The Effects of Psychedelic-Assisted Therapy on Illness and Death Anxiety

by

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Abstract

Objective: This thesis aims to systematically analyze the efficacy of serotonergic psychedelic-assisted therapy for illness and death anxiety.

Methods: A literature search of was conducted through the Ovid database using Medline®, PsychINFO®, and Embase® in February 2024. Randomized controlled trials were included.

Results: The literature search identified 3194 publications after removing duplicates. After screening, 5 studies were included in the analysis. The results showed that serotonergic psychedelics were associated with sustained decreases in illness anxiety (SMD = -0.85, 95% CI -1.42 to -0.27, $p < 0.01$) and death anxiety (SMD = -0.62, 95% CI -1.04 to -0.21, p = <0.01) in the context of having a life-threatening illness.

Conclusion: This meta-analysis highlights the potential for serotonergic psychedelic assisted therapy to treat illness and death anxiety. Future studies should attempt to discern the biological mechanisms of action, and to replicate these findings in contexts other than having a life-threatening illness, such as somatic symptom disorders.

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Contributions

Aron Amaev (author) solely prepared this thesis. All aspects of this body of work, including planning, execution, analysis, and writing of all original research were performed in whole or in part by the author. Further, I had the privilege to significantly contribute to the psilocybin MCI trial, "Does psilocybin change synaptic density in Amnestic Mild Cognitive Impairment?" (NCT06041152). My contributions to this project included research design, obtaining research ethics board and Health Canada Approval, grant applications, participant recruitment and management, conducting neuropsychological testing, primary data collection, manuscript preparation, neuroimaging analyses (i.e., MRI and PET imaging), and others. This trial was my original thesis project. Regretfully, the recruitment target was not achieved at the time of my thesis defence. However, I am incredibly grateful for the opportunity to work on a pertinent research topic, and to develop a variety of research skills.

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List of Abbreviations

ACC	Anterior cingulate cortex
ACT	Acceptance and commitment therapy
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
BP	Binding potential
CADI	Concerns About Dying Instrument
CBF	Cerebral blood flow
CBT	Cognitive Behavioural Therapy
CI	Confidence interval
CORT	Cortisol
CVLT	California Verbal Learning Test
DA	Death anxiety
DABBS	Death Anxiety Beliefs and Behaviours Scale
DAP	Death Attitudes Profile
DAQ	Death Anxiety Questionnaire
DAS	Death Anxiety Scale
DMN	Default mode network
DMT	N,N-dimethyltryptamine
DSM	Diagnostic and Statistical Manual
EEG	Electroencephalogram
EKG	Electrocardiogram

FC	Functional Connectivity
GABA	Gamma-aminobutyric acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LD	Low dose
LDFR	Long delay free recall
LMT	Logical Memory Test
LSD	Lysergic acid diethylamide
REBUS	Relaxed Beliefs Under Psychedelics
ROI	Region of interest
RSFC	Resting-state functional connectivity
SE	Standard error
SMD	Standardized mean difference
SS	Standardized score
SSD	Somatic symptom disorder
SSRI	Selective serotonin reuptake inhibitors
STAI	State-Trait Anxiety Inventory
CO	Carbon Monoxide
dFC	Dynamic functional connectivity
DR	Delayed recall
FAIR	Frankfurt Attention Inventory
HC	Healthy control
HD	High dose
HPA	Hypothalamic-pituitary-adrenal
IA	Illness anxiety

IAD	Illness anxiety disorder
aMCI	Amnestic mild cognitive impairment
MDMA	3,4-methylenedioxymethamphetamine
MRI	Magnetic resonance imaging
NAA	N-acetylaspartate
OCD	Obsessive compulsive disorder
PAT	Psychedelic assisted therapy
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRL	Prolactin
PTSD	Post-traumatic stress disorder
SD	Standard deviation
SV2A	Synaptic vesicle glycoprotein 2a
SVD	Synaptic vesicular density
SWA	Slow-wave sleep activity
TMT	Terror management theory
TSH	Thyroid stimulating hormone
VLD	Very low dose
5-HT	5-hydroxytryptophan
5-HT2A-R	5-hydroxytryptophan type 2A receptor

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Chapter 1
Background

1 Overview

Sections 1.3.3.1.1, 1.3.3.2, and 1.3.4.1 of the subsequent background chapter are modified from the following: Song, J., Kambari, Y., Amaev, A., et. al, (2023). Psilocybin to promote synaptogenesis in the brains of patients with mild cognitive impairment. *Medical Hypotheses*, *175*, 111068.

1.1 Illness Anxiety

1.1.1 Definition

Health anxiety, also referred to as illness anxiety (IA), is characterized by worry or fear in response to living with a chronic illness (Lebel et al., 2020) or a preoccupation with having or acquiring a serious disease in conjunction with absent to mild somatic symptomatology (i.e., disease conviction, disease fear, and bodily preoccupation) (Ferguson, 2009; Scarella et al., 2019). IA has been conceptualized on a continuum ranging from mild and transient to severe and chronic, as seen in Illness Anxiety Disorder (IAD) (American Psychiatric Association, 2013; Lebel et al., 2020; Maheu et al., 2021; Substance Abuse and Mental Health Services Administration, 2016) (i.e., previously referred to as hypochondriasis (Bailer et al., 2016)). Minor and acute levels of IA may reflect normal health concerns, whereas moderate to severe levels of IA can present as heightened somatosensory perception, cyberchondria (i.e., internet health browsing), engaging in safety behaviours (i.e., checking their body for signs of illness), and/or consistently seeking reassurance from health care providers (Tyrer & Tyrer, 2018). There are two subtypes of IAD, care-seeking and care-avoidant (American Psychiatric Association, 2013; Substance Abuse and Mental Health Services Administration, 2016). Individuals with care-seeking IAD frequently use medical services to receive reassurance about their worries, whereas individuals with care-avoidant IAD rarely use medical services in fear of receiving a life-threatening diagnosis

(American Psychiatric Association, 2013; French & Hameed, 2022). Most individuals with IAD fluctuate between care seeking and care avoidance, while the state of care-seeking is thought to be more common (Newby et al., 2017), resulting in greater economic burden on health care systems (Horenstein & Heimberg, 2020).

Although the diagnosis of hypochondriasis and IAD are similar, there are distinctions to be made as there are differences in diagnostic criteria (Table 1) (Substance Abuse and Mental Health Services Administration, 2016).

Table 1: Summary of changes from DSM-IV diagnostic criteria for hypochondriasis to DSM-5 diagnostic criteria for Illness Anxiety Disorder

DSM-IV	DSM-5
Name: Hypochondriasis	Name: Illness Anxiety Disorder
Disorder Class: Somatoform Disorders	Disorder Class: Somatic Symptom and Related Disorders
A. Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of bodily symptoms.	A. Preoccupation with having or acquiring a serious illness.
B. The preoccupation persists despite appropriate medical evaluation and reassurance.	DROPPED
	B. Somatic symptoms are not present or, if present, are only mild in intensity. If another medical condition is present or there is a high risk for developing a medical condition (e.g., strong family history is present), the preoccupation is clearly excessive or disproportionate.

DSM-IV	DSM-5
C. The belief in Criterion A is not of delusional intensity (as in delusional disorder, somatic type) and is not restricted to a circumscribed concern about appearance (as in body dysmorphic disorder).	DROPPED
	C. There is a high level of anxiety about health, and the individual is easily alarmed about personal health status.
D. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	DROPPED
	D. The individual performs excessive health-related behaviors (e.g., repeatedly checks his or her body for signs of illness) or exhibits maladaptive avoidance (e.g., avoids doctor appointments and hospitals).
E. The duration of the disturbance is at least 6 months.	E. Illness preoccupation has been present for at least 6 months, but the specific illness that is feared may change over that period of time.
F. The preoccupation is not better accounted for by generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a major depressive episode, separation anxiety, or another somatoform disorder.	F. The illness-related preoccupation is not better explained by another mental disorder, such as somatic symptom disorder, panic disorder, generalized anxiety disorder, body dysmorphic disorder, obsessive-compulsive disorder, or delusional disorder, somatic type.
Specify if:	DROPPED

DSM-IV	DSM-5
• With poor insight: If, for most of the time during the current episode, the person does not recognize that the concern about having a serious illness is excessive or unreasonable.	
	Specify whether: • Care-seeking type: Medical care, including physician visits or undergoing tests and procedures, is frequently used. • Care-avoidant type: Medical care is rarely used.

Adapted from the Substance Abuse and Mental Health Services Administration (2016)

1.1.2 Etiology

The etiology of IA and IAD are understudied, however, both share similar risk factors. The risk factors for developing IA include experiencing threatening and/or traumatic life events, modelling parental health-anxious behaviours, personality predisposition to negative affectivity, and comorbidity with concurrent medical illness (French & Hameed, 2022; Tyrer & Tyrer, 2019). Risk factors for developing IAD include mislabeling normal bodily sensations as pathological, being raised in a family where health concerns are disproportionately brought up, experiencing serious illness in childhood or observing family members experience serious illness, cyberchondria (i.e., “repeated internet searches regarding medical information result in excessive concerns about physical health (Mathes et al., 2018)), and having underlying anxiety disorders (Alberts et al., 2016; French & Hameed, 2022; Newby et al., 2017; Scarella et al., 2019).

1.1.3 Epidemiology and Impact

Studies have reported the prevalence of IA to range from 3.4 to 19% (Tyrer & Tyrer, 2019). The prevalence of IAD as defined by the DSM-5 is unclear due to the recency of the new diagnostic criteria, however, epidemiological studies report a point prevalence ranging from 0.04% to 7.4% for hypochondriasis (Scarella et al., 2019; Tyrer & Tyrer, 2019). When considering data from the United States, Sweden, Great Britain/United Kingdom, and Denmark, the economic

burden of hypochondriasis ranges from $857.19 to $21,137.55 USD per capita per year (Hannah et al., 2023). Relatedly, it is estimated that preoccupation with physical symptoms without a discernible cause contributes to $256 billion a year in medical care costs in the United States (Barsky et al., 2005).

1.1.4 Differential Diagnosis

The DSM-IV diagnosis of hypochondriasis was replaced by IAD and Somatic Symptom Disorder (SSD) in the DSM-5, which is under the "Somatic Symptom and Related Disorder" class (Newby et al., 2017). SSD is characterized by "one or more physical symptoms that may or may not be explained by a medical condition, that is accompanied by an excessive amount of time, energy, emotion, and/or behaviour related to the symptom that results in significant distress and/or dysfunction" (D'Souza & Hooten, 2024). The diagnostic criteria for SSD is presented in Table 2. Given that somatic symptoms are present in both SSD and IAD, SSD should be ruled out after excluding potential organic causes of physical symptoms (French & Hameed, 2024).

Table 2: DSM-5 diagnostic criteria for Somatic Symptom Disorder

DSM-5
Name: Somatic Symptom Disorder
Disorder Class: Somatic Symptom and Related Disorder
B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following: 1. Disproportionate and persistent thoughts about the seriousness of one's symptoms. 2. Persistently high level of anxiety about health or symptoms. 3. Excessive time and energy devoted to these symptoms or health concerns.

DSM-5
C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).
A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
Specify if: • With predominant pain (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain. *Specify* if: • Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 months). *Specify* current severity: • Mild: Only one of the symptoms specified in Criterion B is fulfilled. • Moderate: Two or more of the symptoms specified in Criterion B are fulfilled. • Severe: Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom).

From the Substance Abuse and Mental Health Services Administration (2016)

Obsessive-compulsive disorder (OCD) is characterized by obsessions, that is, “recurrent and persistent thoughts, urges or images that are experienced, at some time during the disturbance, as intrusive, unwanted, and that in most individuals cause marked anxiety or distress” (Substance Abuse and Mental Health Services Administration, 2016). Additionally, the individual performs compulsions, that is, “the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some thought or action” (Substance Abuse and Mental Health Services Administration, 2016). Both OCD and IAD share similar presentations, such as intrusive thoughts, body checking compulsions, and overestimation of the likelihood of threats (Hedman et al., 2017; Kikas et al., 2024; Scarella et al., 2019). However, OCD is ego-dystonic (i.e., symptoms do not align with a person’s sense of self and/or beliefs), and IAD is ego-syntonic (i.e., symptoms align with a person’s sense of self and/or beliefs) (Purdon et al., 2007).

Other anxiety disorders should also be considered as differential diagnoses and may be comorbid, such as generalized anxiety disorder and panic disorder, as hypervigilance of physical symptoms, autonomic dysregulation, and pathological cognitive biases may also be comorbid symptoms (Kikas et al., 2024; Scarella et al., 2019). Relatedly, IAD may also co-occur with other anxiety disorders (Kikas et al., 2024; Newby et al., 2017; Scarella et al., 2016, 2019).

1.1.5 Treatments for IAD

Meta-analyses of randomized controlled trials have demonstrated that Cognitive Behavioural Therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are effective in treating IAD for up to two years following treatment initiation (i.e., Hedges's g for SSRIs: -0.29 [95% CI -0.57 to -0.01], k = 3, $p = 0.04$, Hedges's g for CBT: $g = -0.70$ [95% CI -0.99 to -0.41], k = 18; $p < 0.001$, from Fineberg et al., 2022) (Cooper et al., 2017; Fineberg et al., 2022; Khalili Torghabeh et al., 2022; Tyrer et al., 2014). However, other studies suggest that up to 70% of individuals with IAD continue to meet criteria even after long-term treatment (Scarella et al., 2019). Further complicating the treatment of IAD, many individuals are preoccupied with medication adverse effects, which may contribute to worsening health anxiety and treatment nonadherence (Higgins-Chen et al., 2019). In addition, due to the global shortage of CBT trained therapists, in particular those with expertise in the treatment of IAD, CBT is typically inaccessible (A. Lin & Espay, 2021).

1.2 Death Anxiety

1.2.1 Definition

Death anxiety (DA) is defined as "emotional distress and insecurity aroused by reminders of mortality, including one's own memories and thoughts of death" (*APA Dictionary of Psychology, 2nd Ed*, 2015). DA is a common human emotional reaction (Furer and Walker, 2008), which in extreme forms, can lead to the development and maintenance of other psychopathologies (aan de Stegge et al., 2018; Iverach et al., 2014). This is highlighted in panic disorder where individuals commonly use primary and emergency care services as they mistake anxiety induced chest tightness/pain for a heart attack; OCD where individual's compulsions are often driven by

a fear of fatal consequences if they do not engage in their compulsive behaviours; phobias where exposure to specific fears are associated death; and others disorders such as Post-traumatic Stress Disorder (PTSD), depressive disorders, eating disorders, and other anxiety disorders (Becker et al., 2023; Huffman et al., 2002; Iverach et al., 2014). As such, DA is viewed as a transdiagnostic construct (Iverach et al., 2014).

1.2.2 Death Anxiety and Illness Anxiety Disorder

Given that preoccupation with having or acquiring a serious physical illness (typically a life-threatening disease) is a core feature of IA, it is theorized that DA underpins IA and IAD (Iverach et al., 2014; Menzies, Sharpe, & Dar-Nimrod, 2021). In support of this, DA is an essential psychological construct to address when treating IAD (Furer & Walker, 2008; Iverach et al., 2014; Noyes et al., 2002; Starcevic, 2005). Further, aan de Stegge et al., (2018) conducted a systematic review of 9 studies on the association between DA with hypochondriasis, and medically unexplained symptoms, in which all studies demonstrated that DA was associated with hypochondriasis and/or medically unexplained symptoms.

Evidence also suggests that DA is more common and severe in individuals experiencing life-threatening illness, which may provoke heightened levels of IA (Iverach et al., 2014). However, individuals with IA and/or a life-threatening illness may not be subjectively aware of or experience DA (i.e., due to repression) (aan de Stegge et al., 2018; Iverach et al., 2014).

