*Psychiatria Danubina, 2024; Vol. 36, No. 2, pp 174-184 https://doi.org/10.24869/psyd.2024.174* *Review*


# CURRENT STATE OF PSILOCYBIN-ASSISTED THERAPY IN MOOD DISORDERS

**Astrid Kaiserman[1], Laetitia Vanderijst[2] & Charles Kornreich[3]**

*1 Erasme Hospital – Université Libre de Bruxelles (ULB), Faculty of Medicine, Department of Adult Psychiatry, Brussels, Belgium*
*2 Université Libre de Bruxelles (ULB), Faculty of Medicine, Laboratory of Medical Psychology and Addictology. Brussels, Belgium*
*3 Brugmann Hospital – Université Libre de Bruxelles (ULB), Faculty of Medicine, Department of Adult Psychiatry, Brussels, Belgium*

*received: 1. 6. 2023; revised: 23. 6. 2023; accepted: 16. 10. 2023*

***Summary***

***Background:*** *Psychedelics are currently undergoing a scientific renaissance, with modern studies investigating therapeutic efficacy of psychedelic-assisted therapy in a range of psychiatric conditions. In particular, psilocybin-assisted therapy (PAT) has been suggested to have positive effects on patients suffering from depression and psychiatric distress associated with life-threatening disease – contexts with growing needs for alternative treatments – in a therapeutic setting involving fewer doses and less important adverse effect compared to that of classic psychotrope administration. Psychedelics are partial agonists of the serotonin 2A (5-HT2A) G protein-coupled receptors, whose activation likely mediates the acute psychoactive effects. Furthermore, psychedelics seem to induce a hyper-plastic state which allows for adaptation of inflexible pathological thinking patterns. Post-acutely, they are suggested to induce rapid, robust and sustained neuroplasticity.*

***Sources of data:*** *Eight clinical PAT trials have been conducted between January 1st 2001 and March 31st 2023 and are reviewed here. Five of them evaluate the effect on depressive symptomatology in an otherwise general population. The other three evaluate effect on depression and anxiety in patients suffering from somatic life-threatening disease.*

***Results:*** *The studies reviewed here show that PAT is safe and feasible to administer in current clinical models. Preliminary efficacy shows significant improvements in depressive and anxious symptomatology which are immediate and partially sustained. One study comparing PAT to selective serotonergic reuptake inhibitors showed no significant difference of efficacy between the two treatments.*

***Conclusions:*** *Preliminary results regarding efficacy of PAT on mood disorders are promising, but further research is warranted for stronger inferences, with a particular focus on larger, multicentric studies, more diverse populations and a stronger control for expectancy and unblinding.*

***Keywords:*** *psychedelics, psilocybin, psilocybin-assisted therapy, mood disorders*

* * * * *

## INTRODUCTION

Indigenous societies in Asia and the Americas have been using psychedelic substances for centuries, often in ritual contexts. In the Western world, the use of psychedelics and psychedelic-assisted therapy has been revived since the beginning of the 21st century. The synthesis of lysergic acid diethylamide (LSD) by Albert Hofmann in 1938 triggered an initial spike of use amongst researchers, psychiatrists and therapists in the 1950s and 1960s, which resulted in more than 1000 clinical papers on approximately 40,000 patients (Grinspoon, 1981). However, the prohibition on psychedelic substances aimed at stopping recreational use in the 1960s effectively stopped all research. In what is now labeled the "psychedelic renaissance", research on the effects of psychedelics and psychedelic-assisted therapy on various psychiatric conditions such as mood disorders, obsessive-compulsive disorder and substance use disorder have re-emerged. This narrative review will examine and discuss the current state of clinical research involving psilocybin in patients suffering from mood disorders and psychiatric distress associated with life-threatening diseases from the beginning of the 21st century until the end of March 2023.

## PSYCHEDELIC SUBSTANCES

The term "psychedelics" stems from the Greek words ψυχή (psycho) and δηλόω (deloo) meaning "mind-manifesting." A psychedelic substance is one that induces an altered state of consciousness, characterized by profound modifications in perception, mood and cognitive processes (Nichols 2017). This temporary state, or "trip", which lasts between a few minutes and hours depending on the substance, dose and context, is often associated with spiritual and mystical experiences. Psychedelic users generally describe these experiences as highly significant moments, contributing to their understanding of themselves and providing them with existential insights into their lives (Peill et al. 2022). Classic psychedelics include psilocybin, found in hallucinogenic mushrooms, LSD, mescaline, typically found in the San Pedro cactus, and N-dimethyltryptamine (DMT) contained in the ayahuasca brew.

**Psilocybin**

Psilocybin is a naturally occurring psychedelic that has been found in hundreds of species of mushrooms, many falling within the genus *Psilocybe* (Stamets, 1996). Psilocybin is a relatively small compound based on the structure of tryptamine, metabolized through in vivo dephosphorylation to psilocin, the active compound (Johnson et a. 2017). It produces an altered state of consciousness lasting from three to six hours, with a peak activity at around 45 minutes post-ingestion. This relatively short time makes it an apt candidate, and the most widely used classic psychedelic in recent clinical trials, as patients can reasonably be assessed and monitored during the entirety of their session in one day.

