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Which Psychotherapy Model Should be Used in Psilocybin Treatment for Depression?

Short Title: Models of Psilocybin Therapy for Depression

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Abstract

Objective: Unipolar and bipolar depression severely impact millions of individuals worldwide, with a significant subset of cases remaining unresponsive to conventional treatments. Psilocybin-assisted psychotherapy (PAP) has demonstrated therapeutic efficacy; however, the optimal psychotherapeutic approach remains undefined, ranging from unstructured models rooted in historical practices to modern frameworks that are structurally tailored for depression. This narrative review proposes a conceptualization of psychotherapeutic models employed in existing interventional trials of PAP for depression and provides a preliminary comparison of their main characteristics and evidence for efficacy.

Methods: The online databases PubMed, PsycINFO, and Google Scholar were searched for interventional trials evaluating PAP for individuals with unipolar or bipolar depression.

Results: A total of 38 publications were reviewed, contributing to the conceptualization of two main types of psychotherapy models: 1) 'Specific' approaches (most commonly Acceptance and Commitment Therapy and Perceptual-Control Therapy) and 2) 'Non-specific' models of psychological support. Both models emphasize the critical role of the therapeutic alliance, yet differ in mechanistic focus, with specific models being developed to enhance psychological flexibility and non-specific models emphasizing the concept of the 'inner-healer.' Importantly, critical gaps in the literature were identified, including methodological limitations of current evidence and the need for standardized reporting guidelines.

Conclusion: Although each PAP model differs, both may have clinical relevance in depression treatment. Future work should explore the standardized reporting of

psychological interventions in PAP and comparative study designs to better evaluate non-specific and specific models and inform treatment guidelines.

Keywords: psilocybin, psychotherapy, psychedelics, major depressive disorders, psychedelic-assisted psychotherapy.

Introduction

Unipolar and bipolar depression are mental disorders that severely impact quality of life and daily functioning in over 300 million people worldwide.¹ Approximately one third of cases do not respond to standard antidepressant medications and, although the addition of psychotherapy improves outcomes by over two-fold, there is still a significant population that remains symptomatic.^{2,3} Untreated depression contributes to the development or worsening of medical and psychiatric comorbidities, including a greater risk of suicide, representing a critical problem in psychiatry.^{4,5}

Psychedelics are a group of naturally occurring and synthetic psychoactive substances that, when combined with psychological support, have yielded therapeutic potential in psychiatry and represent an area of active investigation.^{6,7} For millennia, psychedelic substances have been used by Indigenous communities for medicinal and spiritual purposes, emphasizing community and experiential elements.⁸ This traditional knowledge influenced the Western medical introduction to psychedelics in the mid-twentieth century, in part canonized by Robert Gordon Wasson's 1955 psilocybin ceremony with María Sabina of the Mazatec community, for example.^{9,10}

From origin to modern day, there has been a blending of traditional knowledge about psilocybin with scientific and medical practice, including ideals of rationality, empiricism and a focus on improving symptoms of well-defined mental disorders.^{11,12}

Throughout the twentieth century, psychiatrists and psychotherapists investigated different treatment models using classical psychedelics. For example, Hanscarl Leuner's psycholytic therapy is an approach that was commonly used in the 1960s, in which small doses of psychedelics were used to bring about new material for discussion during psychotherapy.¹³ The modern 3-phase model of psychedelic therapy evolved from these early pioneers and involves preparation and integration sessions before and after dosing, respectively.^{6,14}

There is emerging clinical evidence for the therapeutic efficacy and safety of psilocybin-assisted psychotherapy (PAP), with meta-analyses demonstrating robust antidepressant effects.^{7,15,16} Psilocybin is a classical psychedelic that acts as an agonist at serotonergic receptors, most notably 5-HT_{2A}, altering neural connectivity and plasticity, changes that are associated with increased emotional processing and cognitive flexibility.^{12,17} In concert with the acute neurobiological effects of psilocybin, the incorporation of humanistic approaches (i.e., psychological support) is considered essential to promote safety and bring about enduring therapeutic changes to mood and well-being—this knowledge has been largely garnered from traditional psychedelic practices.^{18,19}

PAP has recently been considered a promising experimental treatment for major depressive disorder (MDD) in the latest Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.^{20,21} Various psychotherapy models have been developed by academic, corporate and nonprofit entities in the clinical evolution of PAP; however, most models are ambiguously referred to as 'psychological support' or 'integration' and there is an emphasized need for standardized naming conventions.^{22–24} Further, it remains to be determined which psychotherapy approach is optimal for use in combination with psilocybin for the treatment of individuals with depression,

including the clinical characteristics that should be considered in the selection of an evidence-based model.^{23,25}

The objective of this narrative review is to examine and characterize psychotherapy models employed in studies of psilocybin treatment in depression, including the intensity and duration, provider, congruence with the psilocybin experience, for which subgroups of depression they have been employed, and the implications for future PAP treatment guidelines. The evidence synthesized herein is presented to stimulate advancements in psychedelic psychiatry, including critical discussion about the identification of the most appropriate model for the treatment of individuals with unipolar or bipolar depression.