1.2.3 Correlates of Death Anxiety

There are several predictors which may influence experiencing DA: (i) women report higher levels of DA than men; (ii) higher education is inversely associated with DA; (iii) higher socioeconomic status is inversely associated with DA; (iv) good physical health is associated with lower levels of DA; and (v) lower psychological well-being is associated with higher DA (Iverach et al., 2014; Yüksel et al., 2024). Further, older age and/or having strong religious beliefs are not associated with lower DA (Iverach et al., 2014; Jong, 2021). Lastly, higher levels of DA are associated with life-threatening illnesses, such as cancer, acquired immunodeficiency syndrome (AIDS), and cardiovascular disease (Miller et al., 2012; Şahan et al., 2018; Soleimani, Bahrami, Allen, et al., 2020; Soleimani, Bahrami, Zarabadi-Pour, et al., 2020).

1.2.4 Theoretical Models of DA

The experience of DA can be conceptualized through several theoretical lenses, including existential psychology, psychoanalytic theory, terror management theory (TMT), and cognitive behavioural theory (Furer & Walker, 2008; Iverach et al., 2014).

1.2.4.1 Existentialism

Existential psychology posits that the themes of death, freedom, isolation, identity, and meaning significantly influence behaviours at a conscious and unconscious level (Iverach et al., 2014). Existentialists view DA as not a consequence of psychological distress, but rather, at the core of all anxiety, in which life itself is only a means to defend against the experience of DA (Stolorow, 1973). Consequently, accepting the reality of death allows for the experience of freedom (Stolorow, 1973).

1.2.4.2 Psychoanalytic Theory

In psychoanalytic theory, the conceptualization of DA has evolved throughout history from Freudian and Neo-Freudian theorists (Tomer, 1992). Freud was one of the first psychoanalytical theorists to explore DA and viewed that unresolved childhood conflicts would manifest into death-related fears (Furer & Walker, 2008). Further, he held the idea that the unconscious views itself as immortal, resulting in individuals not believing in their own death (Furer & Walker, 2008; Tomer, 1992). Other psychoanalytical theorists (i.e., Rank and Brown) built on this through the lens of conventional psychoanalytical theory, in which the ego uses defence mechanisms (e.g., repression, denial, and projection) to defend against DA (Tomer, 1992). They posited that DA comes into conscious awareness due to insufficient defence mechanisms, in which one should turn to repression or illusions to convince themselves of their immortality (Tomer, 1992). Becker extended this theory by positing that cultural systems act as an awareness buffer of mortality, which gave rise to TMT (Iverach et al., 2014; Tomer, 1992).

1.2.4.3 Terror Management Theory

TMT was formulated by Rosenblatt, Greenberg, Solomon, Pyszczynski, & Lyon based on Becker's writings (Iverach et al., 2014; Tomer, 1992). TMT integrates and builds on concepts

from existentialism, psychoanalytic theory, and others, to characterize DA (Iverach et al., 2014; Tomer, 1992). TMT outlines how behaviour and cognition are influenced by the awareness of death and is characterized by 4 key concepts: mortality salience, cultural worldviews, self-esteem, and defense mechanisms (Furer & Walker, 2008; Greenberg, 2012; Iverach et al., 2014). Specifically, the awareness of mortality, referred to as mortality salience, can generate an immense fear of death. To cope with mortality salience, people identify with cultural worldviews (i.e., systems or beliefs) to achieve existential order and meaning. If one adequately conforms to their cultural worldviews, their self-esteem increases which protects against anxiety. Consequently, if one does not conform to their cultural worldviews, their self-esteem decreases and results in vulnerability to experiencing DA. Thus, self-esteem acts as an anxiety buffer. Defense mechanisms in TMT are described as proximal or distal. Proximal defences occur when reminders of one's mortality come into conscious awareness, which may result in death denial. Distal defences occur when DA is out of conscious awareness, resulting in a propensity to adhere to cultural worldviews and subsequent enhancement of self-esteem (Furer & Walker, 2008; Greenberg, 2012; Iverach et al., 2014).

1.2.4.4 Cognitive Behavioural Theory

Cognitive behavioural theory (CBT) focuses on the relationships between cognition, emotion, and behaviour, in which automatic thoughts, cognitive distortions, and underlying schemas are emphasized (Chand et al., 2024). Through the lens of CBT, DA may be elicited either through a situation or thought about death, which elicits anxiety (Menzies, Sharpe, Helgadóttir, et al., 2021). Consequently, this may result in physiological symptoms, such as heart palpitations or hot flushes, and maladaptive coping behaviours, such as repeated body checking, in which hypervigilance of physical symptoms and maladaptive coping behaviours reinforce DA (Furer et al., 2007; Menzies, Sharpe, Helgadóttir, et al., 2021). Recognizing the potential utility of CBT, Menzies, Sharpe, Helgadóttir, et al., (2021) have developed an online CBT program for the treatment of DA.

1.2.5 Treatments for Death Anxiety

Treatments for DA include pharmacological (i.e., SSRIs, benzodiazepines, anticholinergics, and opioids) and psychotherapeutic interventions (i.e., CBT, acceptance and

commitment therapy (ACT), relaxation training, and death education) (Grossman et al., 2018; Jansen et al., 2018; Menzies, Sharpe, & Dar-Nimrod, 2021; Sussman & Liu, 2014). Evidence suggests that CBT is the most effective psychotherapeutic modality in treating DA, and that SSRIs are recommended as a first line pharmacologic agent in the context of life-threatening illness (Atkin et al., 2017; Menzies et al., 2018, 2023). However, SSRIs and psychotherapy, in which receiving more therapy sessions moderates treatment efficacy (Atkin et al., 2017; Grossman et al., 2018; Menzies, Sharpe, & Dar-Nimrod, 2021), may take weeks to months to achieve therapeutic effects, which is particularly problematic if DA is related to a life-threatening illness with a short prognosis (Schimmel et al., 2022). Further, benzodiazepines, opioids, and anticholinergics have limited efficacy in treating anxiety in individuals experiencing life-threatening illness (Atkin et al., 2017; Candy et al., 2012; Jansen et al., 2018; Nübling et al., 2012; Salt et al., 2017). A survey in the United Kingdom further demonstrated that 93% of palliative care physicians report difficulties in managing anxiety, reflective of the limited interventions available to effectively treat DA (Atkin et al., 2017). This suggests that novel and alternative therapeutics are needed for addressing DA.

1.2.6 Measures of Death Anxiety

DA is commonly assessed through self-report scales. A recent systematic review by Zuccala et al., 2022 assessed the psychometric properties of 21 self-report measures and 6 subscales of DA measures based on criteria of adequacy for measurement properties of health status questionnaires (Terwee et al., 2007). The criteria include content validity, internal consistency, criterion validity, construct validity, reproducibility, longitudinal validity, responsiveness, floor and ceiling effects, and interpretability (Terwee et al., 2007). None of the measures demonstrated adequacy on all criteria (Zuccala et al., 2022). However, the Templer Death Anxiety Scale (DAS), Concerns About Dying Instrument (CADI), Death Concern Scale (DCS), and Death Anxiety Questionnaire (DAQ) demonstrated the best psychometric properties out of all measures (Menzies, Sharpe, Helgadóttir, et al., 2021; Zuccala et al., 2022).

1.2.6.1 The Death Anxiety Scale

The DAS was originally designed as a 15 item self-report true or false questionnaire (Templer, 1970). More recently, a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree) has also been used for the scale's items (Saleem et al., 2015). Some items on the scale include "I am very much afraid to die", "the thought of death seldom enters my mind", and "I am not particularly afraid of getting cancer" (Templer, 1970).

1.2.6.2 Concerns About Dying Instrument

The CADI employs a 10 item self-report questionnaire that are rated on Likert scale ranging from 1 (disagree somewhat) to 5 (agree completely) (Mazor et al., 2004). Some items on the scale include "I get anxious or uncomfortable when I think about my own death," "I am worried that my own death may be painful," and "I get anxious or uncomfortable when I think about someone I care about dying" (Mazor et al., 2004).

1.2.6.3 Death Concern Scale

The DCS is a 30 item self-report questionnaire that is rated on a Likert scale ranging from 1 (never) to 4 (often) (Dickstein, 1972). Some items on the scale include "I think of how I would act if I knew I were to die within a given period of time," "I think about my own death," and "When I am outside during a lightning storm I think about the possibility of being struck by lightning" (Dickstein, 1972).

1.2.6.4 Death Anxiety Questionnaire

The DAQ is a self-report questionnaire consisting of 15 items that are rated on a Likert scale ranging from 0 (not at all) to 2 (very much) (Conte et al., 1982). Some items on the scale include "Does it bother you that you may die before you have done everything you wanted to," "Does the thought bother you that you might lose control of your mind before death?" and "Do you worry that those you care about may not remember you after your death" (Conte et al., 1982).

1.2.6.5 Death Anxiety Beliefs and Behaviours Scale

The Death Anxiety Beliefs and Behaviours Scale (DABBS) was developed by Menzies et al., 2022 to address the limitations in previous measures of DA, namely that no other measure of DA assesses maladaptive beliefs and behaviours that are specific to DA. Through generating items from a community sample and conducting exploratory and confirmatory factor analyses, an 18-item instrument was generated (Menzies et al., 2022). The first 4 items ask about how much an individual agrees with statements about death (e.g., "I feel anxious about death, the fact that I will dies someday is terrifying," "I am scared of dying," and "Death frightens me") on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Items 5 to 11 ask how frequently a person experiences death-related thoughts, beliefs and attitudes (e.g., "It would be terrible to not have time to experience everything I want to," "I could not cope with growing old without my loved ones," and "On my deathbed, I will not be able to face death as bravely as I should"), and are rated on a Likert scale ranging from 1 (never have the thought disagree) to 5 (always have the thought). Items 12 to 18 inquire about how frequently individuals avoid activities or situations related to DA (e.g., "Watching or reading media stories about dying," "Watching a film or TV show with a character who is dying," and "Thinking about being diagnosed with a terminal illness") and are rated on a Likert scale ranging from 1 (I would never avoid) to 5 (I would always avoid). Ultimately, the DABBS is a novel instrument that is comprehensive, valid, and reliable in assessing DA in general populations and populations that are seeking mental health treatments.

1.3 Serotonergic Psychedelics

The word 'psychedelic' stems from the Greek language, which means 'mind manifesting', which reflects the consciousness altering properties of psychedelics (i.e., also referred to as hallucinogens) (Kelmendi et al., 2022). Psychedelic use, such as ayahuasca, psilocybin, and peyote is documented as early as 2000 years ago for religious and medicinal practices, as seen in the Olmec, Zapotec, Maya, Aztec, and Ancient Greek cultures (Maia et al., 2024; Nichols, 2016).

1.3.1 The History of Psychedelics

The first wave of psychedelic research began after Arthur Heffter isolated mescaline from the peyote cactus in 1896, and when lysergic acid amide (LSD) was first synthesized by Albert Hofmann in 1938, where their psychedelic effects were discovered through self-experimentation (J. J. H. Rucker et al., 2018). Specifically, the psychedelic effects of LSD were discovered in 1943

when Hofmann accidentally contaminated himself with a small amount, and later ingested 250 mcg purposefully (Nichols, 2016; J. J. H. Rucker et al., 2018). Hofmann also isolated psilocybin, the active component in psilocybin mushrooms, in 1958 (J. J. H. Rucker et al., 2018). After initial research experimentation with mescaline in the 1930's, an increase in susceptibility to psychotherapeutic influence was observed amongst research participants, which catalyzed interest in using psychedelics for psychiatric medicine (J. J. H. Rucker et al., 2018). Although, most early psychedelic research and therapeutic efforts were focused on LSD, as mescaline was not a marketed substance, and LSD was given to psychiatrists free of charge (J. J. H. Rucker et al., 2018).

The initial psychedelic studies were conducted between 1895 to 1970 in healthy volunteers, participants with psychotic disorders, neurotic disorders, alcoholism, and other mental illness (J. J. H. Rucker et al., 2018). Between 1950 and the mid-1960s alone, there were "more than a thousand clinical papers discussing 40,000 patients, several dozen books, and six international conferences on psychedelic drug therapy" (Grinspoon & Bakalar, 1997), as cited in (Nichols, 2016). Some study findings demonstrated therapeutic potential, as a meta-analysis of 19 studies for mood disorders published between 1949 and 1973 demonstrated 'clinically judged improvement' in 79 patients (J. J. Rucker et al., 2016). However, these studies were limited by suboptimal methodology, such as "inadequate and inconsistently defined treatment groups and treatments, absent control groups, absent attempts to blind study teams, non-validated outcome measures, inconsistent reporting of outcome measures, lack of reporting of adverse outcomes, lack of statistical analysis of results, and lack of power calculations" (J. J. H. Rucker et al., 2018).

Despite motifs for continued psychedelic research efforts, political pressures and anti-drug views contributed to psychedelics being designated as Schedule I drugs after passage of the Controlled Substances Act of 1970 (R. L. Carhart-Harris & Goodwin, 2017; Nichols, 2016; J. J. H. Rucker et al., 2018). Consequently, researching psychedelics was not possible.

1.3.2 Pharmacodynamics

There are three classes of psychedelics: i) Tryptamines (e.g., Psilocybin from *psilocybe* mushrooms, *N*,*N*-dimethyltryptamine (DMT) from ayahuasca, 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) from *bufo alveris* frog secretions); ii) ergolines (e.g., LSD),

and iii) phenethylamines (e.g., mescaline from e*chinopsis pachanoi* cacti, and 3,4-methylenedioxymethamphetamine (MDMA)) (Kelmendi et al., 2022). Tryptamines, ergolines, and phenethylamines have direct effects on serotonergic receptors to increase 5-hydroxy tryptophan (5-HT) (i.e., serotonin) within the central nervous system. However, certain phenethylamines, like MDMA, have indirect effects on serotonergic receptors to increase serotonin within the central nervous system (Kalant, 2001; López-Giménez & González-Maeso, 2018). Further, tryptamines, ergolines, and phenethylamines are structural analogs to 5-HT (Maia et al., 2024).

1.3.2.1 Classic Psychedelics

Classic psychedelics of the tryptamine, ergoline, and phenethylamine classes (i.e., psilocybin, DMT, mescaline, and LSD) are agonists of 5-Hydroxytryptophan type 2A receptors (5-HT2A-R) (Husain et al., 2023; Nichols, 2016; Slocum et al., 2022). The direct agonism of 5-HT2A-R agonism induced by classic psychedelics was first confirmed in an experiment by Vollenweider, et al., 1998. Their experiment demonstrated that the psychedelic effects of psilocybin were blocked by a selective 5-HT2A-R antagonist ketanserin or risperidone (i.e., atypical antipsychotic), but were exacerbated by haloperidol (i.e., a typical antipsychotic that is a dopamine antagonist) (Nichols, 2016; Vollenweider, et al., 1998).

5-HT2A-R is a G-protein-coupled receptor (GPCR) and is widely expressed on the pyramidal neurons of the neocortex in humans (Hoyer et al., 1986; López-Giménez et al., 1998). Activation of 5-HT2A-R results in coupling to $G_{q/11}$ proteins, resulting in the activation of phospholipase C (López-Giménez & González-Maeso, 2018). This then causes the production of inositol phosphate and diacylglycerol, which functions to mobilize intracellular calcium to cause the release of glutamate, the primary excitatory neurotransmitter within the central nervous system (López-Giménez & González-Maeso, 2018, pp. 5-; Nichols D.E., 2004; Vollenweider & Kometer, 2010). Ultimately, serotonergic psychedelic 5-HT2A-R agonism causes asynchronous glutamate release in the absence of appropriate sensory input, which would otherwise be processed by the thalamus, resulting in hyperexcitability and hypersensitivity of sensory cortical processing (Aghajanian & Marek, 1999; R. L. Carhart-Harris & Friston, 2019; Nichols D.E., 2004). It is the hyperexcitability and hypersensitivity of cortical processing that is viewed to cause the perceptual and cognitive effects of psychedelics (Nichols D.E., 2004).