## Safety Profile

Unlike reputation suggests, psychedelics generate little harm. In 2010, the United Kingdom's Independent Scientific Committee on Drugs (now DrugScience) compared the severity of harm caused by the abuse of various drugs (Nutt et al. 2010). Twenty recreational drugs were scored according to 16 criteria, nine of which assessed the harm inflicted on the user (for example mortality, dependence, loss of tangibles and of relationships), and nine of which assessed the harm inflicted on others (for example injury, crime, environmental damage or economic cost). Overall, alcohol was the most harmful drug, with heroin and crack cocaine in second and third places. Psychedelic drugs occupied the other side of the spectrum with LSD and psilocybin on respectively the 18th and last positions. Additionally, results have repeatedly shown that careful preparation and a clinically supervised setting further limit the prevalence of adverse effects (Schlag et al. 2022, Roscoe & Lozy 2022).

Somatic side effects are usually minimal, consisting of transient increases in heart rate and blood pressure, nausea, headaches, mydriasis and occasional hyperreflexia (Schlag et al. 2022). Psychedelics cause very limited physical toxicity (Halpern & Pope 1999, Studerus et al. 2012).

The main psychological and psychiatric risks traditionally thought of as associated with psychedelic intake are anxiety, hallucinogen persisting perception disorder (HPPD), psychotic symptoms and dependency. However, recent epidemiological and scientific data question these associations.

Anxiety occurring during the acute experience, which has been commonly associated with the feared notion of "bad trip" in recreational settings, is rather seen as a gateway to emotional breakthroughs in the supportive clinical context, potentially yielding therapeutic benefits (Roseman et al. 2019). Additionally, transient anxiety is generally contained with psychological support only and rescue medications – benzodiazepines, which help alleviate anxiety, or anxtipsychotics such as olanzapine or risperidone, which shorten the trip – to prevent escalation have rarely been necessary in clinical studies (Roscoe & Lozy 2022).

HPPD is a state characterized by visual experiences persisting after psychedelic use and causing significant clinical suffering, and does not seem to be correlated with dosage or number of drug exposures (Halpern et al. 2003). No case of HPPD has been reported in any clinical study since 2000. This absence is likely attributable to effective screening and preparation, as well as therapeutic support during the trip. Indeed, HPPD can potentially be seen as a trauma response caused by lingering effects of the original experience: in a study of 19 subjects with HPPD, all remembered feeling anxious during the event that triggered the symptoms (Halpern et al. 2018). The effective management of anxiety during therapeutically supervised trips could thus explain the absence of HPPD.

Addressing the issue of whether psychedelic use increases the risk of mental health problems, a population study on 130 000 adults, among which 29 000 have used psychedelics at least once, showed no positive correlation between mental health problems and psychedelic use, including psychotic symptoms (Krebs & Johansen 2013).

Research has repeatedly shown that psychedelics do not cause dependence or compulsive use (Halberstadt 2015, Johnson et al. 2018, Nichols 2017); no withdrawal symptoms have been described (Rucker et al. 2018). Tolerance develops quickly and is not overcome with dose escalation, indicating that patients do not feel the need to increase doses or frequency of usage.

Given these indications and the precaution imposed by the limited data, current studies exclude patients who are medically unstable, particularly in terms of cardiovascular health; those with immediate personal or family history of psychotic or bipolar disorder or with moderate to severe substance use disorders; patients exhibiting active suicidality; as well as pregnant or breastfeeding patients or those refusing contraception.

## Therapeutic Context

Psychedelic substances have been widely shown to induce antidepressant and anxiolytic effects in humans, in a context of administration that stands in stark contrast to that of classic psychotropes (such as selective serotonergic reuptake inhibitors [SSRIs] or benzodiazepines). Acute (three hours to one day after treatment) improvements in anxiety and depressive symptomatology are observed following one or two administrations, unlike

classic psychotropes which require daily oral administration. These improvements may persist on longer term without additional dosage, with several studies finding sustained improvements in depressive and anxiety symptoms several months or – in one case – years post-administration (Carhart-Harris et al. 2018b, Griffiths et al. 2016, Ross et al. 2016, Agin-Liebes et al. 2020).

The quality and intensity of the psychedelic experience is known to be highly dependent on psychological, environmental and social factors coined *Set* and *Setting* (Carhart-Harris et al. 2018). *Set* refers to the inner state of the patient during the psychedelic experience: their emotional state, mood, thoughts, hopes. *Setting* refers to the physical and social environment surrounding the patient during the psychedelic experience. In current studies, patients lie on a bed and are equipped with fully blinding eye shades and headphones playing emotion-accompanying systematized music playlists.

Current clinical models administer the psychedelic substance in a clinical setting along with psychological support. Two – or, in one instance, one (von Rotz et al. 2023) – therapists accompany the patient during the psychedelic experience and are also responsible for the support preceding the trip (called preparation) and following the trip (called integration). Preparation involves psychoeducation about the upcoming trip and the establishment of an intention, which refers to a desired and psychological goal or quest established by the patient. Support during the tri p is based on the concept of non-interference: patients are encouraged to experience the trip wholly and to minimize resistance; therapists aim to minimize their interference with the process, supporting the patient through difficult phases of their trip with reassurance and, at most, by holding their hand upon request. Integration focuses on debriefing, making sense of the experience by constructing a meaningful narrative, and matching it to the intention and pre-trip struggles.