Methodology

A review was conducted of all the interventional studies using PAP for individuals with unipolar or bipolar depression. The online databases PubMed, PsycINFO and Google Scholar were searched for scientific articles published in English before November 2024. The search strategy involved the terms “psilocybin AND therapy,” “psilocybin AND assisted AND therapy,” “psilocybin AND enhanced AND psychotherapy” in combination with the terms “depression,” “major AND depressive AND disorder,” “bipolar depression.” Inclusion criteria were interventional trials (i.e., open-label or randomized controlled) that evaluated PAP for unipolar or bipolar depression, published before November 2024. Exclusion criteria included non-interventional studies (e.g., reviews, preclinical), non-depression populations (e.g., anxiety only), or psychedelic interventions that did not involve psilocybin administration. The initial search conducted by identified 1369 potentially relevant articles in which 876 duplicates were removed, yielding 493 articles to undergo

screening. Title and abstract screening resulted in the exclusion of 446 articles, in which 47 articles proceeded to full-text screening. Following review of the retrievable full-text articles (n=41), seven were excluded for not being available in English (n=2) or not being the correct publication format (n=5). Following the updated search, an additional four publications covering two interventional trials were included. Authors E.K. and P.B. conducted the search and screening, using a custom standardized template for non-blinded data extraction. Disagreements were resolved by consensus with author E.B. Risk of bias was appraised narratively based on study design, blinding adequacy, and sample size, per guidelines for narrative reviews.^{26,27}

In total, 38 publications were included, covering 15 different interventional trials, including six open-label and nine randomized controlled trials (See Table 1). The target population for most trials is moderate to severe MDD or treatment-resistant depression, although three trials were conducted on depressive symptoms in cancer patients and two trials included individuals with treatment-resistant bipolar depression. A discussion of the results is presented in a narrative format below as follows: 1) common elements in all models of PAP, both in the included trials and more broadly; 2) a comparison of specific and non-specific models of PAP in the included trials; and 3) the implications of these findings for the conceptualization of an optimal psychotherapy approach.

Table 1. Characteristics of the included publications of PAP for depression, with each row representing separate interventional trials.

Citations	Population	Study Design	PAP model	Intensity & Duration	Provider	Main Outcome
(25,28–38)	Moderate to severe TRD	Open-label feasibility study with neuroimaging	Non-specific	1 preparation (4h) 2 dosing sessions (>6h) 1 integration	Psychotherapist and psychiatrist	Significant reduction in QIDS scores: mean change –11.8 at 1 week, Hedges g=3.1; –9.2 at 3 months, Hedges g=2; no serious adverse events

(39–43)	Moderate to severe MDD	Double-blind, RCT	Specific (ACT)	1 preparation (1.5h) 2 dosing (8h) 2 in-person integration (1.5-2h) 1 remote integration (0.5-0.75h)	2 therapists (psychotherapist and psychiatrist)	Primary outcome QIDS-SR-16 at 6 weeks showed no significant between-group difference (psilocybin –8 vs. escitalopram –6); safety profiles were similar.
(44)	Bipolar TRD	Open-label trial	Non-specific	1 dosing (8h) 3 integration (2-3h)	2 therapists (psychologists)	Large MADRS reductions (–24 points at week 3), sustained to week 12; no serious adverse events.
(45,46)	Cancer patients with MDD	Open-label trial	Specific (group therapy, supplemented with individual therapy)	1 individual preparation 1 group preparation 1 dosing session (8h) 2 integration	therapists (1-to-1 therapist-to-patient ratio)	Mean MADRS reduction of –19.1 points by week 8 (95% CI –22.3 to –16.0); response rate of 80% (24/30) and remission rate of 50% (15/30); no serious adverse events.
(47)	TRD	Double-blind RCT	Non-specific	3 preparation (1-1.5h) 1 dosing (8h) 2 integration	2 therapists	Qualitative results
(48–51)	Moderate to severe MDD	Randomized, waitlist-controlled trial	Non-specific	2 preparatory (8h total) 2 dosing sessions ("daylong") 2 integration (2-3h)	Research staff of varying educational levels and professional disciplines	Large reductions in GRID-HAMD (22.8 at baseline to 8.0 at week 1 and 8.5 at week 4); response rate of 71% and remission rate of 54–58% across follow-up; no serious adverse events.
(52–54)	TRD	Double-blind, parallel-group RCT	Specific (PCT-based)	1 dosing session (6h) 1 integration 2 visits with discussions	Therapists and psychiatrists	Psilocybin 25 mg MADRS reduction of –12.0 at week 3 vs. –5.4 with 1 mg (difference –6.6); response rate of 37% and remission rate of 29% at week 3; no sustained benefit at week 12; adverse events were common (suicidal ideation occurred across all groups).
(55)	TRD	Exploratory, open-label trial	Specific (PCT-based)	1 preparation 1 dosing session (6-8h) 2 integration	Licensed mental healthcare professionals	MADRS reduction of –14.9 at week 3; response rate of 42% and remission rate of 42% at week 3; no serious adverse events.
(56)	Depressive symptoms in cancer patients	Randomized, double-blind cross-over trial	Non-specific	3 preparation (total 8h) 2 dosing 2 or more integration (~1h)	Trained staff of various educational levels	Large reductions in depression (GRID-HAMD) and anxiety (HAM-A), both decreasing by ~50–80% at 5 weeks; remission rate of 80% at 6 months.
(57)	MDD	RCT	Non-specific	1-6 preparatory sessions (total 6-8h) 1 dosing (7-10h) 3 integration	Therapists and psychiatrists	Psilocybin 25 mg MADRS reduction of –19.1 at day 43 vs –6.8 with niacin (difference –12.3); sustained response rate of 42% vs 11% and remission rate of 25% vs 9%; no serious adverse events