1.3.2.2 Non-Classic Phenethylamine Psychedelics

Phenethylamines, such as MDMA, are not direct 5-HT2A-R agonists and are not considered to be classic psychedelics (R. L. Carhart-Harris & Friston, 2019). However, MDMA does indirectly stimulate 5-HT2A-R by eliciting a potent release of 5-HT and blockade of 5-HT reuptake (R. L. Carhart-Harris & Friston, 2019; Kalant, 2001; Nichols, 1986, 2016, p. 20; Vollenweider, Gamma, et al., 1998). Other effects of MDMA include increasing dopamine, norepinephrine, and oxytocin. This contributes to its differential psychedelic effect in comparison to classical psychedelics, such as its stimulatory, empathogenic, and prosocial effects (Dumont et al., 2009; Green A.R. et al., 2003). However, the significance of 5-HT2A-Rs role in eliciting and mediating the psychedelic effects of MDMA is illustrated in a study that showed the psychedelic effects of MDMA were markedly attenuated by a serotonin uptake inhibitor, citalopram (Liechti et al., 2000).

1.3.3 Contemporary Serotonergic Psychedelic Research

1.3.3.1 Clinical Studies

1.3.3.1.1 Psilocybin

Psilocybin is a hallucinogenic prodrug (i.e., it is metabolized to its bioactive form, psilocin) that can be found in over 150 mushroom species around the world (Peredy & Bradford, 2014). As a therapeutic intervention, psilocybin is commonly administered as either a 'microdose' or 'macrodose.' Microdoses, as the name implies, are small doses that are not intended to have a psychedelic effect. Thus far, there is questionable evidence of any therapeutic benefit of psilocybin microdosing (T. Anderson et al., 2019; Polito & Stevenson, 2019; Rootman et al., 2021)**.** Macrodosing occurs in conjunction with psychological support over one or two sessions, separated by one to two weeks, at doses of 20 to 30 mg per session which usually results in a 4 to 8-hour hallucinogenic episode (Nutt et al., 2020). Certain cross-sectional studies have associated the intensity of psychedelic experiences with positive therapeutic effects (Bogenschutz et al., 2015; R. L. Carhart-Harris et al., 2018; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Roseman et al., 2017; Ross et al., 2016). Recent studies suggest that psilocybin-assisted psychotherapy has

potential to remedy treatment-resistant mood, anxiety, existential distress in life-threatening illness, eating disorders, substance use disorders, and others (Agin-Liebes et al., 2020; Bogenschutz et al., 2022; Goodwin et al., 2022; Griffiths et al., 2016; Johnson et al., 2017; Peck et al., 2023; Rosenblat et al., 2024; Ross et al., 2016). Higher doses (i.e., up to 36mg / 70kg) and increased frequency of psilocybin administration are also associated with greater therapeutic effects (Li et al., 2022; Perez et al., 2023; Yu et al., 2022).

1.3.3.1.2 LSD

LSD is a highly potent serotonergic psychedelic that was first synthesized in 1948 (J. J. H. Rucker et al., 2018). As a therapeutic agent, it has been investigated as a microdose (i.e., doses up to 20 μg) and as a macrodose (i.e., doses up to 800 μg) (Fuentes et al., 2020; Kuypers et al., 2019). Evidence suggests that microdosing LSD may sub-acutely improve visuospatial memory and phonological verbal fluency (Wießner et al., 2022), and may increase sleep duration (Allen et al., 2024). However, the evidence of therapeutic benefit of microdosing is limited (de Wit et al., 2022). Studies investigating macrodoses of LSD in conjunction with psychological support demonstrated potential efficacy in treating substance use disorders, anxiety, and anxiety associated with life-threatening illness (Fuentes et al., 2020).

1.3.3.1.3 DMT and Ayahuasca

N,N-Dimethyltryptamine (DMT) is the psychoactive component in ayahuasca, which is a traditionally brewed psychedelic medicine used by indigenous groups from the Northwestern Amazon that consists of *Banisteriopsis caapi vines and* leaves of the *Psychotria viridis* shrub (dos Santos et al., 2017). In research, DMT has been administered through ayahuasca brews, vaporization, intravenous injection and others, and is typically given in macrodoses (Aicher et al., 2023; Dos Santos et al., 2016; Timmermann et al., 2024). The effects of ingested DMT, like other classic psychedelics, can last from 4 to 10 hours (Timmermann et al., 2024). However, when inhaled or injected, the duration of effect is approximately 20 minutes (Timmermann et al., 2024). Studies investigating the effects of DMT in conjunction with psychological support have demonstrated potential efficacy in treating substance use disorders, depressive disorders, and grief (Gonçalves et al., 2023; Timmermann et al., 2024).

1.3.3.1.4 Mescaline

Mescaline is a naturally occurring phenethylamine psychedelic that exists in various cacti species (i.e., the North American peyote cactus (*Lophophora williamsii*), South American San Pedro cactus (*Echinopsis pachanoi*), the Peruvian torch (*Echinopsis peruviana*), Bolivian torch (*Echinopsis lageniformis),* and Pereskia aculeata (Vamvakopoulou et al., 2023). Historically, mescaline was investigated for use in schizophrenia and participants with former substance use disorders between the 1950's to the 1960's, with macrodoses of up to 500mg and 5mg / kg (Vamvakopoulou et al., 2023). To the best of our knowledge, only one contemporary randomized, double-blinded, placebo-controlled crossover clinical trial has been conducted (Ley at al., 2023). The effects of mescaline (300 and 500 mg), LSD (100 µg), and psilocybin (20mg) were compared in 32 healthy participants (Ley et al., 2023). Besides differences in the duration of psychedelic effects, with mescaline being the longest (11.1 hours), there were no differences in subjective experience between these classic psychedelics (Ley et al., 2023). However, epidemiological evidence suggests that mescaline was associated with improvement of symptoms in depression, anxiety, substance use disorders, and PTSD (Vamvakopoulou et al., 2023).

1.3.3.1.5 MDMA

MDMA is a synthetically derived non-classic psychedelic from sassafras oil of the phenethylamine class (Gimeno et al., 2005; Murnane et al., 2009). As a therapeutic agent it is given as macrodoses ranging from 75 mg to 150 mg, with optional supplemental doses ranging from 15 mg to 62.5 mg, in conjunction with psychotherapy (Illingworth B.J.G. et al., 2021; Smith et al., 2022). Some studies demonstrate that MDMA may induce anti-depressive effects (Majumder et al., 2012), however other research suggests that MDMA drug use may exacerbate depressive symptoms (de Win et al., 2004; Matthews & Bruno, 2010). Further, MDMA has demonstrated potential in treating anxiety and psychological distress related to life-threatening illness (Wolfson et al., 2020). Most notably, the effects of MDMA on PTSD have been promising. Meta-analytical studies of randomized controlled trials demonstrate efficacy for treating PTSD with MDMA assisted psychotherapy (Bahji A. et al., 2019; Illingworth B.J.G. et al., 2021; Smith et al., 2022; Tedesco et al., 2021). In light of this, a large-scale phase III randomized, placebo-

controlled trial with 104 participants investigating MDMA-assisted therapy for moderate to severe PTSD demonstrated efficacy in reducing PTSD symptoms and functional impairment (Mitchell et al., 2023).

1.3.3.2 Safety

There are several safety considerations with psychedelic use. Risks include moderate to severe anxiety, headaches/migraines, hypertension, nausea/vomiting, prolonged psychosis, lasting perceptual abnormalities, and dangerous behaviour during hallucinogen action (Rossi et al., 2022). In more extreme cases hallucinogen persisting perception disorder (HPPD), a post-hallucinogen intoxication disorder which involves continuation of visual hallucinations after cessation of drug use (Hermle et al., 2012), has also been observed post-psychedelic use (Johnson et al., 2008). However, HPPD is more commonly observed in illicit psychedelic use (Halpern & Pope, 2003). To mitigate risk of adverse events (AEs) and serious adverse events (SAEs), several safeguards are implemented in psilocybin clinical trials. This includes selecting participants with good cardiovascular health, excluding participants that use medications which influence serotonin, excluding participants with a family history or that have schizophrenia, other psychotic disorders, and bipolar I or II disorder (Johnson et al., 2008). The presence of two trained psychedelic therapists and/or monitors are another safeguard, which assists to (i) prepare participants before dosing (i.e, education on the psychedelic experience, building rapport, guidance on how to handle difficult hallucinogenic experiences), (ii) provide support during dosing, and (iii) follow up with participants after dosing to ensure psychological safety and assist with integrating their experiences to their lives (Johnson et al., 2008). Participant oversight from study physicians is also implemented in clinical trials (Davis et al., 2023; Raison et al., 2023; J. Rucker et al., 2021).

The most common side effects reported from serotonergic psychedelic use are elevated heart rate, hypertension, nausea, headaches, transient anxiety, transient delusions, and decreased concentration or appetite (Romeo et al., 2024; Yao et al., 2024). Systematic reviews and meta-analyses investigating the safety of serotonergic psychedelics for mental illness demonstrate that only 9 serious adverse events are reported in the literature (Romeo et al., 2024; Yao et al., 2024). One of the serious adverse events reported was a case of acute transient anxiety during LSD

treatment for anxiety amongst patients with and without a life-threatening illness (Holze et al., 2023). Another study investigating psilocybin for treatment resistant depression showed that two subjects who received 25mg of psilocybin and one subject that received 10 mg of psilocybin demonstrated non-suicidal self-injurious self-harm, and one subject that received 10mg was hospitalized for severe depression (Goodwin et al., 2022; Romeo et al., 2024). Between 3 and 12 weeks post dosing, three participants that received 25 mg, one participant that received 10mg, and one that received active placebo (i.e., 1mg) demonstrated suicidal and/or self- aggressive behaviours, and one participant that received 10 mg of psilocybin demonstrated suicidal ideation (Goodwin et al., 2022; Romeo et al., 2024). Lastly, a study investigating the effects of psilocybin on cognitive and emotional function in healthy participants demonstrated suicidal ideation in one participant that received 10mg of psilocybin at 19 days post dosing, and in one participant that received 1mg of psilocybin active placebo at days 4, 5, and 18-25 post dosing (Romeo et al., 2024; J. Rucker et al., 2021).

1.3.4 Therapeutic Theories

1.3.4.1 Neuroplasticity

Psychiatric illness such as PTSD, depressive disorders, anxiety disorders, and others, are associated with synapse loss and associated aberrations in neural networks (Chen et al., 2015; Duman, 2014; Holmes et al., 2019; Krystal et al., 2017; MacNamara et al., 2016; R. Vose & K. Stanton, 2017; Socodato et al., 2020; Sripada et al., 2012; Sun et al., 2023; Vargas et al., 2023). Serotonergic psychedelics are shown to increase brain plasticity and alter connectivity across multiple brain regions (R. Carhart-Harris et al., 2021; Catlow et al., 2013; Kuypers et al., 2019; Wood et al., 2012), which is viewed to be elicited through 5HT2A-R agonism (Ly et al., 2018). For example, LSD, psilocin (i.e., bioactive form of psilocybin), MDMA, DMT, and other psychedelics have demonstrated increased neuritogenesis (i.e., formation of neurites), increased dendritic spine density, and increased synaptogenesis in rats, *in vitro* and *in vivo* (Ly et al., 2018). Further, pre-task 5HT2A-R activation in mice improved post-task hippocampus long-term potentiation and enabled the re-consolidation of fear training (Catlow et al., 2013; Zhang et al., 2013), which was replicated in rats and rabbits (Cameron et al., 2019; Romano et al., 2010). These effects may be mediated through the expression of genes that are associated with promoting

synaptic plasticity, such as brain derived neurotrophic factor (BDNF) (Calder & Hasler, 2023; de Vos et al., 2021).

Notably, a recent animal study suggests that a single dose of psilocybin can increase synaptic density in the pig brain using synaptic vesicle glycoprotein 2a (SV2a) as a biomarker (Raval et al., 2021). SV2a represents an excellent surrogate biomarker of synaptic density (Cai et al., 2019), as it is expressed ubiquitously throughout the brain, predominantly in glutamatergic and GABAergic synaptic vesicles (Bajjalieh et al., 1994; Varnäs et al., 2020). Specifically, it was found that one day following a single psilocybin injection, hippocampal SV2a levels increased by 4.42%. Moreover, seven days post-intervention, there were further increases in SV2a density in the hippocampus (+9.24%) and prefrontal cortex (+6.10%) (Raval et al., 2021). Thus, serotonergic 5-HT2A-R psychedelic agonists may enhance synaptic density and neuroplasticity as measured by increased SV2a levels (Raval et al., 2021).

In humans, psilocybin doses up to 30 mg have demonstrated changes in cerebral blood flow, resting-state functional connectivity (e.g, within the default mode network), neurochemical levels (e.g., glutamate, N-acetylasperate, ACTH, cortisol, TSH), and other neurophysiological markers of brain activity (e.g., EEG, regional glucose metabolism) (Song et al., 2023). In one representative fMRI study of 16 human participants with depression, resting state functional connectivity was altered in regions with high 5HT2A-R concentrations (R. L. Carhart-Harris et al., 2017). Taken together, evidence suggests that reorganization of dysfunctional neural networks may be an important component of the neuroplastic effects of 5HT2A-R agonists, which may contribute to therapeutic outcomes (Deco et al., 2018; Tagliazucchi et al., 2016). Table 3 presents a summary of selected psilocybin studies on biomarker outcomes.