## Mechanisms of Action

Serotonergic psychedelics act as partial agonists of the serotonin 2A (5-HT2A) G protein-coupled receptors, which are mainly located in the pyramidal neurons in layer 5 of the neo-cortex. 5-HT2A activation likely mediates the acute psychoactive effects of psychedelic: 5-HT2A receptors affinity has been correlated with psychoactive potency in humans (Liechti 2017) and pre-treatment with the 5-HT2A receptor antagonist ketanserin blocks the acute subjective effects of LSD (Preller et al. 2017, Kraehenmann et al. 2017).

Of the several models seeking to explain the mechanisms of action of classic psychedelics (see van Elk & Yaden 2022 for a review), the REBUS model (RElaxed Beliefs Under Psychedelics; Carhart-Harris & Friston 2019) bridges several levels of understanding. It starts from the premise that our brain constantly generates internal models to predict incoming external and internal (thoughts, feelings, sensations) stimuli. Only prediction errors are fed upward the processing hierarchy to be consciously treated and update our world models. However, prediction-error signaling is modulated by two factors: the level of precision of incoming stimuli, and the degree of confidence in one's priors, such that rigid priors may limit predictive errors processing and subsequent model updating.

The molecular cascade induced by psilocybin upon binding onto 5HT2A receptors leads to a cortical desynchronization in neuronal activity (Celada et al. 2008). These alterations induce a dramatic decrease in the low-frequency alpha rhythm (Lebedev et al. 2015), which has been associated with top-down prediction and inhibition (Carhart-Harris & Friston 2019). This decrease in alpha oscillations is linked with functional disintegration of the default-mode network (DMN) and alterations in other higher-order cognitive networks (Lebedev et al. 2015, Tagliazucchi et al. 2016). This dysregulation in high-level networks reduces the precision-weighting of predictive priors, resulting in increased bottom-up signaling (prediction-error signaling), a phenomenon coined the "anarchic brain" (Carhart-Harris & Friston 2019) and associated with a greater repertoire of brain connectivity motifs (Schartner et al. 2017, Varley et al. 2020). This 'hyper-plastic' state is postulated to allow the revision of rigid, maladaptive priors and associated inflexible pathological thinking patterns characteristic of a range of psychiatric disorders.

Regarding post-acute changes, decreased brain network modularity was observed one day and three weeks after psilocybin administration in two trials of PAT for treatment-resistant depression (Daws et al. 2022). This modular network 'disintegration' correlated with improvements in depressive symptomatology, implying that psilocybin's therapeutic action may depend on a global increase in brain network integration, whereby the brain's functional repertoire of states is broadened, as opposed to remaining stuck in specific patterns of networks connectivity (Daws et al. 2022). These findings point towards potential long-lasting functional reorganization effects that may help to restore normal connectivity patterns in the brain (Rieser et al. 2022).

Additionally, psychedelics have been shown to induce rapid, robust and sustained neuroplasticity (see Calder & Hasler 2022 for a review), which might further support the process of meaningful therapeutic change by fostering learning in the days following psychedelic intake.

### Current State of Clinical Research

Psilocybin-assisted therapy (PAT) has been designated by the Food and Drug Administration (FDA) as "breakthrough therapy" for treatment-resistant depression (Reiff et al. 2022). This name is given to a process designed to accelerate the development and review of drugs whose preliminary clinical evidence is promising and indicative of a substantial improvement over available therapy on clinically significant endpoints for treating a serious condition.

Depression is one of the world's leading causes of morbidity and mortality and an important economic burden on society (Greenberg et al. 2015). It is widely accepted that current pharmacological treatments have limited effects and success (Thase et al. 2001). Indeed, a large fraction of patients suffering from depression do not respond adequately to antidepressant treatment (Cipriani et al. 2018, Hengartner & Plöderl 2018, Kirsch 2014, Munkholm et al. 2019). Furthermore, if and when they do, the latency of effect associated with these treatments often requires a window of two to six weeks and/or induces undesirable effects, resulting in discontinuation of treatment (Carvalho et al. 2016, Posternak & Zimmerman 2005). Overall, up to half of all patients suffering from depression fail to achieve remission despite two or more adequate antidepressant trials (Conway et al. 2017, Akil et al. 2018). The discrepancy between the important clinical, societal and economic impact of depression and the limited success of current approaches has led to the renewed and rapid investigation into psychedelic drugs as treatment for depression.

## SOURCES OF DATA

So far, eight clinical trials involving PAT have been conducted (Table 1). Five of them evaluated effect on depressive symptomatology in an otherwise general population; of those, one compared it to SSRI treatment. The other three evaluated effect on depression and anxiety in patients suffering from somatic life-threatening disease.

## RESULTS

### PAT in Depression

In the first clinical trial, Carhart-Harris and his team used psilocybin in an open-label, single-arm feasibility trial on 12 patients with moderate-to-severe, unipolar, treatment-resistant major depression (Carhart-Harris et al. 2016). A longer follow-up (six months) was published two years later (Carhart-Harris et al. 2018b). Two oral doses of psilocybin (a safety dose of 10mg and a treatment dose of 25mg) were administered seven days apart in a psychologically supportive setting. The drug was well tolerated by all patients and was not correlated to any serious or unexpected side effects. Evaluation of efficacy was only preliminary due to the pilot set-up, and showed marked reduction of symptoms one week after the second dose, maximal at five weeks, and sustained at three and six months. Improvements in anxiety and anhedonia were also observed.