(58)	Depressive symptoms in cancer patients	Crossover RCT	Non-specific	3 preparation (2h) dosing session 1 (8h) 3 integration sessions (2h) dosing session 2 3 integration sessions (2h)	psychiatrists, psychologists, oncology social workers, oncology nurses, or master-level counselors	Large reductions in depression and anxiety (GRID-HAMD and HAM-A decreased by ~50–80% at 5 weeks); remission rate of ~80% at 6 months; no serious adverse events.
(59–61)	Moderate to severe MDD	Double-blind placebo-controlled within-subject study	Specific (ACT)	1 preparatory (2h) 1 placebo dosing (8h) 1 psilocybin dosing (8h) 3 integrations (1-2h)	Therapist and psychiatrist	Moderate-dose psilocybin produced GRID-HAMD reductions of –6.3 to –8.7 over 2 weeks, not significantly different from placebo (–4.4 to –5.8); response rate of 66.7% and remission rate of 46.7%; no serious adverse events.
(62)	MDD	Placebo-controlled, parallel-group RCT	Non-specific	2 preparation (~1h) 1 dosing (~6h) 3 integration (~1h)	Therapist or physician	Psilocybin 0.215 mg/kg produced a MADRS reduction of –13.0 at day 14, significantly greater than placebo (difference –13.0; 95% CI –15.0 to –1.3); response rate of 58% and remission rate of 54% at day 14; no serious adverse events.
(63)	TRD	open-label trial	Specific (PCT)	3 preparation (1-1.5h) 1 dosing (~6h) 3 integration (1.5h)	Therapist	MADRS reduction of –23.0 at week 3; response rate of 60% and remission rate of 53% at week 3; 47% and 40% sustained at week 12; no serious adverse events.
(64)	Unipolar or bipolar TRD	Open-label, randomized, waiting list-controlled trial	Non-specific	1 preparation (1-2h) 1 dosing (6-8h) 2 integration (1-2h)	Psychiatrists, psychotherapist, social workers, spiritual care therapists, nurses, and/or primary care providers	MADRS reduction of –9.6 at week 2 vs –3.0 during waitlist (difference –6.6; $g = 1.1$); repeated doses led to further cumulative reductions in MADRS; no serious adverse events.

Abbreviations: TRD, Treatment-Resistant Depression; MDD, Major Depressive Disorder; RCT, Randomized Controlled Trial; PAP, Psilocybin-assisted Psychotherapy; ACT, Acceptance and Commitment Therapy; PCT, Perceptual Control Theory; CFT, Compassion Focused Therapy; QIDS, Quick Inventory of Depressive Symptomatology; QIDS-SR-16, QIDS Self-report; MADRS, Montgomery-Asberg Depression Rating Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

Common elements in all models of psilocybin-assisted psychotherapy

Three phases

All models of PAP to date include three phases: preparation, dosing and integration. Preparation is the first phase which occurs to establish the therapeutic alliance with the provider and to prepare the participant for the psilocybin dosing session, taking anywhere from one to eight hours and occurring in one or multiple (1-

6) sessions that are typically held between one and 21 days before the dosing session. Intentions may be set during this phase with a focus on finding relief from psychological distress and establishing reasonable expectations for the psilocybin experience. The rapport between the therapists and participants may be considered in determining the substance and dose. Importantly, informed consent is reviewed during the preparation phase, including preparation for possible psychological side-effects and consent for therapeutic touch and/or session recording. Preparation sessions may also include psychiatric and/or psychological interviews to assess depressive symptoms and related domains.

The second phase is the dosing session in which psilocybin is administered orally in a medically supervised context that is specifically curated for the use of psychedelics. Ten of the included studies employed one dosing session and four included two dosing sessions. The randomized controlled trial (RCT) conducted by Rosenblat et al. (2024) included up to three dosing sessions for participants that demonstrated tolerability, safety, and cumulative reductions in MADRS scores associated with prior doses.⁶⁴ Dosing typically occurs in a secured room with a living-room ambience where the participant can comfortably lie supine. The intentions are often reiterated, and the participant is encouraged to shift their attention inward, assisted by the use of eyeshades and ambient music played through headphones. Typically, two therapist guides will be present to provide verbal and non-verbal support to the participant, including throughout any challenging experiences. Guides are most commonly psychotherapists, psychologists, or physicians, although four studies employed guides of a broader range of educational backgrounds (e.g., social workers, nurses).^{48,57,58,64} The nature of the therapeutic guide varies from non-specific and passive to specific and directive, depending on the PAP model. Predominant goals of

the dosing session are to minimize adverse psychological reactions and facilitate the therapeutic session. As the subjective effects of the substance wear off, participants may be encouraged to discuss the experience for memory consolidation purposes.