Table 3: Summary of psilocybin protocols and biomarker outcomes in human

	Sample size	Study design	Psilocybin protocol		Biomarkers	Biomarker outcomes	Behavioural outcomes in relation to biomarkers
Multi-session psilocybin studies							
R. L. Carhart-Harris et al., 2017	19	Pre- and one day post psilocybin treatment fMRI scanning	**Session 1**	**Session 2**	1. CBF 2. Seed-based RSFC	Decreased CBF in the temporal lobes, including the left amygdala, and increased RSFC within the DMN was observed one day after psilocybin treatment.	Increased vmPFC-bilateral inferior lateral parietal cortex RSFC and decreased parahippocampal-prefrontal cortex RSFC was predictive of treatment response at 5-weeks.
			10mg	25 mg			
			Duration: one week				
Doss et al., 2021	24	See Davis et al., 2020	**Session 1**	**Session 2**	1. Glutamate and NAA concentrate in ACC and hippocampus 2. dFC in ACC and PCC	One week after psilocybin treatment, the glutamate and NAA was decreased in ACC and dFC was increased between ACC and PCC.	Greater increases in dFC between the ACC and PCC were associated with less improvement in cognitive flexibility after psilocybin therapy.
			20mg/70kg	30mg/70kg			
			Duration: ~1.6 weeks				
Lewis et al., 2017	LD group: 29	Randomized, double-	**Session 1**	**Session 2**	CBF	Psilocybin induced both increases and	N/A
			LD: 0.16mg/kg	placebo			

	HD group: 29	blind, placebo-controlled	(11.2mg/70kg); or HD:0.215 mg/kg (15.5/70kg) **Duration:** at least 10 days. *Randomized		decreases in absolute and relative perfusion in various areas. No dose-effect was detected.	
Roseman et al., 2018	19	See (Carhart-Harris et al., 2016)	**Session 1** 10mg **Session 2** 25mg **Duration:** one week	Amygdala activity associated with the emotional face recognition task	Psilocybin increased right amygdala responses to fearful and happy faces.	Increased amygdala responses were predictive of positive clinical outcomes.
Kraehenmann et al., 2015	25	Randomized double-blind, cross-over design	**Session 1** 0.16mg/kg (11.2mg/70kg); **Session 2** Placebo **Duration:** at least 14 days * Counterbalanced	Amygdala activity associated with negative stimuli	Amygdala reactivity to negative and neutral stimuli was lower after psilocybin administration than after placebo administration.	Right amygdala reactivity in response to negative stimuli was associated with psilocybin-induced increase in positive mood state.
Dudysová et al., 2020	20	Double-blind, placebo-controll	**Session 1** 0.26mg/kg; (absolute value **Session 2** Placebo	1. Whole night EEG spectral power 2. SWA	Psilocybin did not affect EEG power spectra, but suppressed	No significant changes in subjective total sleep time or sleep quality were observed.

		ed crossover design; see Baverm anova et al., 2018	18.35mg ± 2.21) **Duration**: at least 28 days (mean = 49 days)				SWA in the first sleep cycle.	Participants perceived time to fall asleep significantly longer after psilocybin administration compared to placebo condition.
Hasler et al., 2004	8	Random ized, double-blind, placebo-controll ed	**S1** VLD: 3.15mg/70kg	**S2** 8.05mg/70kg	**S3** MD: 15.05mg.70kg	**S4** HD: 22.05mg/70kg	**S5** placebo	1. 24-h EKG 2. Blood pressure 3. Plasma concentrations of TSH, PRL, CORT, ACTH	The mean arterial blood pressure was moderately elevated only following HD administration; TSH, ACTH, and CORT were elevated during peak effects of HD psilocybin; PRL plasma levels were increased following MD and HD psilocybin; EKG and body temperature was not affected by any psilocybin.	Psilocybin dose dependently increased scores of all 5D-ASC core dimensions. MD and HD psilocybin led to a 50% reduction of performance in the FAIR test comparing to placebo.
			Duration: at least two weeks							
			* Randomized							
Single-session psilocybin studies										

Vollenweider et al., 1999	7	Single-blind design with pre- and post-treatment PET scan	0.25mg/kg (17.5mg/70kg) or Placebo administered randomly	D_2-dopamine receptors in the striatum	Psilocybin significantly decreased [^{11}C]raclopride receptor BP bilaterally in the caudate nucleus and putamen with an increase in endogenous dopamine.	Changes in [^{11}C]raclopride BP in the ventral striatum were related to depersonalization associated with euphoria.
Smigielski et al., 2019	Active group: 20 Control group: 18	Randomized, double-blinded placebo-controlled design	315ug/kg (absolute dose: 21.82±3.7mg) or placebo * 5-Day Daily meditation routines with treatment administered on the fourth day	DMN connectivity	Psilocybin modulated the DMN connectivity during a meditative state	Reduced antero-posterior DMN connectivity was linked to psilocybin-induced ego dissolution.
Gouzoulis-Mayfrank et al., 1999	32; (4 groups, Each group: 8)	Double-blind, placebo-controlled	0.2mg/kg (14mg/70kg) with no more than 15mg; placebo *other groups: METH (0.2mg/kg but no more than 17.5mg and 0.4mg/kg but no more than 35mg), MDE (2mg/kg but no more than 140mg)	rMRGlu	Psilocybin increased rMRGlu particularly in the anterior cingulate and decreased rMRGlu in the thalamus.	N/A

McCulloch et al., 2022	10	See Madsen et al., 2020	0.2-0.3mg/kg (14-21mg/70kg)	RSFC	One week after psilocybin administration, executive control network RSFC was significantly decreased.	Decreased executive control network RSFC at 1 week predicted increased mindfulness at 3 months.
Mason et al., 2020	60	Randomized, double-blind, placebo-controlled	0.17mg/kg (11.9mg/70kg) or placebo	1. Glutamate in mPFC and hippocampus 2. RSFC	Psilocybin induced region-dependent alterations in glutamate and RSFC.	Higher levels of mPFC glutamate were associated with negative ego dissolution; Lower levels in hippocampal glutamate were associated with positive ego dissolution.
Madsen et al., 2020	10	Single psilocybin session with pre- and post-treatment PET and MRI scans	0.2mg/kg or 0.3mg/kg (14/70kg or 21/70kg)	5-HT2AR levels	Cerebral 5-HT2AR binding did not change across individuals.	Psilocybin intake is associated with long-term increases in Openness and Mindfulness. There was a negative association between 5-HT2AR binding and mindfulness.

Mertens et al., 2020	19	Single psilocyb in session with fMRI scan one day after	25mg	Amygdala reactivity associated with the face/emotion perception task	After psilocybin treatment, decreased vmPFC-right amygdala functional connectivity during face processing was observed.	The decrease in functional reactivity was associated with levels of rumination at one week.
Madsen et al., 2019	8	Single-blind design	Between 3 and 30mg psilocybin *Participants were blinded to the dose given	1. 5-HT2AR occupancy 2. Psilocin plasma concentrations	Psilocybin ingestion of between 3 and 30 mg was associated with dose-dependent occupancy of cerebral 5-HT2ARs.	Both psilocin plasma level and 5-HT2AR occupancy are closely associated with subjective psychedelic intensity ratings.
Barrett et al., 2020	15	Blinded, placebo-controlled study	10mg/70kg or placebo	Claustrum FC	Psilocybin significantly decreased the variance of BOLD signal in bilateral claustrum, and induced various FC change.	Subjective effects of psilocybin predicted the variance of BOLD signal in both left and right claustrum.

Abbreviations: 5D-ASC: 5 Dimension Altered States of Consciousness; ACC: anterior cingulate cortex; ACTH: adrenocorticotropic hormone; BOLD: blood-oxygen level dependent; BP: binding potential; CBF: cerebral blood flow; CO:

carbon monoxide; CORT: cortisol; dFC: dynamic functional connectivity; DMN: default mode network; EKG: electrocardiogram; EEG: electroencephalogram; FAIR: Frankfurt Attention Inventory; HD: high dose; LD: low dose; MD: medium dose; mPFC: medial prefrontal cortex; NAA: N-acetylaspartate; PCC: posterior cingulate cortex; PRL: prolactin; rMRGlu: regional metabolic rate of glucose RSFC: resting-state functional connectivity; SWA: slow-wave sleep activity; TSH: thyroid-stimulating hormone; vmPFC: ventromedial prefrontal cortex; VLD: very low dose

Adapted from Psilocybin to Promote Synaptogenesis in the Brains of Patients With Mild Cognitive Impairment (Song et al., 2023)

1.3.4.2 The Relaxed Beliefs Under Psychedelics Model

Carhart-Harris and Friston (2019) proposed the "Relaxed Beliefs Under Psychedelics (REBUS) and the Anarchic Brain" theory to explain the effects of psychedelics on the brain. The REBUS and Anarchic Brain model posits that psychedelics decrease the precision weighting of high-level priors, or established beliefs, in the brain's predictive coding hierarchy. Consequently, this relaxation of established beliefs leads to a state where top-down constraints are loosened, allowing for increased sensitization to bottom-up sensory processing. As a result, the brain experiences increased cognitive flexibility and entropic effects, translating to decreased weighting and revisions of overweighted beliefs (i.e., that are pathological). By promoting a more fluid and flexible brain state, psychedelics may enable the formation of new, adaptive neural pathways and perspectives.

Chapter 2
Rationale, Hypothesis, and Objectives

2 Study Overview

2.1 Rationale

The primary treatments for IA and DA include psychotherapies such as CBT, ACT, relaxation training and death education, and medications such as selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines. However, there are several limitations in available treatment modalities: 1. There is limited guidance and evidence for the use of pharmacological interventions for DA; 2. Up to 70% of individuals with Illness Anxiety Disorder continue to meet diagnostic criteria after long-term follow-up; 3. Psychotherapy, in which receiving more therapy sessions moderates treatment efficacy and SSRIs, which may take weeks to months to achieve therapeutic effects, are problematic if DA and/or IA is related to a life-threatening illness with a short prognosis; and 4. Due to the global shortage of therapists with expertise in the treatment of anxiety disorders, including IA and DA, psychotherapy is less accessible.

Serotonergic psychedelics have recently been revisited to investigate their therapeutic effects in a variety of medical contexts. Promisingly, serotonergic psychedelics administered in conjunction with supportive psychotherapy have demonstrated efficacy in rapid and sustained decreases of depression and anxiety, as well as in treating existential distress in individuals with terminal illness.

2.1.1 Objectives

The goal of this thesis is to systematically investigate if serotonergic psychedelic administration in conjunction with supportive psychotherapy is effective in treating IA and DA that is related to and independent of life-threatening illness through meta-analytical methods.

2.1.2 Hypothesis

We hypothesized that serotonergic psychedelic administration in conjunction with supportive psychotherapy will be associated with decreases in illness and DA that is related to and independent of life-threatening illness.

Chapter 3
Psychedelic Assisted Therapy for Illness and Death Anxiety

3 The Effects of Psychedelic-Assisted Therapy on Illness and Death Anxiety: A Systematic Review and Meta-Analysis

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3.1 Abstract

Illness anxiety (IA) is characterized by worry or fear in response to living with a chronic illness or a preoccupation with having or acquiring a serious disease in conjunction with absent to mild somatic symptomatology. Death anxiety (DA) may underpin IA and is more common in individuals with life-threatening illness. Treatments for IA and DA, such as psychotherapy and antidepressant drugs, are limited. Serotonergic psychedelic assisted therapy (PAT) is a promising treatment alternative as it acts more rapidly than antidepressants and has been shown to decrease anxiety associated with life-threatening illness. This meta-analysis aims to systematically analyze PATs efficacy for IA and DA. A literature search of English language publications was conducted through the Ovid database using Medline®, PsychINFO®, and Embase® from date of inception to February 2024. After screening, 5 randomized controlled trials were included. The results showed that PAT was associated with sustained decreases in IA and DA in the context of having a life-threatening illness. This meta-analysis highlights the potential for PAT to treat IA and DA. Future studies should attempt to discern the biological mechanisms of action of serotonergic psychedelics, and to replicate these findings in other contexts, such as IAD and somatic symptom disorders.

3.2 Introduction

Health anxiety, also referred to as illness anxiety (IA), is characterized by worry or fear in response to living with a chronic illness (Lebel et al., 2020) or a preoccupation with having or acquiring a serious disease in conjunction with absent to mild somatic symptomatology (Ferguson, 2009). IA has been conceptualized on a continuum ranging from mild and transient to severe and chronic, as seen in Illness Anxiety Disorder (IAD) (American Psychiatric Association, 2013; Lebel et al., 2020; Maheu et al., 2021; Substance Abuse and Mental Health Services Administration, 2016) (i.e., previously referred to as hypochondriasis (Bailer et al., 2016)). Although the etiology of IA is understudied, some risk factors for developing IA are experiencing threatening and/or traumatic life events, modelling parental health-anxious behaviours, personality predisposition to negative affectivity, and is often comorbid with concurrent medical illness (French & Hameed, 2022; Tyrer & Tyrer, 2019). Studies report the prevalence of IA to range from 3.4-19% (Tyrer & Tyrer, 2019). The prevalence of IAD as defined by the DSM-5 is unclear due to the recency of the new diagnostic criteria. However, epidemiological studies have reported a point prevalence ranging from 0.04% to 7.4% for hypochondriasis (Scarella et al., 2019; Tyrer & Tyrer, 2019). Individuals with high levels of IA or that have IAD tend to seek care to receive reassurance about their worries, resulting in greater economic burden on health care systems (American Psychiatric Association, 2013; Barsky et al., 2001; Bermingham et al., 2010; French & Hameed, 2022; Newby et al., 2017; Tyrer & Tyrer, 2019).

Given that preoccupation with having or acquiring a serious physical illness (typically a life-threatening disease) is a core feature of IA, it has been theorized that death anxiety (DA) underpins IA and IAD (Menzies, Sharpe, & Dar-Nimrod, 2021). DA is a common human emotional reaction (Furer & Walker, 2008), which in extreme forms, can lead to the development and maintenance of other psychopathologies, such as IAD (aan de Stegge et al., 2018; Iverach et al., 2014). Although DA occurs in non-clinical populations, evidence suggests that it is more common and severe in individuals experiencing life-threatening illness (Iverach et al., 2014). However, individuals with IA or a life-threatening illness may not be subjectively aware of or experience DA (i.e., due to repression) (aan de Stegge et al., 2018; Iverach et al., 2014).

Psychotherapies (i.e., Cognitive Behavioural Therapy, Acceptance and Commitment Therapy, relaxation training and death education) and anxiolytic medications (SSRIs,

benzodiazepines, anticholinergics, and opioids) have been used to treat IA and DA (Fineberg et al., 2022; Furer & Walker, 2008; Grossman et al., 2018; Jansen et al., 2018; Menzies et al., 2018; Scarella et al., 2019; Sussman & Liu, 2014; Tyrer et al., 2014). Despite treatment options, there is limited guidance and evidence for the use of pharmacological interventions for DA (Atkin et al., 2017; Candy et al., 2012; Jansen et al., 2018; Nübling et al., 2012; Salt et al., 2017), and up to 70% of individuals with IAD continue to meet diagnostic criteria after long-term follow-up (Scarella et al., 2019). Psychotherapy, in which receiving more therapy sessions moderate treatment efficacy (Atkin et al., 2017; Grossman et al., 2018; Menzies, Sharpe, & Dar-Nimrod, 2021), and SSRIs, which may take weeks to months to achieve therapeutic effects, are problematic if DA and/or IA is related to a life-threatening illness with a short prognosis (Schimmel et al., 2022). Lastly, due to the global shortage of therapists with expertise in the treatment of anxiety disorders, including IA and DA, psychotherapy is less accessible (A. Lin & Espay, 2021). Ultimately, the available treatment modalities for DA and IA are inadequate.

Psychedelics have recently been revisited to investigate their therapeutic effects in a variety of medical contexts (Lowe et al., 2021). Intriguingly, psychedelics, when delivered in conjunction with psychological support (i.e., psychedelic-assisted therapy; PAT), have shown to be effective in treating existential distress in individuals with a terminal illness, in addition to related symptoms of depression and anxiety (Schimmel et al., 2022). The perceptual and cognitive effects of psychedelics are viewed to be attributable to serotonin receptor 2A (5-HT2A-R) agonism, which may increase mental flexibility, allowing pathological beliefs and expectations to be "relaxed", reassessed, and altered (R. L. Carhart-Harris & Friston, 2019). Notably, serotonergic psychedelics when used in PAT have demonstrated efficacy in rapid and sustained decreases of depression and anxiety (Leger & Unterwald, 2022; van Amsterdam & van den Brink, 2022).

Although studies have demonstrated that PAT is effective in treating existential distress in individuals dealing with life-threatening illness (Schimmel et al., 2022), the data has not been assessed systematically with respect to IA and DA. Given the need to develop novel treatments for IA, DA, and related symptoms, the objective of this meta-analysis was to systematically analyze whether PAT is effective for IA, IAD, and DA.

3.3 Methods

3.3.1 Literature Search

A literature search of English language publications was conducted through the Ovid database using Medline®, PsychINFO®, and Embase® from date of inception to February 2024 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines using the following search strategy: (Serotonin 5-HT2 Receptor Agonist OR Receptor, Serotonin, 5-HT_{2A} OR Hallucinogens OR Psychedelic OR Psilocybin OR Lysergic Acid Diethylamide OR LSD OR N-Methyl-3,4-methylenedioxyamphetamine OR MDMA OR N,N-Dimethyltryptamine OR DMT OR Mescaline) AND (Hypochondriasis OR Illness Anxiety OR Illness Anxiety Disorder OR Death Anxiety OR Health Anxiety OR Anxiety OR Anxiety Disorders). Two authors (AA and JS) independently performed the search and assessed eligibility. In the event of disagreements, a third author was consulted (PG).