In 2021, the first randomized clinical trial (RCT) evaluating the effects of PAT on major depressive disorder (MDD) was published (Davis et al. 2021). In this trial, 24 adults with moderate-to-severe MDD were randomized to either an immediate treatment condition group or a delayed (eight weeks) treatment condition group. Each group was administered a first, moderately high dose of psilocybin (20mg/70kg) followed by a high dose (30mg/70kg) on average 1.6 weeks later, alongside psychological support. The delayed treatment control was chosen to differentiate the psilocybin intervention from spontaneous symptom improvement. GRID-Hamilton Depression Rating Scale (GRID-HAM-D) scores were significantly lower for the treatment group both one and four weeks post-psilocybin than for the control group at the same time points, suggesting efficacy of the treatment. Seventy-one percent of patients showed a clinically significant response, with over 50% in remission. A longer follow-up study showed sustained improvement at 12 months, with 75% response and 58% remission (Gukasyan et al. 2022).

COMPASS Pathways, a United Kingdom-based mental healthcare pharmaceutical company, has recently published the largest randomized controlled trial for PAT so far (Goodwin et al. 2022). This phase IIb trial, multicentered around 22 sites in Europe and the United States of America (USA), compared the efficacy of PAT with a single dose of 25mg (high dose), 10mg (low dose) or 1mg (placebo) of psilocybin on 223 patients suffering from treatment-resistant depression. Results, as measured on the Montgomery-Åsberg Depression Rating Scale (MADRS), showed a significant therapeutic effect in terms of score reduction for the 25mg dose group compared to the placebo group at three weeks, but not for the 10mg group. This effect was not sustained at 12 weeks.

Another RCT compared the therapeutic effect of PAT with a moderate dose of psilocybin (0.215mg/kg) to that of a placebo on 52 patients with MDD (von Rotz et al. 2023). This study was the first in which only one therapist administered psychological support. Results supported those of previous trials involving repeated higher doses and two

**Table 1:** Psilocybin-assisted therapy clinical studies in patients with depression and with psychiatric distress associated with life-threatening disease between January 1st 2001 and March 31st 2023

| Study | N | Patients | Psilocybin dose | Control | Design | Primary outcomes | Results | Follow-up |
|---|---|---|---|---|---|---|---|---|
| *Grob et al. 2011* | 12 | Patients with advanced-stage cancer and anxiety | 0.2mg/kg | Active placebo (niacin 250mg) | Pilot study Within-subject | Feasibility & safety (BP, HR, t°; subjective experience intensity score)<br>Preliminary efficacy: BDI, POMS, STAI-S, STAI-T | Feasibility & safety: well tolerated, no important or unexpected adverse effects, limited intensity of subjective experience<br>Preliminary efficacy:<br>• Trend towards mood improvement (↓BDI sustained, and significant at 6 mo)<br>• Trend towards anxiety improvement (↓STAI-S sustained, and significant at 1 and 3 mo) | 6 mo |
| *Carthart-Harris et al. 2016 + Follow-up (Carhart-Harris et al. 2018)* | 12 - *20* | Patients with MDD (treatment resistant, moderate to severe) | 10mg (safety dose) followed by 25mg (therapeutic dose) | None | Pilot study Open-label | Feasibility and safety (BP, HR, acute effects; subjective experience intensity score)<br>Preliminary efficacy: QIDS 1 week (until 6 months) post-2nd dose | Feasibility and safety: well tolerated, no important or unexpected adverse effects, limited intensity of subjective experience<br>Preliminary efficacy: significant ↓ in score at 1-5 weeks, maximal at 5 weeks, sustained at 3 and 6 mo | 3 mo – 6 mo |
| *Ross et al. 2016* | 29 | Patients with LT-cancer and anxiety | 0.3mg/kg | Active placebo (niacin 250mg) | Cross-over | Anxiety & depression: BDI, HADS-A, HADS-D, HADS-T, STAI-S, STAI-T | • Significant, immediate and sustained (up to 8 mo) ↓ in anxiety and depression scores after psilocybin, not observed after niacin-only<br>• Significant antidepressant and anxiolytic response rates (60-80% at 8 mo) in both groups, significantly superior to those after niacin only<br>• 4.5-year follow-up: 60-80% antidepressant and anxiolytic response (surviving patients) | 8 mo |
| *Griffiths et al. 2016* | 51 | Patients with LT-cancer and anxiety/ depression | 22 or 30mg/70kg | Psilocybin 1 or 3mg/70kg | Cross-over | Depression: GRID-HAM-D<br>Anxiety: HAM-A | Significant, immediate and sustained (up to 6 mo) ↓ in both scores after high dose, significantly more so than after low dose<br>Significant and sustained (up to 6 mo) antidepressant and anxiolytic response rates after high dose, significantly superior to those after pre-cross-over low dose | 6 mo |
| *Davis et al. 2021* | 24 | Patients with MDD (moderate to severe) | 20mg/70kg followed by 30mg/70kg | Delayed treatment | RCT | GRID-HAM-D<br>• within-group: weeks 1&4 post-dosage<br>• between-group: weeks 5&8 post-recruitment | Within-group:<br>• significant ↓ (at weeks 1&4)<br>• response: 71% at week 1, 71% at week 4<br>• remission: 58% at week 1, 54% at week 4<br>Between-group:<br>significant difference in score at weeks 5&8 in favor of immediate-treatment group | 4 weeks |