The final phase, integration, occurs to process the insights gained during the dosing session and to make meaning of them as relevant to the participant's daily life. The included studies employed between one and three integration sessions (1-3 hours in duration each) that were held following dosing. Each integration session has the objective to employ therapeutic support and guidance and promote the psychological stability of the participant. During integration, participants are encouraged to discuss the psychedelic experience and to incorporate any relevant insights in a way that promotes positive and sustained changes to their daily lives. All integration sessions were conducted in-person, except for the third session of the RCT conducted by Carhart-Harris et al. (2021) which included a shorter (30-45 minute) online integration session and the RCT conducted by Rosenblat et al. (2024) which included virtual options for all non-dosing study visits and psychotherapy sessions.^{39,64}

Mental State and Openness to the Experience (Set)

The mental state or 'set' of the participant is an important factor in therapeutic change following PAP, encompassing mindset, expectations and personality traits that are largely addressed during preparation sessions. Personality traits of openness and acceptance have been associated with positive psychedelic experience, while individuals who were preoccupied or apprehensive were more likely to experience acute adverse effects.⁴² Growth motivations represent another predictor of positive outcomes following psychedelic experiences and can be cultivated during preparation.⁴³ The only included trial that applied an assessment of openness was

described by Weiss et al. (2024) in which positive personality changes were associated with PAP, including increased openness at week six of the RCT; however, observed changes in personality were significantly moderated by participant expectancy.⁴⁰

Expectancy bias refers to a cognitive bias in which an individual's expectations about a process of outcome may influence the perception of their own or someone else's behavior.⁴⁴ In psychedelic research, expectancy represents a significant challenge to obtaining objective findings, especially considering widespread public enthusiasm about psychedelics and the predominance of functional unblinding during dosing.⁴⁵ Unblinding or 'breaking the blind' occurs when participants or researchers infer treatment allocation due to perceived psychedelic effects and further threatens the validity of PAP trials. Questionnaires such as the Credibility/Expectancy Questionnaire (CEQ) may be administered at baseline to determine the effect of expectancy on research findings, as employed in the double-blind RCTs described by Carhart-Harris et al. (2021) and Goodwin et al. (2022).^{39,52} Preparation is an influential phase for establishing the expectations of the participant in PAP, but there is little consensus about the content that should be used to establish the appropriate therapeutic set.⁴⁶

Environment and Context (Setting)

The 'setting' of psychedelic therapy is the physical environment, social and cultural context of dosing and integration sessions. There is importance in creating a safe and welcoming environment to avoid adverse events and to promote therapeutic change. For example, the included interventional trials commonly described a dosing room that is designed to simulate a calming, non-clinical, living room like ambience

with warm tones, plants and a window for natural light.^{23,47} The environment also includes the sensory information available during dosing. For example, carefully curated music is typically played through either headphones or high-quality speakers to promote introspection and guide the psychedelic experience.^{31,38} Participants are often encouraged to wear an eye mask and direct their attention inward during the psilocybin sessions. A pair of therapist guides are often present as part of the social context but are directed to only engage in participant-initiated conversation and maintain unconditional positive regard and non-directive psychological support.⁴⁸⁻⁵⁰

Dosing

The typical range for a dose of psilocybin during an interventional trial is 10-25 milligrams.¹⁵ Administration is typically oral and the duration of effects is dose-dependent, usually lasting four to six hours.^{51,52} Most of the acute side effects reported in the reviewed studies included transient, delayed headache of dose-dependent severity, nausea, vomiting, delayed headache, and sympathomimetic effects that normalize within 24 hours of administration.⁵³⁻⁵⁵ The only included trial reporting serious adverse events was the double-blind RCT conducted by Goodwin et al. (2022), in which suicidal ideation/behavior or self-injury occurred in all dose groups (i.e., 1mg, 10mg, 25mg).⁵²

Unpleasant Psychological Experiences

The psilocybin experience is associated with a heightened state of psychological vulnerability, including increased suggestibility, alteration of interpersonal boundaries, and the potential to re-experience intense negative emotions that may be associated with trauma. There is a risk for acute adverse

psychological reactions, involving affective, cognitive, and somatic symptoms that were assessed using neuropsychological tools such as the CEQ, 5-Dimensional Altered States of Consciousness Questionnaire or Emotional Breakthrough Inventory, which were commonly employed by the included studies.^{34,39,56–58} Only one of the included trials employed a qualitative assessment of challenging experiences and three trials did not include any measure.⁵⁹

Challenging and unexpected experiences during psilocybin dosing often involve anxiety, paranoia and/or confusion, described by participants as a “feeling of losing oneself” or “going crazy,” but are considered potentially valuable to the long-term therapeutic outcomes.^{77,78} Addressing these challenging experiences is typically accomplished on an individual basis with unconditional positive regard and psychological support by the psychotherapist being associated with improved outcomes.^{77–79} In severe cases, rescue from experiences that are too distressing has been accomplished with a 5-HT_{2A} receptor blocker such as olanzapine, although this did not occur in any of the included trials.^{54,63}

Integration in a Time-Limited Framework

Interventional trials often work within a time-limited framework for integration and on-going support for participants.^{52,53} Resource requirements include the cost of highly trained staff that are deemed necessary for PAP, especially for specific psychotherapy models. However, a similar number and duration of integration sessions were employed for specific and non-specific psychotherapy models in the included trials.

Ethical Considerations

Several aspects of PAP require unique ethical consideration when compared to conventional forms of psychotherapy. First, the subjective and ineffable nature of the psilocybin experience makes it difficult to obtain informed consent and the mechanistic underpinnings and long-term effects of PAP remain to be fully delineated, limiting the ability to fully determine safety risks.^{17,81} All of the included trials addressed this challenge by informing participants about potential risks and benefits and providing a description of commonly reported aspects of the psychedelic experience.