3.3.2 Eligibility Criteria

Randomized controlled trials studying the effect of PAT on IAD/hypochondriasis, IA or DA independent of a life-threatening illness, and IA or DA related to a life-threatening illness (i.e., cardiovascular disease, cancer, etc.) were included if they reported sufficient anxiety data to calculate an effect size. Crossover randomized controlled studies were included if data before crossover (i.e., before unblinding) was available. Case studies, systematic/literature reviews, and cross-sectional works were excluded.

3.3.3 Outcome Measures

Based on the studies meeting inclusion criteria, the outcome measures utilized in this meta-analysis were measures of IA and DA in populations with life-threatening illness.

State Trait Anxiety Inventory (STAI) - State and Trait (Spielberger, 1983) scores were used as primary outcome measures. The STAI State and Trait scales consist of 20 items each, that

are rated on a 4-point Likert scale. The STAI State scale assesses transient anxiety which may be elicited from stressful circumstances (Skapinakis, 2014), and as such, was used as a measure of IA in the context of a life-threatening illness in this meta-analysis. The STAI - Trait measure assesses one's vulnerability to experiencing anxiety (i.e., dispositional anxiety) (Skapinakis, 2014), and was used to assess the effects of psychedelic 5-HT2A-R agonists on dispositional anxiety.

The Death Anxiety Scale (DAS) (Templer, 1970), Life Attitude Profile-Revised (LAP-R) Death Acceptance subscale (Reker, 2001), and the Death Attitudes Profile (DAP) – Fear of Death subscale (Gesser et al., 1988), were used as measures of DA. The DAS is a 15 item self-report true/false scale that assesses fear of death. Life Attitude Profile-Revised (LAP-R) scale is a multidimensional measure of meaning and purpose in life, where the Death Acceptance subscale is an 8 item self-report scale that assesses the absence of DA (Reker, 2001). Each item is rated on a 7-point Likert scale. The DAP is a self-report measure of different attitudes towards death (i.e., Fear of Death, Death Avoidance, Neutral Acceptance, Approach Acceptance, and Escape Acceptance). The Fear of Death subscale consists of 7 items that are rated on a 7-point Likert scale which assesses fear of death.

3.3.4 Demographic and Clinical Characteristics

Age, sex, study population, psychiatric comorbidities, and psychedelic experimental dose were collected.

3.3.5 Data Extraction

The Cochrane Handbook for Systematic Reviews of Interventions was used as a guideline for data extraction methodology (https://training.cochrane.org/handbook). The means and standard deviations (SD) for IA and DA measure scores post-PAT for treatment and placebo groups were collected at primary end points as specified per study. For double-blinded randomized controlled cross-over trials, data was extracted at primary end points as specified per study, before unblinding and/or cross-over. This strategy was employed to mitigate risk of bias (Higgins et al., 2023). Post-treatment mean differences, paired-sample t-test and p-values, and SD

of mean differences were extracted if the mean and SD were not available. WebPlotDigitizer was used to extract graphical data if reported data was not sufficient.

3.3.6 Meta-Analysis

Effect size measures included the standardized mean difference (SMD) for continuous outcomes (i.e., measures of anxiety and DA). SMDs were calculated by dividing the difference in mean outcome between groups by the SD of outcomes among participants (https://training.cochrane.org/handbook). The Review Manager software (Version 5.4) (*Review Manager 5 (RevMan5)*, 2020) was used to conduct the statistical analyses and to generate forest plots with a 95% confidence interval (CI). A pooled effect size (ES) was calculated by pooling the effect sizes of all included studies. A random-effects model and inverse variance statistical method was used due to heterogeneity of the study designs (DerSimonian & Laird, 1986). A meta-regression was not performed because less than 10 studies were included in the final analysis (see results) (Geissbühler et al., 2021).

3.3.7 Risk of Bias

The Cochrane Guide for Review Authors on Assessing Study Quality was used to assess the risk of publication bias in each study included in the final analysis based on: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6), selective reporting, and (7) other bias (Higgins et al., 2023). Studies were ranked as low risk of bias, high risk of bias, or unclear risk of bias. Two authors (AA and JS) independently performed the risk of bias analysis. In the event of disagreements, a third author was consulted (PG). The Review Manager software (Version 5.4) (*Review Manager 5 (RevMan5)*, 2020) was used to generate the risk of bias graph.

An Egger's regression test was used to assess publication bias, where a trim-and-fill procedure was performed to correct any publication biases that were detected (Higgins et al., 2023).

3.3.8 Quality Assessment

Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schünemann et al., 2013). This method involved examining the risk of bias, inconsistencies among studies, imprecision, and indirectness. Based on these criteria, the quality of evidence was classified as high, moderate, low, or very low. The assessment was conducted by two reviewers (AA and YK). In the event of disagreements, a third author was consulted (PG).

3.3.9 Sensitivity Analysis

Chi-square statistics were used to assess heterogeneity between studies. I^2 statistics were used to assess the level of heterogeneity based on the following criteria: 0% to 40% may not represent significant heterogeneity, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, and 75% to 100%: considerable heterogeneity (Higgins et al., 2023). If heterogeneity was substantial or greater, a leave-one-out sensitivity analysis was done to analyze if the results were significantly biased from one study.

3.4 Results

3.4.1 Included Studies

The literature search identified 3194 publications after removing duplicates. No studies investigating the effects of PAT on IAD or either IA or DA independent of life-threatening illness were identified. Five studies investigating the effects of PAT on IA in individuals with life-threatening illness (Gasser et al., 2014; Griffiths et al., 2016; Holze et al., 2023; Ross et al., 2016; Wolfson et al., 2020), three of which further investigated its effects on DA (Griffiths et al., 2016; Ross et al., 2016; Wolfson et al., 2020). Figure 1 demonstrates the PRISMA flow diagram for study selection. Table 4 summarizes the demographic, clinical, and study characteristics of the included studies.

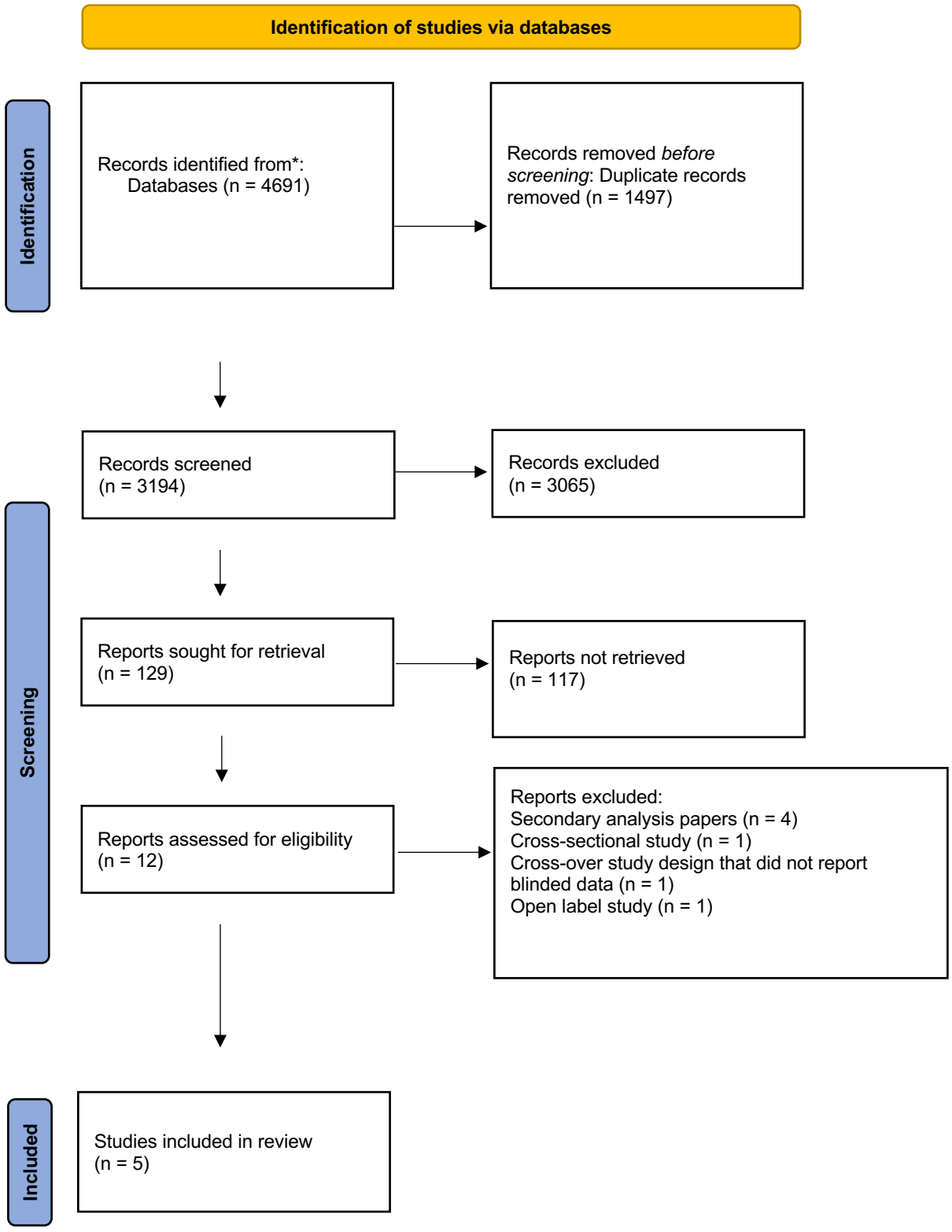


Figure 1: PRISMA 2020 flow diagram for study selection

Table 4: Summary of study characteristics

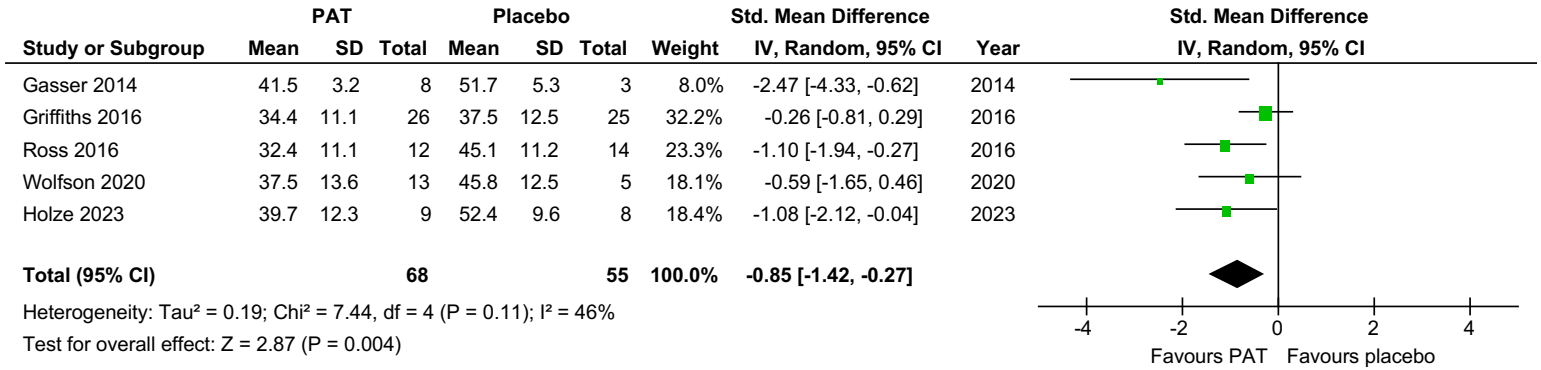
Author (Year)	Population	Total N	Age Mean (SD)	% Male	Serotonergic Psychedelic	Experimental Dose	Placebo Type and Dose	Study Design	Psychiatric Comorbidities
Gasser et al. (2014)	life-threatening illness	12	51.7 (9.1)	63.6%	LSD	200ug	20ug LSD (active placebo)	crossover double-blinded randomized controlled trial	generalized anxiety disorder (54.5%), major depression (63.6%), reactive depression (9.1%), dysthymia (18.2%), PTSD (8.3%), panic disorder (27.3%), social phobia (8.3%).
Griffiths et al. (2016)	life-threatening cancer	51	56.3 (1.4)	51.00 %	psilocybin	22 or 30mg/70kg	1 or 3 mg /70 kg of psilocybin (active placebo)	crossover double-blinded randomized controlled trial	chronic adjustment disorder with anxiety (21.57%), chronic adjustment disorder with anxiety and depressed mood (21.57%), dysthymic disorder (9.8%), generalized anxiety disorder (9.8%), major depression (27.45)
Ross et al. (2016)	life-threatening cancer	29	56.3 (12.9)	38%	psilocybin	0.3mg/kg	250 mg niacin (active placebo)	crossover double-blinded randomized	chronic adjustment disorder with anxiety and depressed mood (28%), chronic

								controlled trial	adjustment disorder with anxiety (62%)
Wolfson et al. (2020)	life-threatening illness	18	54.9 (7.9)	22.20 %	MDMA	Two 125mg doses, with an optional supplementary dose of 62.5mg after 1.5-2.5 hours, separated by one week	125 mg lactose (inert placebo)	crossover double-blinded randomized controlled trial	anxiety (83.3%), major depression (77.8%), PTSD (72.2)
Holze et al. (2023)	Life-threatening illness	20	46 (13)	45%	LSD	Two 200ug doses separated by 6 weeks	Ethanol solution (inert placebo, dose unspecified)	crossover double-blinded randomized controlled trial	OCD (5%), major depression (25%)

3.4.2 Main Outcomes

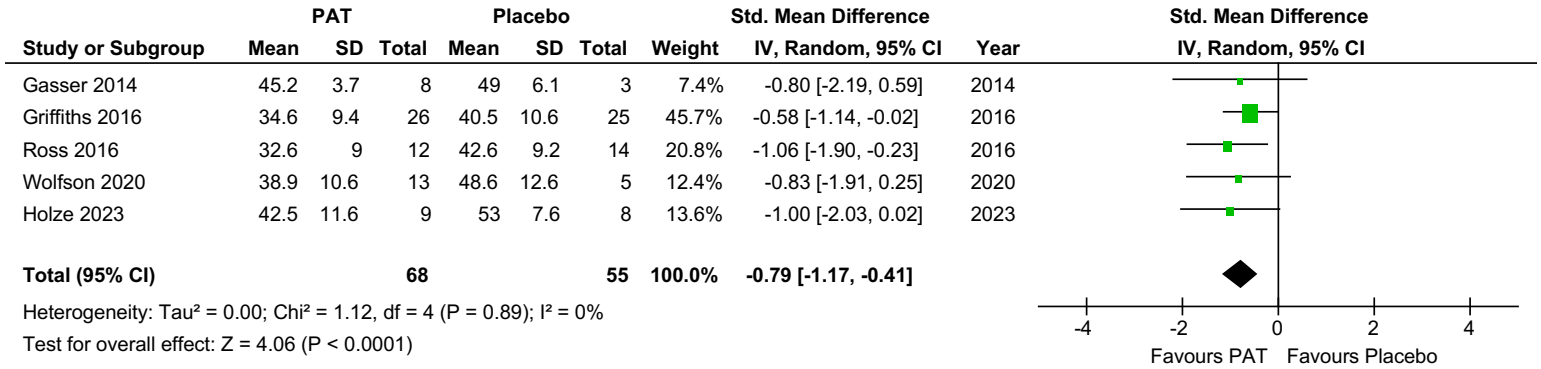
All included studies assessed IA with the STAI - State scale and dispositional anxiety with STAI - Trait scale. Four of the five included studies used these measures as primary outcomes (Gasser et al., 2014; Holze et al., 2023; Ross et al., 2016; Wolfson et al., 2020). The random effect models indicated that administration of PAT resulted in reductions in IA (i.e., STAI State) (SMD = -0.85, 95% CI -1.42 to -0.27, $p < 0.01$) (Figure 2) and dispositional anxiety (i.e., STAI Trait) (SMD = -0.79, 95% CI -1.17 to -0.41, N = $p < 0.0001$) (Figure 3) from 4 weeks up to 4 months in 123 participants (i.e., 68 participants that received PAT and 55 that received placebo).