**Table 1:** Psilocybin-assisted therapy clinical studies in patients with depression and with psychiatric distress associated with life-threatening disease between January 1st 2001 and March 31st 2023 (continuation)

| Study | N | Patients | Psilocybin dose | Control | Design | Primary outcomes | Results | Follow-up |
|---|---|---|---|---|---|---|---|---|
| *Carhart-Harris et al. 2021* | 59 | Patients with MDD (moderate to severe) | 25mg followed by 25mg | Escitalopram | RCT | QIDS at week 6 | No significant difference between groups<br>Secondary outcomes (including response & remission rates at 6 weeks, BDI, MADRS) trend in favor of psilocybin group but no adjustment for multiple comparisons | 6 weeks |
| *Goodwin et al. 2022* | 233 | Patients with treatment-resistant MDD | 25mg or 10mg | Psilocybin 1mg | Phase IIb RCT Multicentric | MADRS at week 3 | 25mg vs. 1mg: significant ↓ (-6.6)<br>10mg vs. 1mg: no significant ↓ (-2.5)<br>Secondary outcomes<br>• 25mg group remission & response rates at week 3: seem to follow primary outcome trend but not considered significant<br>• 25mg group response rate sustained at 12 weeks: not significant | 12 weeks |
| *Von Rotz et al. 2023* | 52 | Patients with MDD | 0.215mg/kg | Mannitol | RCT | MADRS & BDI at week 2 | Within-group:<br>• significant ↓ in both scores (MADRS -13.0; BDI -13.2)<br>• response:<br>- psilocybin: 58% MADRS, 54% BDI<br>- placebo: 15% MADRS, 12% BDI<br>• remission:<br>- psilocybin: 54% MADRS, 46% BDI<br>- placebo: 12% MADRS, 12% BDI<br>Between-group: significant difference (score) in favor of psilocybin group (-13.0 MADRS; -10.5 BDI) | 2 weeks |

MDD = major depressive disorder; LT = life-threatening; BP = blood pressure; HR = heart rate; t° = temperature; RCT = randomized controlled trial;
BDI = Beck Depression Inventory; POMS = Profile of Mood States; STAI-S = State-Trait Anxiety Inventory-State; STAI-T = State-Trait Anxiety Inventory-Trait;
QIDS = Quick Inventory of Depressive Symptomatology; HADS-A = Hospital Anxiety and Depression Scale-Anxiety;
HADS-D = Hospital Anxiety and Depression Scale-Depression; HADS-T = Hospital Anxiety and Depression Scale-Total;
GRID-HAM-D = GRID-Hamilton Depression Scale; MADRS = Montgomery-Åsberg Depression Rating Scale

therapists. Indeed, significant decreases in symptom severity on the MADRS and BDI scales at two weeks were observed (-13.0 MADRS, -10.5 BDI). In the psilocybin group, response rates at two weeks were 58% (MADRS) and 54% (BDI), compared to 15% (MADRS) and 12% (BDI) in the placebo group. Remission rates were 54% (MADRS) and 46% (BDI) in the psilocybin group compared to 12% on both scores in the placebo group.

Carhart-Harris and his team compared the effects of PAT to that of an SSRI (escitalopram) on 59 patients with moderate-to-severe MDD (Carhart-Harris et al. 2021). In an RCT, they administered, along with psychological support, either two doses of psilocybin (25mg) three weeks apart combined with a daily placebo for six weeks, or two doses of placebo (psilocybin 1mg) combined with daily escitalopram for six weeks. Both groups showed a significant decrease in depressive symptoms on the QIDS-SR scale after six weeks; no significant difference was observed between them. While secondary outcomes, including response and remission, MADRS and State-Trait Anxiety Inventory (STAI) scores, were in favor of psilocybin, no conclusions could be drawn due to the absence of adjustment for multiple comparisons.

## PAT in Depression and Anxiety Associated with Life-Threatening Disease

Patients suffering from psychiatric disorders associated with life-threatening disease, in particular patients with cancer and depression and/or anxiety, have been suggested to benefit from PAT. Indeed, patients with cancer often develop a clinically significant syndrome of psychosocial distress in which the core is made up of depression and anxiety symptoms, as well as reduced quality of life; up to 40% of cancer patients meet criteria for a mood disorder (Holland 2013, Mitchell et al. 2011). These symptoms interact dynamically to negatively affect each other as well as treatment adherence (Arrieta et al. 2013, Colleoni et al. 2000), length of hospitalization (Prieto et al. 2002) and suicidality (Shim & Park 2012). Furthermore, depression has been shown to be an independent risk factor of early death in patients suffering from cancer (Arrieta et al. 2013, Pinquart & Duberstein 2010).