Second, participants of psychedelic studies undergo a unique state of psychological vulnerability. The risks associated with such psychological vulnerability are compounded by the tendency for the participant to attribute a disproportionate amount of wisdom and power to the therapist guide(s). Specific risks can include therapist sexual abuse and the inappropriate imposition of therapist beliefs to the participant.⁸² To address these ethical considerations, therapist talk engagement should only occur when initiated by the participant, as highlighted in the methodology sections of most included trials.^{28,39,83} To our knowledge, there is no universally accepted, field-wide professional code specific to PAP for individuals with unipolar or bipolar depression, although some safety guidelines and institutional manuals exist.^{74,84}

Specific and Non-Specific Models of Psilocybin-Assisted Psychotherapy

The variation in PAP interventions is often related to the type and intensity of psychotherapy that is incorporated. Therefore, we propose two main categories of psychotherapy models employed in PAP for depression, based on the available evidence. Below, we provide a description of each type of model and a synthesis of

the clinical evidence for its efficacy in the treatment of depression. A summary of key elements of each model is illustrated in Figure 1.

Specific Models

A total of six interventional trials have employed a specific model of PAP, involving the incorporation of evidence-based psychotherapy tools and frameworks, most notably during the preparation and integration sessions, although additional psychotherapy sessions may be added.^{34,40,48,69–71} The specific type of model may be selected based on different understandings of how psilocybin promotes neurobiological change. The most common specific models of psychotherapy employed in PAP for individuals with unipolar or bipolar depression were Acceptance and Commitment Therapy (ACT) and Perceptual-control therapy (PCT).

The ACT approach has a basis in cognitive-behavioural therapy and was designed with the goal to promote psychological flexibility—the ability to cope with difficult situations—and experiential acceptance, value clarification, mindfulness, and awareness. ACT challenges the idea that there is an internal healing power that can be somehow released by the use of psilocybin, instead positing that depression is multifactorial, influenced by social and contextual factors, and requiring internal work during the therapeutic process in order to be improved. There is evidence that psilocybin-assisted ACT increases psychological flexibility and experiential acceptance in individuals with depression and is associated with improvements in symptoms severity, although improvements did not differ from comparator study arms for the included studies. For example, the double-blind within-subject RCT conducted by Sloshower et al. (2023) demonstrated high rates of response (66.7%) and

remission (46.7%), although degree of change in depression scores was not significantly different from placebo.⁶¹

Developed as part of ACT, the Accept, Connect and Embody (ACE) model was adapted specifically for use alongside psilocybin treatment. It includes a focus on the promotion of acceptance via diffusion, willingness, and focus on the present, as well as the promotion of connection via contextualizing the self, prioritizing values and engaging in committed action. The ACE model was applied in the double-blind RCT conducted by Carhart-Harris et al. (2021), which demonstrated significant reductions in experiential avoidance and increased connectedness that were associated with mental health outcomes following PAP, but not escitalopram. However, depression scores showed no significant between-group differences at 6 weeks posttreatment.^{39,41,42} Together, interventional trials applying ACT concepts such as the ACE model of PAP may be particularly useful to target experiential avoidance, psychological inflexibility, and lack of connectedness in individuals with depression—targets that may accelerate therapeutic outcomes of PAP. However, further studies are needed to delineate comparative efficacy.

PCT is a psychotherapy framework that emphasizes the role of goal-directed activity as a method to control perception and overcome negative thought patterns.^{85,86} PCT was employed by one open-label trial and a double-blind parallel-group RCT, both conducted by Goodwin et al. (2022 and 2023), which demonstrated rates of 42% response and 42% remission at week three in the open-label trial and lower rates (37% and 29%, respectively) at the same timepoint in the RCT. Another open-label trial conducted by Ellis et al. (2024) employed a PCT psychotherapy model, leading to a significant reduction in depressive symptoms (i.e., MADRS change of -23 at three

weeks posttreatment) with no serious adverse events and 40% of participants maintaining remission at 12-weeks after dosing.⁶³

Only one trial included a group therapy approach to PAP. Agrawal et al. (2023) conducted a single-center fixed-dose open-label trial of PAP for individuals with cancer and MDD, resulting in significant reductions in depressive symptom severity (mean MADRS reduction of -19.1 by week eight), rates of 80% response and 50% remission, and no serious adverse events.⁴⁵ Upon qualitative analysis, acceptability of the group therapy model was positive, including fostering a sense of safety, preparedness, connection, and belonging that was complementary in value with individual sessions.⁴⁶

Specific models of PAP propose that a specific psychotherapy framework may enhance treatment efficacy beyond the administration of psilocybin alone. There are several advantages in adopting specific therapeutic models. For example, the patient may better understand the therapeutic process and objective of the treatment. The use of specific therapeutic models also makes the proper documentation of effectiveness possible and more objective comparison between studies using this model. We also acknowledge that even the least intrusive therapist won't be "neutral," so a defined framework may protect the patient from iatrogenic effects, especially well-established psychotherapies. However, curated psychotherapeutic frameworks may not allow for as much freedom for participant-led introspection and may redirect attention away from the dimensions of the experience that are most meaningful to the participant. The majority of specific models were not originally designed to be incorporated with psychedelic medicines and therefore may not be optimally conducive to the types of insights that are associated with PAP.