Three of the five studies assessed DA (Griffiths et al., 2016; Ross et al., 2016; Wolfson et al., 2020) using the DAS, LAP-R Death Acceptance subscale, and the DAP - Fear of Death subscale. The random effect model indicated that administration of PAT resulted in reductions in DA (SMD = -0.62, 95% CI -1.04 to -0.21, p = <0.01) (Figure 4) from 2 weeks up to 5 weeks in 98 participants (i.e., 52 participants that received PAT and 46 that received placebo).



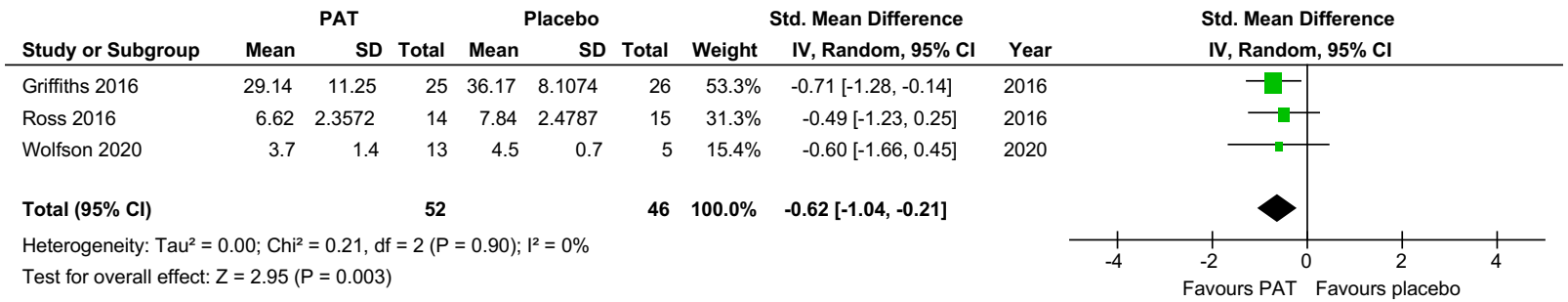
Abbreviations: CI=confidence interval; df=degrees of freedom; PAT = psychedelic assisted therapy; SD=standard deviation; IV=weighted mean difference;

Figure 2: Forest plot demonstrating the effect of PAT on Illness Anxiety (i.e., STAI State anxiety) in the context of life-threatening illness



Abbreviations: CI=confidence interval; df=degrees of freedom; PAT = psychedelic assisted therapy; SD=standard deviation; IV=weighted mean difference;

Figure 3: Forest plot demonstrating the effect of PAT on Dispositional Anxiety (i.e., STAI Trait anxiety) in the context of life-threatening illness



Abbreviations: CI=confidence interval; df=degrees of freedom; PAT = psychedelic assisted therapy; SD=standard deviation; IV=weighted mean difference;

Figure 4: Forest plot demonstrating the effect of PAT on DA in the context of life-threatening illness

3.4.3 Risk of Bias

The risk of bias for randomization for the study by Gasser et al. (2014) was unclear because there were substantial differences in baseline STAI scores between groups. The risk of bias for randomization was also unclear for the study by Griffith's et al. (2016) due to a lack of randomization information. The risk of allocation concealment was low for all studies. The risk of bias for blinding of participants, personnel, and outcome assessment was unclear for 4 studies (Gasser et al., 2014; Holze et al., 2023; Ross et al., 2016; Wolfson et al., 2020). This was due to the high risk of unblinding as a result of the profound psychedelic experiences elicited by high dose 5-HT2A-R agonists versus placebos (Muthukumaraswamy et al., 2021). In the study by Griffiths et al. (2016), the risk of bias for blinding of participants, personnel, and outcome assessment was high because the investigators lowered the psilocybin dose of the experimental group after two of the first three participants discontinued the study due to vomiting and undisclosed personal reasons. In the same study, the dose of the active placebo was also lowered after 12 participants due to suspicion that the dose elicited some unintended psychedelic effects. The risk of bias for selective reporting was low for all studies. The studies by Gasser et. al (2014) and Holze et al (2023) were deemed high risk for other biases because the extent and severity of some participants' life-threatening disease was unclear. The risk of bias graph and summary is presented in Figures 5 and 6.

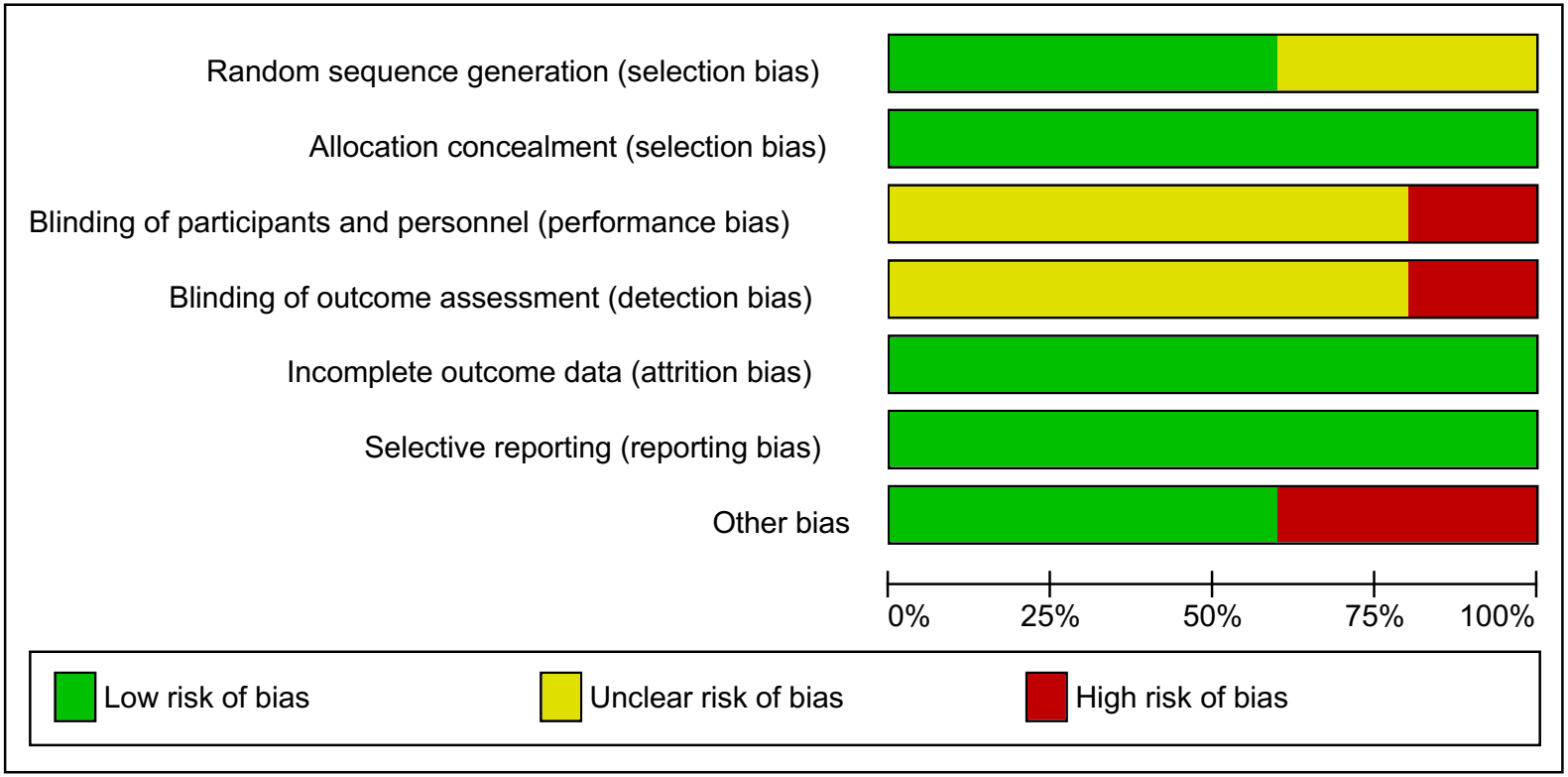


Figure 5: Risk of bias graph of the included studies

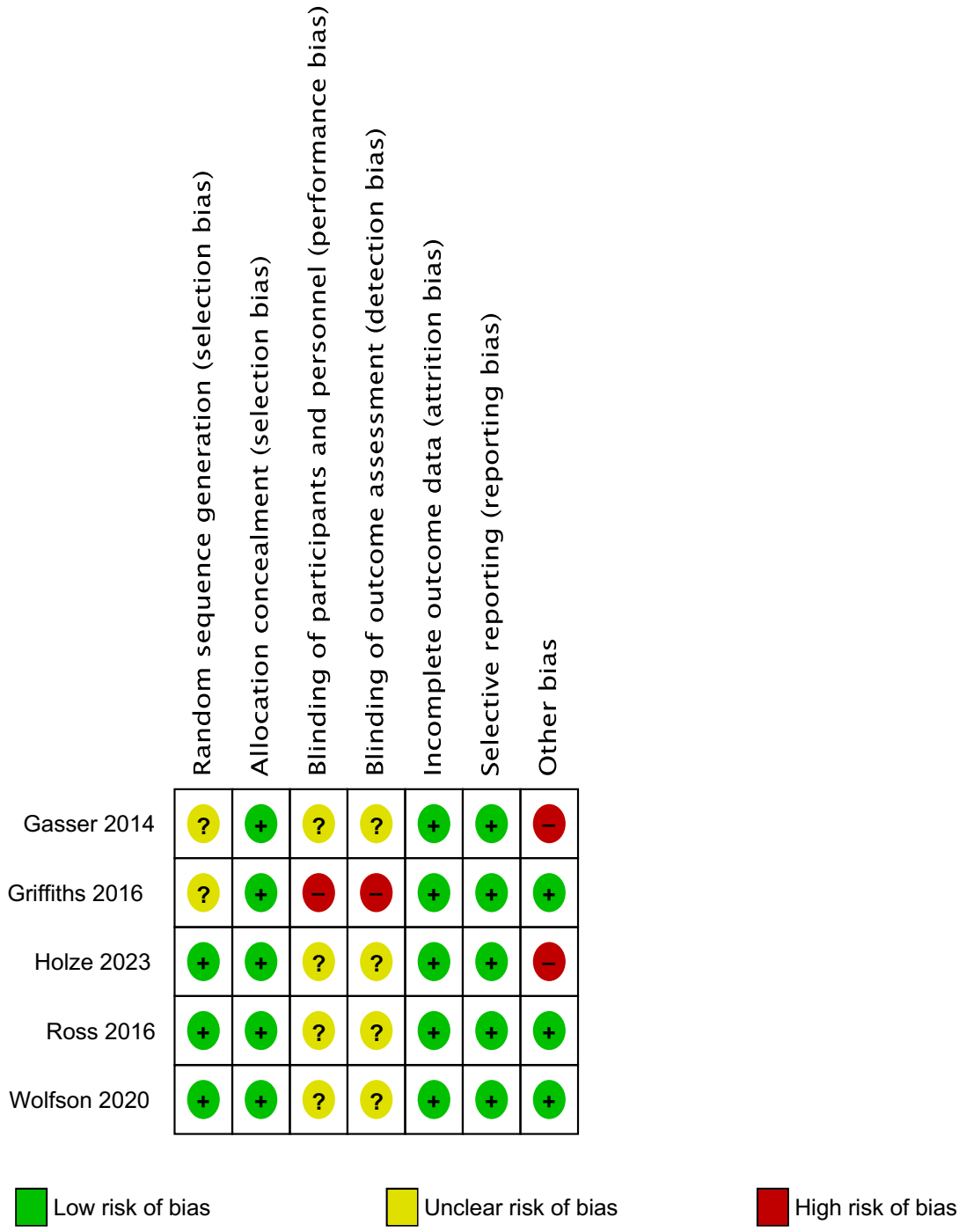


Figure 6: Risk of bias summary of the included studies

Tests for funnel plot asymmetry should only be used when there are at least 10 studies, so an Egger's test was not done (Higgins et al., 2023).

3.4.4 Quality Assessment

The certainty assessment for risk of bias was deemed serious for all outcomes due to the unclear and high risk of bias for performance and detection bias. Overall, moderate to high levels of certainty demonstrates that PAT may have benefit in alleviating IA, dispositional anxiety, and DA when compared to control groups (Figure 7).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Experimental Dose	Control	Relative (95% CI)	Absolute (95% CI)		
Illness Anxiety (i.e., STAI State)												
5	randomised trials	serious	not serious	not serious	not serious	strong association	68	55	-	SMD **0.85 lower** (1.42 lower to 0.27 lower)	⊕⊕⊕⊕ High	CRITICAL
Dispositional Anxiety (i.e., STAI Trait)												
5	randomised trials	serious	not serious	not serious	not serious	strong association	68	55	-	SMD **0.79 lower** (1.17 lower to 0.41 lower)	⊕⊕⊕⊕ High	CRITICAL
Death Anxiety												
3	randomised trials	serious	not serious	not serious	not serious	none	52	46	-	SMD **0.62 lower** (1.04 lower to 0.21 lower)	⊕⊕⊕◯ Moderate	CRITICAL

Abbreviations: CI = Confidence Interval; SMD = Standardized Mean Difference, STAI = State - Trait Anxiety Inventory

Figure 7: Grading evidence quality and strength of recommendations

3.4.5 Sensitivity Analysis

The I^2 statistic was 0% in studies reporting the effect of PAT on STAI Trait anxiety and on DA, indicating no heterogeneity. The I^2 statistic was 46% in studies reporting the effect of PAT on IA (i.e., STAI State anxiety), suggesting moderate heterogeneity (Higgins et al., 2023). I^2 can be biased in small meta-analyses, such as the current study, in which there are not enough studies to reliably assess heterogeneity (Higgins et al., 2023; von Hippel, 2015).

3.4.6 Analysis of Included Studies

Gasser et al. (2014) investigated the safety and efficacy of lysergic acid diethylamide (LSD) assisted psychotherapy in 12 participants with anxiety associated with a life-threatening illness by using a randomized double-blind active placebo-controlled design. Life-threatening illnesses included cancer (n=9), Celiac disease (n=1), Parkinson's disease (n=1), and ankylosing spondylitis (n=1). Psychotherapy occurred before dosing for rapport building, during dosing for support, and after dosing for integration. Two 200 μg doses of LSD were used as the experimental dose, and two 20 μg doses of LSD were used as an active placebo dose, separated by 2-3 weeks apart. Blinded follow up data was completed two months after the last LSD session. There were significant reductions in STAI State, but not STAI Trait anxiety, in the experimental group in comparison to the active placebo group at the two month follow up. This study did not assess DA.

Griffiths et al. (2016) investigated the efficacy of psilocybin in 51 life-threatening cancer patients and symptoms of depression and/or anxiety by using a randomized, double-blind, placebo controlled, crossover trial design. Monitors would meet with participants prior to dosing to build rapport, during dosing to facilitate openness to the experience, and after dosing to explore novel thoughts and feelings that arose in the session. During the experimental visit, participants received either a high dose (22 or 30mg/70kg) or an active-placebo low-dose of psilocybin (1 or 3 mg/70kg). Anxiety was assessed at 5 weeks after the first dosing session, before cross-over. Participants in the experimental group demonstrated greater reductions in STAI Trait anxiety and DA, as assessed by the LAP-R Death Acceptance scale, in comparison to participants in the active placebo group. No significant group differences were found in STAI State anxiety.