After several unblinded studies during the first wave of psychedelic research (Grof et al. 1973, Kast 1967, Richards et al. 1977), more scientifically solid studies have attempted to assess the effect of PAT on psychiatric distress associated with life-threatening disease. In the first pilot study, 12 patients with advanced-stage cancer and a DSM-IV anxiety-related diagnosis received a modest (0.2mg/kg) dose of psilocybin on one occasion and an active placebo (niacin 250mg) on another (Grob et al. 2011) several weeks later in randomized order. The main aim was to establish feasibility and safety: the treatment was well tolerated, no cardiovascular sequelae, adverse psychological effects or severe anxiety episodes were observed. Statistically significant efficacy conclusions could not be drawn due to the modest dose and pilot set-up; however, it allowed for some indication as to therapeutic potential, in particular regarding reduction in anxiety which was sustained and significant at one and three months, and an improvement in mood which was sustained and became significant at six months.

In 2016, Griffiths and his team evaluated the efficacy of PAT on depression and anxiety symptoms in patients suffering from cancer in a randomized cross-over trial (Griffiths et al. 2016). Fifty-one patients with life-threatening cancer diagnoses and symptoms of depression and/or anxiety were administered a placebo dose (3 or 1 mg/70kg) of psilocybin followed or preceded by a moderate dose (30 or 22 mg/70kg) five weeks apart. Primary outcomes GRID-Hamilton Depression Rating Scale (GRID-HAMD 17) and Hamilton Anxiety Rating Scale (HAM-A) showed immediate significant improvements on both scores with high-dose psilocybin that were sustained at six months. Response rates were significant and sustained after high-dose psilocybin: at six months, 78% showed antidepressant and 83% anxiolytic response. These rates were significantly higher than those after low-dose pre-crossover administration. At six months follow-up, 65% fulfilled remission criteria for depression and 57% for anxiety.

Another randomized controlled crossover trial administered psilocybin (0.3mg/kg) vs. an active control (niacin 250mg), in conjunction with psychotherapy, to 29 patients with a life-threatening cancer diagnosis and anxiety and/or depression (Ross et al. 2016). Improvements in anxiety and depression following psilocybin administration were immediate, clinically significant, and persisted at eight months, as measured by the Hospital Anxiety and Depression Scale (HADS), self-rated scales of anxiety and depression, BDI and STAI. In 2020, a longer follow-up study found antidepressant and anxiolytic effects lasting up to 4.5 years after the dosing sessions, with 60-80% of surviving patients (n=15) responding to anxiolytic and antidepressant remission criteria (Agin-Liebes et al. 2020). This constitutes the longest follow-up study on PAT to this day.

## DISCUSSION

While these modern clinical trials provide hopeful insights into the effects of psilocybin on mood disorders, further research is indubitably warranted.

Indeed, the discussed trials show many characteristics of research that is still in its early stages. With the exception of the COMPASS study, all studies sample sizes were small (less than 60 patients) and two had open-label designs, making strong inferences about efficacy unrealistic. Set-ups varied between studies, administering between one and two doses of psilocybin of various dosages, and the type of psychological support was not homogenized across studies, making it difficult to extrapolate results.

All trials have so far been conducted in North America and/or Europe, which should encourage us to conduct similar trials on more diverse populations, and hold important discussions including but limited to biological and cultural variations, to determine how to best extrapolate the contexts and effects to a more general population. In particular, authors have suggested a lack of diversity with regards to people with sensory and physical disabilities (Mintz et al. 2022) and people of color (Michaels et al. 2018).

For safety reasons, only unipolar depression has so far been evaluated among mood disorders. A currently ongoing open-label pilot study by COMPASS is investigating the safety and preliminary efficacy of a single 25mg dose of psilocybin in patients with type II disorder, and shows no increase in suicidality score, manic symptoms, or other adverse effects so far (NCT04433845). This could encourage further investigation into patients suffering from this group of mood disorders.

Expectancy is a known and anticipated problem in psychedelic research.

Psychedelic trips are phenomenologically powerful experiences, and it seems close to impossible to maintain the double blind (Muthukumaraswamy et al. 2021), which has become a prerequisite for rigorous clinical research. Attempts at controlling the blind have been made, for example by refraining from disclosing psilocybin doses to therapists and patients (Griffiths et al. 2016). Studies should systematically assess and report unblinding and expectancy. Additionally, dose-comparison studies should be prioritized, as they seem the most straightforward way to investigate potential dissociations between acute phenomenological effects and clinical efficacy. For instance, the COMPASS study found the 25mg dose to be clinically significantly more effective than the 1mg dose, whereas the 10mg was not. However, it could be hypothesized that both 25mg and 10mg doses were associated with marked acute subjective effects (Griffihs et al. 2011) reducing unblinding and expectancy bias, although this was unfortunately not assessed.

Finally, it is important to emphasize that the discussed results come from studies with a maximum follow-up period of only fifteen years, and that the longest follow-up to date is 4.5 years. The studies conducted in the 1950s and 1960s, although relatively numerous, were mostly open-label and did not adhere to the rigorous scientific criteria – such as screening and inclusion criteria, control arms, clinical follow-up, evaluation of side-effects – that we currently rely on to draw conclusions about long-term safety and efficacy. In current PAT studies, these criteria – while taken into consideration – are not yet standardized, as has been discussed above. Therefore, it is important to nuance the current encouraging results with not only the need for more extensive and diverse studies, but also the long-term follow-up of patients.

## CONCLUSIONS

Recent research on PAT has shown promising results for improving depression and psychiatric distress associated with life-threatening diseases, in a therapeutic context that requires fewer doses and suggests limited adverse effects compared to classic psychotropes. Further research is warranted for stronger inferences, focusing among others on larger, multicentric studies, more diverse populations and a stronger control for expectancy and unblinding.