Non-specific Models

A total of nine interventional trials employed non-specific models of psychotherapy for individuals with depression.^{23,39,47,49,57,59,75–77} These models are often discussed with the intention to promote psychotherapy as a way to guarantee the safety and psychological well-being of the participant undergoing dosing. The therapist guides have less specialized educational requirements and do not provide direct psychotherapeutic insights, but rather prioritize unconditional positive regard, general psychosocial support, and a familiar person to engage with during the experience, upon initiation by the participant. The included trials employing non-specific PAP models demonstrated significant acute and long-term reductions in depressive symptoms with similar change in depression scores in open-label (e.g., –11.8 at week one, –9.6 at week two, –24 at week three) and placebo-controlled (e.g., –14.8 at week one, –13 at week two, –14.3 at week four) study designs. RCTs of non-specific models reported response rates between 43-71% and remission rates between 25-80%.^{25,39,49,57,76–78}

Non-specific models tend to emphasize the psychedelic and neurotrophic effects of the psilocybin as the primary driver of psychotherapeutic change and include limited therapist-led intervention. Preparation sessions focus on informing the participant about what the dosing session will entail, while integration sessions prioritize empathy, unconditional positive regard, and meaning-making that is primarily led by the participant. In this way, a strength of non-specific PAP is the ability to cater to the individual interpretation of the experience with limited suggestibility imposed by a specific therapeutic model.

The non-specific PAP models are also in line with those proposed by organizations such as the Multidisciplinary Association for Psychedelic Studies for

investigation of psychedelics in mental health or the Yale Manual described by Davis et al. (2021) and typically accept therapist guides from a range of educational backgrounds.⁴⁸ From an economic perspective, non-specific models may benefit from being less resource-intensive because a specialized therapist is not required. However, there are limitations of non-specific models, including the lack of potential benefit added from more evidence-based psychotherapeutic approaches and the lack of consistency which limits the scientific rigor of PAP interventions. Most non-specific therapy models are not developed with a potential therapeutic mechanism in mind, increasing the chance of the therapists' personal views about psychedelics being communicated and thereby exerting undue influence on the participant.

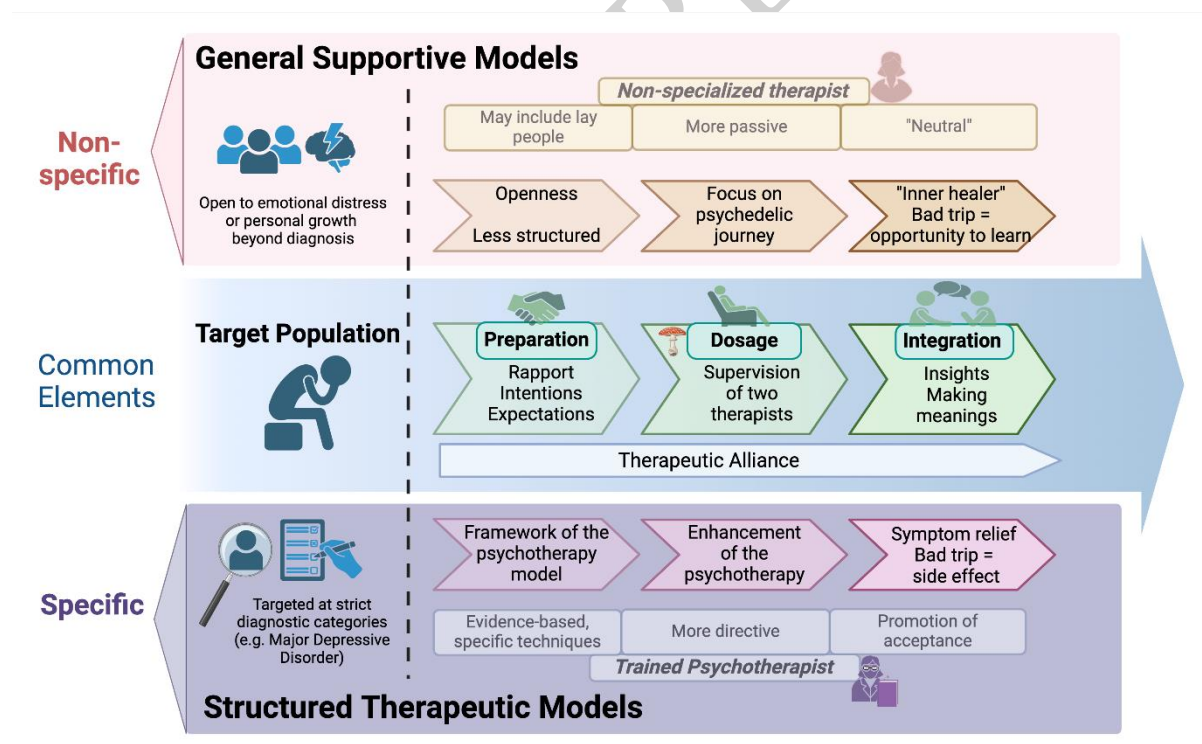


Figure 1. General characteristics of specific and non-specific models of psilocybin-assisted psychotherapy for depression.