Ross et al. (2016) conducted a double blind, crossover randomized placebo-controlled trial investigating the efficacy of psilocybin in conjunction with psychotherapy in treating anxiety and depression in 29 patients with life-threatening cancer. Psychotherapy occurred before dosing for rapport building, during dosing for support, and after dosing for integration. During the experimental visit, participants either received a 0.3mg/kg dose of psilocybin or, the active control, niacin. Measures of anxiety were taken 1 day, 2 weeks, 6 weeks, and 7 weeks (i.e., primary outcome) after the first dose. DA was only measured two weeks after the first dose, and was assessed by the DAS. The experimental group had reduced anxiety as assessed by STAI State and Trait scores at all blinded timepoints in comparison to niacin. Although lower in the experimental group, there was no significant group differences in DA as measured with the DAS. The means and SDs for this study were extrapolated with WebPlotDigitizer.

Wolfson et al. (2020) investigated the efficacy of MDMA-assisted psychotherapy in treating anxiety and psychological distress related to life-threatening illnesses using a double blind, crossover randomized placebo-controlled design. Seventeen participants had diagnoses of cancer, and one participant had a life-threatening musculoskeletal and connective tissue disease. Psychotherapy occurred before dosing for rapport building, during dosing for support, and after dosing for integration. Participants received either two doses of 125mg of MDMA or lactose pills separated by 2 to 4 weeks, with an optional supplementary dose of 62.5mg of MDMA or lactose placebo 1.5 to 2.5 hours after the initial dose at each visit, under blinded conditions. During the experimental sessions, participants received non-directive therapy. STAI Trait and State scores were lower at one month post-treatment (i.e., primary outcome) in the experimental group, however the between group differences were not statistically significant. DA scores were lower in the experimental group in comparison to placebo at one month post-treatment, but were not statistically significant, and the mean DA score only changed by 0.1 within the experimental group at one month post-treatment in comparison to baseline. Death anxiety was assessed by the DAP Fear of Death subscale.

Holze et al. (2023) investigated the effects of LSD assisted psychotherapy in patients with anxiety, with and without a life-threatening illness. The authors included separate analyses of individuals with life-threatening illness, which were used for the current analysis. Of the 20 participants with a life-threatening illness, 11 had cancer. Others had Parkinson’s disease,

Marfan's syndrome, Multiple Sclerosis, blindness due to premature birth, sarcoidosis, kidney transplantation due to a cirrhotic kidney, Guillain Barré Syndrome with partial remission, Human Immunodeficiency Virus, and Juvenile Arthritis with secondary blindness. Similar to the study by Gasser et al. (2014), psychotherapy occurred before dosing for rapport building, during dosing for support, and after dosing for integration. Participants received either two 200 ug doses of LSD or two 20 ug doses of LSD active placebo, separated by 6 weeks. In those with a life-threatening illness, the experimental group demonstrated significant reductions in STAI State and Trait anxiety at 16 weeks post dosing (i.e., primary outcome) in comparison to the placebo group. Of note, significant reductions in STAI State and Trait anxiety were demonstrated in those without a life-threatening illness at two weeks post dosing. Measures of DA were not assessed. The means and SDs for this study were extrapolated with WebPlotDigitizer.

3.4.7 Analysis of Post-Crossover Data from Included Studies

Gasser et al. (2014) demonstrated no mean differences in STAI State and Trait anxiety when comparing scores between the crossover at 2 month follow up and 12 month follow up, indicating long-term reductions in STAI State and Trait anxiety post-treatment.

Griffiths et al. (2016) demonstrated within-group reductions in STAI State and Trait anxiety and DA when comparing scores in the group that received active placebo first (i.e., low dose psilocybin) to one month after receiving the experimental dose in the cross-over period. Further, the difference between baseline and 6-month follow up STAI State and Trait anxiety and DA scores between groups were significant.

Ross et al. (2016) showed within group reductions in STAI State and Trait anxiety at 1 day, 6 weeks, and 26 weeks after the second dosing session for both groups (i.e., in the niacin-first group, which received psilocybin during the second dosing session, and psilocybin-first group, which received niacin placebo during the second dosing session). There were also significant between-group differences after crossover between participants who received niacin first and psilocybin first, in which those that received psilocybin demonstrated lower mean STAI State anxiety scores at 26 weeks and lower mean STAI Trait anxiety 6 weeks after the second dose. Regarding DA, no significant between or within group differences were demonstrated.

Wolfson et al. (2020) demonstrated within-group reductions in STAI State and Trait anxiety in all participants after crossover from the treatment exit point (one month after the third open label MDMA session in each group), 6 month follow up, and 12 month follow up. Further, all participants reported significant improvement in DA in comparison to baseline.

Holze et al. (2023) demonstrated significant reductions in STAI Trait and State anxiety in participants with a life-threatening illness at 2 weeks after crossover dosing visits, and significant reductions in STAI Trait anxiety at 16 weeks after crossover dosing visits.

3.5 Discussion

This systematic review and meta-analysis investigated the effect of PAT on IA and DA in the context of life-threatening illness. To the best of our knowledge, there are no studies which have investigated the effects of PAT on IA or DA independent of having a life-threatening illness. The results of the main analysis demonstrate that PAT is effective in attaining long-term reductions in IA, DA, and dispositional anxiety associated with having life-threatening illness.

Other studies investigating the effects of PAT on anxiety related to life-threatening illness that did not meet inclusion criteria for the current meta-analysis demonstrated similar results. A recent open-label trial demonstrated that reduced STAI State and Trait anxiety scores at 3 and 8 weeks post psilocybin (25 mg) dose in individuals with life-threatening cancer (Agrawal et al., 2024). Additionally, a long term follow up of one of the included studies (Ross et al., 2016) demonstrated significant reductions in STAI State and Trait, and DA at 4.5 years compared to baseline (Agin-Liebes et al., 2020). However, other studies did not replicate these findings. One study demonstrated reductions in STAI Trait anxiety at 1 and 3 months after psilocybin (0.2 mg/kg) treatment in patients with advanced stage cancer, but not in STAI State anxiety (Grob et al., 2011). Another study demonstrated reductions in STAI State and Trait anxiety at 3 weeks post psilocybin (0.3 - 0.36 mg/kg), which was sustained at 3-months follow up for STAI Trait anxiety, but not STAI State anxiety, in older long-term AIDS survivor men (B. T. Anderson et al., 2020). These discrepant results may be attributable to a lack of statistical power (i.e., n = 12 (Grob et al., 2011), n = 18 (B. T. Anderson et al., 2020)). Further, one of the studies used a lower experimental dose of psilocybin (i.e., 0.2 mg/kg) in comparison to other studies which showed efficacy with

higher doses (i.e., 0.3 mg/kg (Ross et al., 2016)), suggesting that a higher dose of psilocybin may be needed for anxiolytic effects in the context of life-threatening illness.

PAT has also demonstrated anxiolytic effects in other contexts, such as clinical depression, where symptoms of anxiety are a common comorbidity (Cuijpers et al., 2023). An open-label psilocybin (10 mg and 25 mg) study for treatment-resistant depression demonstrated acute and sustained reductions in STAI Trait anxiety (i.e., 1 week – 6 months post dosing) (R. L. Carhart-Harris et al., 2016, 2018). Further, a double blind randomized controlled trial demonstrated larger decreases in Trait anxiety in participants with moderate-to-severe depression who received psilocybin (25 mg) in comparison to participants who received escitalopram at 6 weeks post dosing (R. Carhart-Harris et al., 2021). Lastly, a double-blind randomized placebocontrolled study investigating the effects of ayahuasca (i.e., N,N-Dimethyltryptamine (DMT), a 5-HT2A-R agonist (Carbonaro & Gatch, 2016)) (2 mL/kg) on individuals with social anxiety disorder demonstrated improved self-perception of speech performance, suggesting alterations in negative cognitive bias associated with Social Anxiety Disorder (Dos Santos R.G. et al., 2021).

The timing of the primary end-points of the studies included in the current meta-analysis vary widely (i.e., STAI State and Trait: 5 weeks – 4 months (Gasser et al., 2014; Griffiths et al., 2016; Holze et al., 2023; Ross et al., 2016; Wolfson et al., 2020) Measures of DA: 2 weeks – 1 month post dosing (Griffiths et al., 2016; Ross et al., 2016; Wolfson et al., 2020), suggesting that PAT may provide sustained relief in individuals experiencing IA and DA related to life-threatening illness. However, it is important to better discern the immediate effects of PAT in patients with life-threatening illnesses with shorter prognoses. To address this, one of the included demonstrated decreases in STAI State and Trait anxiety at one day post psilocybin dosing (Ross et al., 2016). Another included study demonstrated reductions in STAI State and Trait anxiety at 3 weeks after the first 200ug LSD dose, and 2 weeks after the second 200ug LSD dose in STAI State and Trait anxiety, in comparison to placebo (Holze et al., 2023). Lastly, an excluded pilot study (which did not report pre-crossover data) investigating the effects of psilocybin on 12 participants with advanced stage cancer and reactive anxiety demonstrated substantial, but non-significant decreases in STAI State anxiety at 6 hours post dosing in comparison to scores from the day before dosing (Grob et al., 2011).

3.5.1 Limitations

There are several limitations to be considered with respect to the present work. First, this meta-analysis has a small sample size of only 5 studies, in which even the included studies had small sample sizes (i.e., 12 to 51 participants), which can lead to sampling error (i.e., selecting sample that does not represent the population) and consequently, biased within-study variances (L. Lin, 2018). Second, the results of this meta-analysis would be strengthened if we assessed PAT's efficacy in treating IA and DA, while controlling for changes in dispositional anxiety using a meta-regression approach. However, there were not enough studies available to perform a meta-regression. Third, given that all studies included participants with other psychiatric comorbidity, which is common in life-threatening illness, the results of this meta-analysis may lack specificity for IA and DA. Fourth, although all the included studies assessed anxiety associated with life-threatening illness, measures specific to IA were not included. Fifth, it is also unclear to what extent the administration of psychotherapy, the psychedelic drug itself, or both, are responsible for eliciting therapeutic effects. This issue is present in most PAT research (van Elk & Fried, 2023). Fifth, a common limitation in psychedelic studies is the risk of unblinding due to the challenges of finding an adequate comparator (Muthukumaraswamy et al., 2021; van Elk & Fried, 2023). Last, it is unclear if there are differences in efficacy between different psychedelic agents. The present study was unable to do subgroup analyses based on study drug due to the limited number of studies which met inclusion criteria. Future studies should conduct larger scale, double blinded randomized controlled trials, and include measures specific to IA and DA.

3.6 Conclusion

This meta-analysis suggests PAT is effective in treating IA and DA in the context of life-threatening illness. The promising results and the few studies available for meta-analysis substantiate the need for continued investigation of PAT in not only treating anxiety and existential distress related to life-threatening illness, but also in treating IA, DA, IAD and other forms of somatic symptom disorders independent of life-threatening illness. Future studies should also assess the immediate anxiolytic effects (i.e., one day to one week after dosing) of PAT as the rapid treatment of IA and DA is important in individuals with aggressive life-threatening illnesses with a short prognosis.

Chapter 4
General Discussion, Future Directions, Conclusions

4 Overview

The study in Chapter 3 examined the potential for psychedelic-assisted therapy (PAT) to treat illness and death anxiety (DA). This chapter will provide a summary of findings from Chapter 3, followed by a general discussion.

4.1 Summary of Findings

4.1.1 PAT for the Treatment of Illness Anxiety and Death Anxiety in Life Threatening Illness

In Chapter 3, we performed a systematic review and meta-analysis of double blinded placebo-controlled randomized controlled cross-over studies to examine the effectiveness of PAT on illness and DA.

A meta-analysis of 5 studies demonstrated that PAT is associated with significant reductions in IA and dispositional anxiety in the context of life-threatening illness. Further, a meta-analysis of 3 studies demonstrated that PAT is associated with significant reductions in DA in the context of life-threatening illness.

The current treatment modalities for IA are inadequate as up to 70% of individuals with IAD continue to meet criteria even after long-term treatment, individuals with IAD are preoccupied with the adverse events of medications (i.e., SSRIs), psychotherapies and medications can take months to achieve therapeutic effects, and psychotherapy is typically inaccessible (Higgins-Chen et al., 2019; A. Lin & Espay, 2021; Scarella et al., 2019). This thesis

supports the hypothesis that PAT is an effective treatment for IA in the context of life-threatening illness. Other studies that did not meet inclusion criteria of the meta-analysis further support these findings. A recent open label psychedelic assisted group therapy trial for cancer patients diagnosed with a major depressive disorder demonstrated reductions in IA (i.e., STAI State) and dispositional anxiety (i.e., STAI Trait) at 3 weeks and 8 weeks after dosing (Agrawal et al., 2024). Additionally, significant reductions in STAI State and Trait have been demonstrated 4.5 years after psilocybin PAT compared to baseline (Agin-Liebes et al., 2020). These findings suggest that PAT induced reductions of IA may be mediated by reductions in dispositional anxiety (Agrawal et al., 2024). Conversely, other PAT trials in life-threatening illness have demonstrated significant reductions in only STAI Trait (B. T. Anderson et al., 2020; Grob et al., 2011). However, these discrepancies may be related to smaller sample sizes that are common in pilot studies, and lower doses of psychedelics that were included in the trials (B. T. Anderson et al., 2020; Grob et al., 2011). This suggests that larger psychedelic doses are associated with greater therapeutic effects, which has been demonstrated in other works (Li et al., 2022; Perez et al., 2023; Yu et al., 2022). Lastly, our hypothesis is further supported by other studies which demonstrate anxiolytic effects of psychedelics in other contexts, such as depressive disorders and social anxiety disorders (R. Carhart-Harris et al., 2021; R. L. Carhart-Harris et al., 2016, 2018; Cuijpers et al., 2023; Dos Santos R.G. et al., 2021).

As a transdiagnostic construct, DA is viewed to underpin several psychiatric illnesses, and is especially prominent with respect to IAD (Iverach et al., 2014; Menzies et al., 2019; Menzies, Sharpe, & Dar-Nimrod, 2021). This is highlighted in the psychotherapeutic treatment of IAD, as DA is an essential construct to address when treating IAD (Furer & Walker, 2008; Iverach et al., 2014; Noyes et al., 2002; Starcevic, 2005). Further, evidence suggests DA is associated with reduced quality of life in individuals with life-threatening illness, as well as increased care-giver burden (Gonen et al., 2012; Sherman et al., 2010; Soleimani et al., 2016; Yan et al., 2024). In support of this, a study which administered a retrospective questionnaire to 155 participants that "had at least one significant psychedelic experience that they felt altered their attitudes or anxieties about death" showed significant reductions in DA before and after psychedelic use (i.e., LSD, DMT, psilocybin, ayahuasca, or mescaline) (Moreton et al., 2024). Another retrospective questionnaire study of 201 participants that had a meaningful experience elicited by psychedelic use i.e., (LSD, DMT, psilocybin, ayahuasca, or mescaline) demonstrated that reductions in DA mediated the effects of "mystical experience on satisfaction with life, positive affect, and negative

affect" (Moreton et al., 2023). In combination with the results of the meta-analysis, this supports the hypothesis that psychedelic induced reductions of DA may be a key therapeutic effect of PAT (Moreton et al., 2020). Future studies should investigate if reductions in DA can predict therapeutic outcomes from PAT when used to treat depressive disorders, existential distress related to life-threatening illness, anxiety disorders, and somatic symptom disorders.