***Acknowledgements:*** None

***Ethical Considerations:*** Does this study include human subjects? NO

***Conflict of interest:*** No conflict of interest.

***Funding sources:*** The authors received no funding from an external source.

***Authors contribution:*** dr. Astrid Kaiserman – Data collection, first draft of all sections except “Mechanisms of Action”, correction of all subsections, approval of final version, submission. Ms. Laetita Vanderijst – Thorough proofreading of full paper, additional comments to full paper, first draft of “Mechanism of Action” section. Dr. Charles Kornreich – General guidance and additional comment to full paper.

## References


*Aaronson ST. The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression. [Internet]. clinicaltrials.gov 2022; NCT04433845.*

*Agin-Liebes GI, Malone T, Yalch MM, Mennenga SE, Ponté KL, Guss J et al.: Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. J Psychopharmacol 2020; 34:155–66.*

*Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B et al.: Treatment resistant depression: A multi-scale, systems biology approach. Neurosci Biobehav Rev 2018; 84:272–88.*

*Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D et al.: Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol 2013; 20:1941–8.*

*Calder AE & Hasler G: Towards an understanding of psychedelic-induced neuroplasticity. Neuropsychopharmacology 2023; 48:104–12.*

*Carhart-Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe D, Kaelen M et al.: Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016; 3:619–27.*

*Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE et al.: Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl) 2018; 235:399–408.*

*Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I et al.: Psychedelics and the essential importance of context. J Psychopharmacol 2018; 32:725–31.*

*Carhart-Harris RL & Friston KJ: REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. Pharmacol Rev 2019; 71:316–44.*

*Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R et al.: Trial of Psilocybin versus Escitalopram for Depression. N Engl J Med 2021; 384:1402–11.*

*Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychother Psychosom 2016; 85:270–88.*

*Celada P, Puig MV, Díaz-Mataix L, Artigas F. The hallucinogen DOI reduces low-frequency oscillations in rat prefrontal cortex: reversal by antipsychotic drugs. Biol Psychiatry 2008; 64:392–400.*

*Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y et al.: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357–66.*

*Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. Lancet 2000; 356:1326–7.*

*Conway CR, George MS, Sackeim HA. Toward an Evidence-Based, Operational Definition of Treatment-Resistant Depression: When Enough Is Enough. JAMA Psychiatry 2017; 74:9–10.*

*Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW et al.: Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry 2021; 78:481–9.*

*Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D et al.: Increased global integration in the brain after psilocybin therapy for depression. Nat Med 2022; 28:844–51.*

*Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metab Rev 2017; 49:84–91.*

*Dunlap LE, Andrews AM, Olson DE. Dark Classics in Chemical Neuroscience: 3,4-Methylenedioxymethamphetamine. ACS Chem Neurosci 2018; 9:2408–27.*

*Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC et al.: Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. N Engl J Med 2022; 387:1637–48.*

*Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 2015; 76:155–62.*

*Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl) 2011; 218:649–65.*

*Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD et al.: Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol 2016; 30:1181–97.*

*Grinspoon L & Bakalar JB. The psychedelic drug therapies. Curr Psychiatr Ther 1981; 20:275–83.*

*Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL et al.: Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011; 68:71–8.*

*Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. Int Pharmacopsychiatry 1973; 8:129–44.*

*Gukasyan N, Davis AK, Barrett FS, Cosimano MP, Sepeda ND, Johnson MW et al.: Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. J Psychopharmacol 2022; 36:151–8.*

*Halberstadt AL. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. Behav Brain Res 2015; 277:99–120.*

*Halpern JH & Pope HG. Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend 1999; 53:247–56.*

*Halpern JH, Lerner AG, Passie T. A Review of Hallucinogen Persisting Perception Disorder (HPPD) and an Exploratory Study of Subjects Claiming Symptoms of HPPD. Curr Top Behav Neurosci 2018; 36:333–60.*

*Halpern JH, Pope HG Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend 2003;69(2):109-119.*

*Hengartner MP & Plöderl M. Statistically Significant Antidepressant-Placebo Differences on Subjective Symptom-Rating Scales Do Not Prove That the Drugs Work: Effect Size and Method Bias Matter! Front Psychiatry 2018; 9:517.*

*Holland JC. Distress screening and the integration of psychosocial care into routine oncologic care. J Natl Compr Canc Netw 2013; 11:687–9.*

*Johnson MW & Griffiths RR. Potential Therapeutic Effects of Psilocybin. Neurotherapeutics 2017; 14:734–40.*

*Johnson MW. Psychiatry might need some psychedelic therapy. Int Rev Psychiatry 2018; 30:285–90.*

*Kast E. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. Psychiatr Q 1967; 41:646–57.*

*Kirsch I. Antidepressants and the Placebo Effect. Psychol 2014; 222:128–34.*

*Kraehenmann R, Pokorny D, Aicher H, Preller KH, Pokorny T, Bosch OG et al.: LSD Increases Primary Process Thinking via Serotonin 2A Receptor Activation. Front Pharmacol 2017; 8:814. doi 10.3389/fphar.2017.00814.*

*Krebs TS & Johansen PØ. Psychedelics and mental health: a population study. PLoS One 2013; 8:e63972. doi 10.1371/journal.pone.0063972. doi 10.1186/s12888-018-1824-6.*

