocybjn administered in a supportive environment. *The Journal of nervous and mental disease*, *137*(6), pp.561-573.

Phelps, J., 2017. Developing guidelines and competencies for the training of psychedelic therapists. *Journal of Humanistic Psychology*, *57*(5), pp.450-487.

Tai, S.J., Nielson, E.M., Lennard-Jones, M., Johanna Ajantaival, R.L., Winzer, R., Richards, W.A., Reinholdt, F., Richards, B.D., Gasser, P. and Malievskaia, E., 2021. Development and evaluation of a therapist training program for psilocybin therapy for treatment-resistant depression in clinical research. *Frontiers in psychiatry*, *12*, p.586682.

Watts, R., Day, C., Krzanowski, J., Nutt, D. and Carhart-Harris, R., 2017. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *Journal of humanistic psychology*, *57*(5), pp.520-564.

Wheeler, S.W. and Dyer, N.L., 2020. A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice*, *7*(3), p.279.