4.2 General Limitations

The results of this thesis should be interpreted considering its limitations. First, there were a limited number of studies included in the meta-analysis, of which the included studies had small sample sizes. This can lead to sampling error, and biased within-study variances (L. Lin, 2018). Second, psychiatric comorbidities are common in individuals dealing with life-threatening illness, which may limit the specificity of the thesis to IA and related DA (Heo et al., 2017; Miovic & Block, 2007; Nedelcovych et al., 2017; Niazi et al., 2020; Yssennagger et al., 2015). Third, measures specific to IA were not used in the included studies, which may further contribute to a lack of specificity of the results to IA and related DA. Fourth, it is unclear if there are differences in efficacy between different psychedelic agents. Although, most studies to date that have used PAT with different psychedelic agents (e.g., psilocybin, MDMA, and LSD) in the context of life-threatening illness have demonstrated benefit in treating existential distress (Schimmel et al., 2022). Fifth, this thesis would be strengthened if PAT's efficacy in treating IA and DA was investigated while controlling for changes in dispositional anxiety using a meta-regression approach. However, there were not enough studies available to perform a meta-regression. Last, there are significant limitations to consider with respect to the methodologies behind PAT. Generally, it is unclear if the independent psychedelic effect, the psychotherapy itself, or PAT as a whole, is responsible for eliciting therapeutic effects (van Elk & Fried, 2023). Further, in combination with large expectancy effects that have been reported in PAT literature, related concerns of unblinding due to the profound effects of high doses of psychedelics, and the increased states of suggestibility that are elicited by psychedelics, it is possible that the current literature of PAT as a whole may overestimate its therapeutic potential (Butler et al., 2022; R. L. Carhart-Harris et al., 2015). However, this should not negate the efficacy that PAT has demonstrated in treating mental illness, but rather, encourage optimization of study methodologies, such as including measures to control for expectancy bias and unblinding, and

even conducting naturalistic studies to support findings from randomized controlled trials (Butler et al., 2022).

4.3 Conclusions

Current treatments for IA and DA, related to and independent of life-threatening illness, are limited. PAT has shown to be effective in treating existential distress in individuals with a terminal illness, in addition to related symptoms of depression and anxiety. The results of this thesis demonstrate that PAT may provide sustained relief from IA and DA related to life-threatening illness. To the best of our knowledge, there are no studies that have investigated the effects of PAT for IA and/or DA independent of having a life-threatening illness. Overall, more studies are needed to better discern the immediate effects of PAT in patients with life-threatening illnesses with shorter prognoses.

4.4 Future Directions

4.4.1 Psychedelics for Illness Anxiety Disorder

Our literature search identified no publications which have examined the effects of PAT on IAD/hypochondriasis, and IA and/or DA independent of a life-threatening illness. We encourage continued investigations of psychedelics in these novel contexts, which is supported by the neurobiology of IAD and related symptoms

Aberrations in functional connectivity in individuals with IAD in comparison to healthy controls have been documented in various brain regions (Gehrt et al., 2023; Grossi et al., 2017), and notably in the default mode network (DMN) (Jin et al., 2021). Interestingly, preliminary evidence suggests a ‘reintegration’ and ‘resetting’ effect of psilocybin on the DMN (R. L. Carhart-Harris et al., 2017; R. L. Carhart-Harris & Friston, 2019). In line with the hypothesis proposed by Carhart-Harris and Friston (R. L. Carhart-Harris & Friston, 2019), such psychedelic induced DMN changes may allow for pathological biases and/or beliefs (i.e., as seen in IAD) to be altered. Thus, future studies should investigate the effects of psychedelics on pathological beliefs that are

implicated in IAD, and further investigate if these potential psychedelic induced changes are related to alterations in the DMN using brain imaging methodologies (i.e., fMRI).

Other works have demonstrated that the hypothalamic-pituitary-adrenal (HPA) axis may also be implicated in the neurobiology of IAD. The HPA axis regulates the stress response through modulation of neurohormones (e.g., corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol). Aberrations of the HPA axis that are related to mental illness are well documented (Lightman, 2008). Studies have demonstrated elevated HPA axis activity in participants with somatization syndrome and OCD, both which share similar symptomology to IAD, in comparison to controls (Atmaca et al., 2010; Rief et al., 1998; Sousa-Lima et al., 2019). Specific to IAD, steeper cortisol slopes (i.e., faster decline of cortisol after waking) are associated with health anxiety (Ferguson, 2008), and smaller pituitary volumes in individuals with IAD have been shown in comparison to healthy controls (Atmaca et al., 2010). Interestingly, serotonergic psychedelics have been demonstrated to modulate individuals' cortisol response, the main effector hormone of the HPA axis (Galvão et al., 2018; Mason et al., 2022). As such, future studies should also incorporate measures of HPA axis activity when investigating the use of psychedelics in treating IAD.

4.4.2 Does Psilocybin Increase Synaptogenesis?

My original thesis project was a proof-of-concept clinical trial investigating the effects of psilocybin on synaptic density and cognition in individuals with amnestic Mild Cognitive Impairment (aMCI) (NCT06041152). In addition to safety, feasibility, and tolerability, this trial aimed to investigate if psilocybin can increase synaptic density *in vivo* using positron emission tomography (PET) (Amaev et al., 2023; Song et al., 2023). Due to recruitment barriers, we regrettably were not able to finish our pilot sample target at the time of the completion of my graduate studies. However, given my contributions to this work, and its mechanistic relevance to the potential therapeutic effects of PAT, I will present the preliminary results of this trial below.

The therapeutic mechanisms of action of serotonergic psychedelics are widely unknown, however, it is viewed that 5-HT2A-R agonism may induce synaptogenesis in the brain (see section 1.3.4.1) (Raval et al., 2021). As a result, our research group has designed a randomized controlled

study to examine the effects of psilocybin on synaptic density in healthy participants and participants with aMCI using positron emission tomography (PET) (Amaev et al., 2023; Song et al., 2023).

4.4.2.1 Objectives and Hypotheses

The primary objective of this study is (i) to establish the feasibility, safety, and tolerability a double-blinded randomized controlled trial PET study in which two 25mg doses of psilocybin and two doses of placebo, separated by one week, will be administered to healthy participants (N = 2) and participants with aMCI (N = 4). As this is a proof-of-concept project, the exploratory objectives are to examine for changes in (ii) synaptic vesicular density (SVD), as measured by [^{18}F]SynVesT-1 radiotracer binding (i.e., non-displaceable binding potential (BP_{nd})), and (iii) cognition, and (iv) if increases in SVD are associated with improved cognition.

Our primary hypothesis is that (i) PET imaging, psilocybin, and placebo doses will be well tolerated with no serious adverse events related to psilocybin or study procedures, and that the study design will be feasible marked by completion of all study procedures by 5 of the 6 participants. Further, we hypothesize that (ii) SVD levels in the hippocampus, the parahippocampus, and the dorsolateral prefrontal cortex (i.e., superior and middle frontal gyri) will be higher following ingestion of psilocybin in comparison with placebo. Lastly, (iii) Psilocybin will be associated with cognitive improvement, and (iv) cognitive improvement will be associated with changes in SVD.

4.4.2.2 Methods

The proposed investigation will be a pilot placebo-controlled double-blind randomized study with age- and sex-matched healthy controls in which each participant is randomized to receive one out of two treatment conditions:

(1) Two 25 mg macrodoses of psilocybin separated by 1 week.
(2) Two placebo doses separated by 1 week

In both conditions, participants will take the dose with supervision from a study physician who will monitor participants during the psychedelic experience. Additionally, two trained and qualified therapists will be present at all times to provide psychological support and monitoring during the dosing session. Participants will have the contact information of research personnel to obtain assistance as required. Participants will not be told which condition they are randomly assigned to.

Participants will be scanned with the novel PET tracer [^{18}F]SynVesT-1 to characterize synaptic density levels. PET scans will be timed to coincide with two time-points, before the psilocybin treatment begins and 1 week after the last dose of treatment is taken by the participant. Participants will also be followed-up twice, specifically at 4 and 12 weeks after treatment. Clinical assessments and neuropsychological testing will be done at the same time as the PET scans and two follow-up visits.

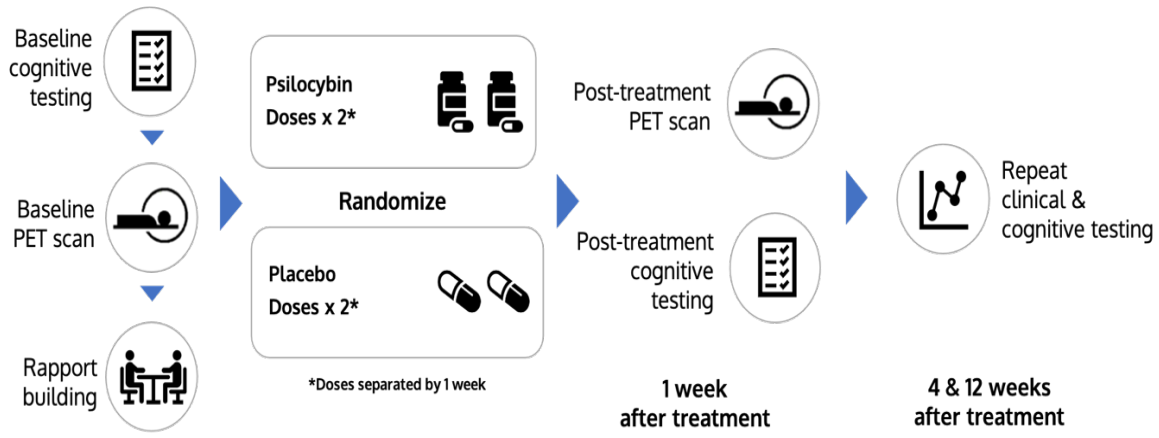


Figure 8: Study design of the psilocybin MCI trial

4.4.2.3 Preliminary Results

A total of 3 participants have completed the study to date (i.e., 2 healthy participants, and 1 participant with aMCI). However, given that the pilot study has not been completed yet, blinding is still in effect, and treatment conditions are unknown. As such, these preliminary results cannot yet be interpreted as it is unknown as to which experimental groups the participants belong to. Our preliminary findings from our three participants (i.e., 2 healthy participants, and 1 participant

with aMCI) does support the feasibility of this trial, as all 3 participants have completed their participation without issue.

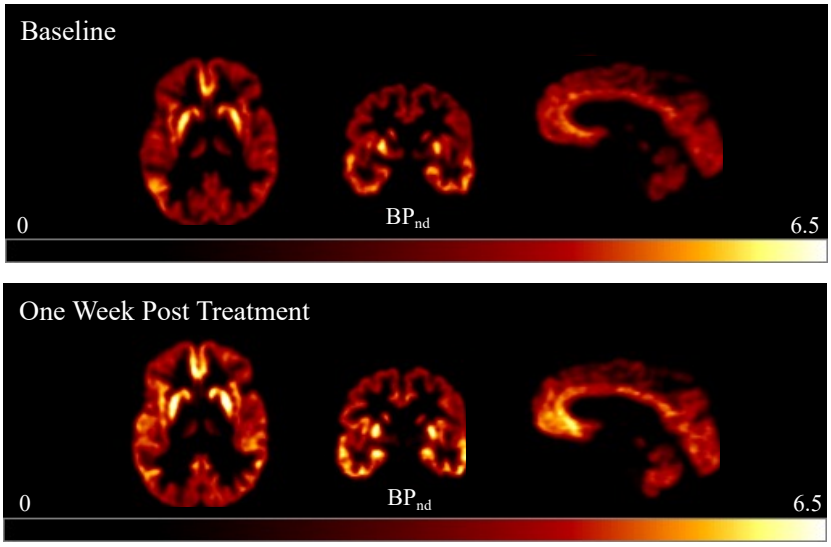


Figure 9: Parametric images at baseline and one week post-treatment of [^{18}F]SynVesT-1 in a healthy control participant. Voxel-level map of BP_{nd} (non-displaceable binding potential) generated using a simplified 2-tissue reference model (i.e., SRTM2)

Table 5: One week pre- and one week post-dose (i) [^{18}F]SynVesT-1 BP_{nd} in the hippocampus, parahippocampus, and dorsolateral prefrontal cortex (i.e., superior and middle frontal gyri) and (ii) cognitive data of two healthy participants and one aMCI participant

	PET Outcomes				Cognitive Outcomes					
Participant[1]	ROI	BP_{nd} (SE %)	BP_{nd} (SE %)	BP_{nd} % Change	LMT DR Total Score (SS)		CVLT LDFR Total Score (SS)		MoCA Total Score	
		Pre[2]	Post[3]		Pre[2]	Post[3]	Pre[2]	Post[3]	Pre[2]	Post[3]
HC	Hippo.	3.36 (1.2)	3.85 (1.5)	14.6%						
Age: 72	Parahippo.	3.35 (1.3)	3.75 (1.4)	11.9%	17/50 (-0.33)	19/50 (0.33)	6/16 (-0.5)	6/16 (-0.5)	28/30	30/30
Sex: Male	dlPFC	3.06 (1.8)	3.71 (1.2)	21.2%						
HC	Hippo.	3.28 (1.3)	4.0 (1.3)	21.6%						
Age: 65	Parahippo.	3.53 (1.4)	4.11 (1.4)	16.4%	25/50 (0.67)	35/50 (2.0)	16/16 (2.5)	16/16 (2.5)	22/30	28/30
Sex: Male	dlPFC	3.68 (1.3)	4.46 (1.3)	21.2%						
aMCI	Hippo.	3.35 (1.2)	2.93 (1.1)	1.4%						
Age: 74	Parahippo.	3.35 (1.3)	3.33 (1.2)	0.01%	1/50 (-2.67)	4/50 (-2.00)	0/16 (-2.5)	0/16 (-2.5)	20/30	21/30
Sex: Female	dlPFC	3.06 (1.1)	3.66 (1.1)	19.6%						

Abbreviations: aMCI = amnestic Mild Cognitive Impairment; BP_{nd} = non-displaceable binding potential; CVLT = California Verbal Learning Test; DR = Delayed Recall; dlPFC = dorso-lateral prefrontal cortex; HC = Healthy Control; Hippo. = hippocampus; LDFR = Long Delay Free Recall; LMT = Logical Memory Test; MoCA = Montreal Cognitive Assessment; Parahippo. = parahippocampal gyrus; PET = Positron Emission Tomography; PFC = Prefrontal cortex; ROI = Region of Interest; SE = Standard Error; % = percent; SS = Standardized score. [1] = Data is blinded to treatment condition; [2] = Baseline (i.e., one week before dosing); [3] = Post-treatment (i.e., one week after the second dose of 25mg of psilocybin or inert placebo)

4.4.2.4 Relevance and Future Directions

To the best of our knowledge, this will be the first study examining the effects of psilocybin on synaptic density in the brains of patients with aMCI. The pilot data acquired through this study will be used to apply for grants to support a large scale randomized controlled trial. This novel PET study of the effects of psilocybin on synaptic density may provide a better understanding of the mechanisms of PAT, with the ultimate aim of improving the health and well-being of individuals and families affected by neuropsychiatric diseases. If a signal of effect on SVD is detected, future studies in aMCI should consider additional PET scans (within the limits of safe radiation exposure to PET within one year) to investigate the enduring effects on SVD (e.g., follow-up scan at 12-weeks post dosing), the relationship between 5HT2A-R agonism by psilocybin and changes in SVD, and tauopathy to quantify disease burden. If efficacious to improve cognition in aMCI and healthy participants, future psilocybin studies may wish to investigate if the avoidance/blocking of the psychedelic experience (i.e., psilocybin microdosing or the use of 5-HT2A-R antagonists in conjunction with psilocybin) (Husain, et al., 2023; Vollenweider, et al., 1998), which would negate the need for PAT and promote the intervention's scalability.

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