*Lebedev AV, Lövdén M, Rosenthal G, Feilding A, Nutt DJ, Carhart-Harris RL. Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. Hum Brain Mapp 2015; 36:3137–53.*

*Liechti ME. Modern Clinical Research on LSD. Neuropsychopharmacology 2017; 42:2114–27.*

*Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. BMC Psychiatry 2018; 18:245.*

*Mintz KT, Gammer B, Khan AJ, Shaub G, Levine S, Sisti D. Physical Disability and Psychedelic Therapies: An Agenda for Inclusive Research and Practice. Front Psychiatry 2022; 13:914458. doi 10.3389/fpsyt.2022.914458.*

*Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10 lessons from 40 years of primary-care research. Psychooncology 2011; 20:572–84.*

*Munkholm K, Paludan-Müller AS, Boesen K. Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. BMJ Open 2019; 9:e024886.*

*Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Review of Clinical Pharmacology 2021; 14:1133–52.*

*Nichols DE, Johnson MW, Nichols CD. Psychedelics as Medicines: An Emerging New Paradigm. Clin Pharmacol Ther 2017; 101:209–19.*

*Nutt DJ, King LA, Phillips LD, Independent Scientific Committee on Drugs. Drug harms in the UK: a multicriteria decision analysis. Lancet 2010; 376:1558–65.*

*Nutt D, Spriggs M, Erritzoe D. Psychedelics therapeutics: What we know, what we think, and what we need to research. Neuropharmacology 2023; 223:109257. doi 10.1016/j.neuropharm.2022.109257.*

*Peill JM, Trinci KE, Kettner H, Mertens LJ, Roseman L, Timmermann C et al.: Validation of the Psychological Insight Scale: A new scale to assess psychological insight following a psychedelic experience. J Psychopharmacol 2022; 36:31–45.*

*Pinquart M & Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med 2010; 40:1797–810.*

*Posternak MA & Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 2005; 66:148–58.*

*Preller KH, Herdener M, Pokorny T, Planzer A, Kraehenmann R, Stämpfli P et al.: The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. Curr Biol 2017; 27:451–7.*

*Prieto JM, Blanch J, Atala J, Carreras E, Rovira M, Cirera E et al.: Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. J Clin Oncol 2002; 20:1907–17.*

*Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI et al.: Psychedelics and Psychedelic-Assisted Psychotherapy. Am J Psychiatry 2020; 177:391–410.*

*Richards WA, Rhead JC, Dileo FB, Yensen R, Kurland AA. The peak experience variable in DPT-assisted psychotherapy with cancer patients. Journal of Psychedelic Drugs 1977; 9:1–10.*

*Rieser NM, Herdener M, Preller KH. Psychedelic-Assisted Therapy for Substance Use Disorders and Potential Mechanisms of Action. Curr Top Behav Neurosci 2022; 56:187–211.*

*Roscoe J & Lozy O. Can psilocybin be safely administered under medical supervision? A systematic review of adverse event reporting in clinical trials. Drug Science, Policy and Law 2022; 8. doi 10.1177/20503245221085222.*

*Roseman L, Haijen E, Idialu-Ikato K, Kaelen M, Watts R, Carhart-Harris R. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. J Psychopharmacol 2019; 33:1076–87.*

*Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B et al.: Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016; 30:1165–80.*

*Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology 2018; 142:200–18.*

*Schartner MM, Carhart-Harris RL, Barrett AB, Seth AK, Muthukumaraswamy SD. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Sci Rep 2017; 7:46421. doi 10.1038/srep46421.*

*Schlag AK, Aday J, Salam I, Neill JC, Nutt DJ. Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. J Psychopharmacol 2022; 36:258–72.*

*Shim EJ & Park JH. Suicidality and its associated factors in cancer patients: results of a multi-center study in Korea. Int J Psychiatry Med 2012; 43:381–403.*

*Paul Stamets: Psilocybin Mushrooms of the World. Ten Speed Press, California, 1996.*

*Studerus E, Gamma A, Kometer M, Vollenweider FX. Prediction of psilocybin response in healthy volunteers. PLoS One 2012; 7:e30800.*

*Thase ME. Strategies for Optimizing the Treatment of Major Depressive Disorder. J Fam Pract 2021; 70(1 suppl [iii]):S11–9.*

*van Elk M & Yaden DB. Pharmacological, neural, and psychological mechanisms underlying psychedelics: A critical review. Neurosci Biobehav Rev 2022; 140:104793. doi 10.1016/j.neubiorev.2022.104793.*

*Varley TF, Carhart-Harris R, Roseman L, Menon DK, Stamatakis EA. Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. Neuroimage 2020; 220:117049. doi 10.1016/j.neuroimage.2020.117049.*

*von Rotz R, Schindowski EM, Jungwirth J, Schuldt A, Rieser NM, Zahoranszky K et al.: Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine 2023; 56:101809. doi 10.1016/j.eclinm.2022.101809.*

*Correspondence:*
*Dr. Astrid Kaiserman*
*Erasme Hospital, Department of Adult Psychiatry,*
*Route de Lennik 808, 1070 Brussels, Belgium*
*astrid.kaiserman@gmail.com,*
*T +32 (0) 2 555 37 41, F +32 (0) 2 555 69 55*