Implications for the Conceptualization of an Optimal Psychotherapy Approach

The current review identified and compared psychotherapeutic models applied in interventional trials of PAP for individuals with depression. Both specific models (e.g., ACT, PCT, and group therapy) and non-specific models have been associated with reductions in depression scores and increased rates of response/remission; however, due in part to the heterogeneity amongst the included studies, there is not sufficient evidence to suggest that one approach is superior to the other. Specific psychotherapy models often incorporate structured frameworks aimed at enhancing psychological flexibility, emotional processing, and connectedness, while non-specific models tend to rely on participant-led introspection and the facilitation of the psilocybin experience. There are several advantages and disadvantages to each model, a discussion that exposes several unanswered questions in the conceptualization of the optimal approach to PAP for depression.

The Importance of the Therapeutic Alliance

Across studies, the strength of the therapeutic alliance emerged as a crucial determinant of therapeutic outcomes. It is well-documented that a stronger therapeutic alliance is associated with positive treatment outcomes across different disorders, demographics, and psychotherapeutic models, including PAP.⁵¹ For example, Murphy et al (2021) conducted a secondary analysis of the RCT that compared psilocybin to escitalopram and found that the strength of the therapeutic alliance predicted pre-session rapport, greater emotional breakthroughs and mysticality, factors that are associated with positive therapeutic outcomes.⁴³ Beyond the acute experience, the strength of the therapeutic alliance directly predicted final depression outcomes following the second dosing session.⁴³ During the preparation phase of PAP in

individuals with depression, a stronger therapeutic relationship was associated with more psychological breakthroughs in the dosing session and reduced depressive symptoms.⁴³ In a group psychedelic ceremony, positive relationships with facilitators was associated with greater improvements in wellbeing.⁸⁸

While most interventional trials of PAP for depression include psychologists and psychotherapists, an emerging question in the PAP field is the requirements and qualifications of therapist guides in PAP, including personal experience with psychedelics.⁸⁹ To improve the feasibility and scalability of PAP for individuals with depression, it may be worth considering the incorporation of allied healthcare professionals, as exemplified in two of the included studies.^{47,82} For example, mental health nurses are also specialized in the development of a therapeutic relationship and response to extreme emotional states in a similar way to psychotherapists and psychiatrists. However, expanding the ability for non-psychotherapists to act as guides in PAP may only be applicable to non-specific models, since specialized training is needed to employ specific psychotherapy approaches, such as ACT or PCT.

The Role of the 'Inner-Healer'

Psilocybin administration is known to promote introspection and emotional processing, aspects of PAP that are considered essential to therapeutic change and often emphasized in non-specific approaches.^{35,36} In this way, therapist guides will often redirect the participant's point of focus inward throughout the psychedelic experience in order to promote such effects. The concept of the 'inner-healer' refers to the ability of the participant to gain insight and promote positive change through introspection which, borrowed from traditional religious contexts, may be operationalized as a valid construct. For example, Peill et al. (2024) conducted a

recent double-blind RCT of high and low dose psilocybin and found a negative correlation between the acute measures of the 'inner-healer' and changes in depressive symptom scores two weeks after the high psilocybin dose.⁹⁰ The ability of inner healer scores to predict improvements in depressive symptoms at follow-up supports the crucial involvement of introspection in therapeutic outcomes.

The concept of 'inner-healer' challenges specific psychotherapeutic models of PAP which may prioritize focus on cognitive-behavioural aspects, whereas non-specific psychological support may provide a space that is more conducive to introspection and 'inner-healing.' Conversely, there are specific psychotherapeutic models implemented in PAP that do emphasize introspection, falling in line with the 'inner-healer' theory and may be implemented to strengthen the patient's self-sufficiency for psychological change.

The Need for the Psychedelic Experience

The concept of psychoplastogens is central to understanding how PAP contributes to therapeutic outcomes in individuals with depression, and the importance of the psychedelic experience for both specific and non-specific psychotherapy models. Psychoplastogens, including psilocybin, are compounds capable of promoting rapid and sustained neuroplasticity—the brain's ability to form new neural connections via dendritic growth and synaptogenesis, promoting changes to neural connectivity.^{91–93} These processes have been implicated as crucially involved in the therapeutic mechanisms of PAP in individuals with depression that may lead to the persisting changes in mood regulation, emotional processing and cognitive flexibility.^{32,33,49,60,94} Roseman et al. (2018) demonstrate a significant effect of the quality of the psychedelic experience on long-term depressive outcomes.³⁷

The psychoplastogenic effects of psilocybin may create an optimal environment or 'window of opportunity' in which patients may be more receptive to the psychotherapeutic intervention and can more easily overcome rigid maladaptive thinking patterns. The concept parallels that of the 'inner-healer' by amplifying the intrinsic capacity for self-directed healing and introspective insights that reinforce the therapeutic effects of PAP. However, it remains a question if the psychedelic experience, which is largely attributed to serotonergic effects, is necessary to obtain the psychoplastogenic and therapeutic effects of PAP.³⁴ For example, preclinical evidence suggests that the antidepressant effects of psilocybin persist despite 5-HT_{2A} blockade.⁹⁵ Husain et al. describe a RCT protocol that will contribute to the advancement of knowledge on the role of the psilocybin experience in PAP therapeutic outcomes in individuals with depression.⁹⁶

Limitations and Challenges

There are limitations that warrant discussion when comparing psychotherapeutic models of PAP based on the available empirical data. For example, there is substantial methodological heterogeneity between the included trials, suggesting the presence of confounding factors that are difficult to quantify and compare to the psychotherapy component. Most publications did not explicitly describe their rationale and methodology for choosing a particular psychotherapy model or its congruence with the psilocybin experience, limiting the ability to draw definitive conclusions about optimal approaches.

The compliance of the PAP study design with the gold-standard RCT remains an unsolved problem in clinical research on psychedelic-assisted psychotherapies.^{42,91} Given the substantial public interest in psychedelic therapies that

has preceded the scientific evidence, expectancy bias is of particular concern and it is unclear how exactly it impacts both positive (placebo) and negative (nocebo) outcomes. 'Breaking the blind' is common in PAP trials due to the noticeable perceptual effects of psilocybin, limiting the ability to maintain a placebo-controlled trial design and threatening internal validity.^{53,97,98}

Szigei et al. (2024) recently found that psychedelic therapy may be less vulnerable to expectancy biases than previously thought, although more trials are needed that implement blinding and expectancy assessments in order to attempt to better quantify these effects.^{99,100} Interestingly, the same trial found that pre-treatment trait suggestibility was associated with the therapeutic effect of psilocybin in individuals with MDD, an important factor implicated in the therapeutic alliance.¹⁰⁰

Future Directions

Expanding on the inherent difficulties in disentangling the pharmacological effects of psilocybin from the psychotherapeutic effects, these elements may interact synergistically to produce therapeutic outcomes. However, no study has systematically compared different psychotherapy frameworks within the context of PAP, leaving unanswered questions about their relative efficacy and suitability for different clinical subgroups of depression. A factorial study design may provide insight by evaluating the unique contributions of psilocybin and specific psychotherapy approaches, as there are ethical concerns with completely isolating psilocybin administration from psychological support. Standardized guidelines for reporting psychotherapy components should be developed to promote consistency in methodological reporting.¹⁰¹

It is also important to consider the psychotherapy models that have demonstrated therapeutic efficacy for individuals with depression but have not yet been explored alongside psilocybin. Our review only identified three different specific approaches to psychotherapy in PAP trials for depression, but there are more approaches with evidence that have not been investigated alongside psilocybin. For example, Crowe et al. (2023) describe several evidence-based psychotherapy models for treatment-resistant depression and their congruence with the psilocybin experience, including cognitive behavioral therapy (not congruent), interpersonal psychotherapy (congruent), and intensive short-term dynamic psychotherapy (congruent).¹⁰² Several qualitative studies report somatic phenomena arising during PAP (Belser et al., 2017; Watts et al., 2017; Bogenschutz et al., 2018), that are not typically considered in most PAP models.^{103,104} Expanding models to incorporate a body-based therapeutic technique may help address these phenomena, although ethical considerations related to boundary violation, therapist abuse, and suggestibility should be prioritized.

Building on the importance of the therapeutic alliance, there remains little known about the moderating effects on the therapeutic alliance and how this may impact clinical outcomes in PAP. The impact of the strength of the therapeutic relationship may warrant relational aspects of PAP to be a point of training for therapist guides, such as empathy, trust-building, and emotional support. In light of these aspects, the suggestibility and state of psychological vulnerability of the patient undergoing PAP warrants consideration for the unique influence of the therapist. Therefore, there is a benefit for non-directive approaches to psychological support and specific models should prioritize limiting the incorporation of therapist views and ideals that could influence the patient.

Understanding how to optimize the effects of the 'inner-healer' via tailored psychotherapeutic approaches remains an important area of development. In addition, more research is needed to fully understand how the psychoplastogenic effects of psilocybin translate into clinical outcomes. For example, Cameron et al. (2021) describe function-oriented chemical synthesis of psychedelic compounds that are non-hallucinogenic and produce similar neurobiological effects as hallucinogenic compounds in rodents.¹⁰⁵ Similarly, a non-hallucinogenic analog of the serotonergic psychedelic lysergic acid diethylamide (LSD) demonstrated potential therapeutic value in a recent preclinical study, with a favorable pharmacological profile.¹⁰⁶ To our knowledge, no study has successfully compared PAP to a similar intervention employing a non-hallucinogenic psilocybin analog in humans.

An enhanced understanding of the neurobiological underpinnings of the therapeutic effects of PAP in individuals with depression will help inform which psychotherapy model aligns most closely with the psychoplastogenic effects of psilocybin. For example, the evidence for an effect of psilocybin on increases in cognitive flexibility provides a potential basis for therapeutic approaches designed to enhance psychological flexibility in individuals with depression (i.e., ACT).^{50,82} Amidst the development of more scalable models of PAP, there is a need for therapist guides having an understanding of factors such as pharmacology, psychotherapy, philosophy, religion studies, music, law and regulatory aspects of the substance, ethics, neuroscience, and socioanthropology. There is an emergent need for cultural considerations to be better attended to in future models of PAP and to diversify participant populations to enhance the accessibility and equity of this emerging intervention.

Conclusion

Together, this narrative review presents and compares the psychotherapy models that have been implemented in PAP trials for individuals with depression. Based on the current literature, both specific and non-specific models of psychotherapy have been implemented with positive outcomes. However, few studies have adequately reported on methodological decisions related to the psychotherapy component or included psychotherapy-related outcomes. It is evident that more work is needed to delineate the optimal psychotherapeutic model to pair with psilocybin in the treatment of depression and which factors should inform selection based on a personalized approach. This review raises critically unanswered questions in the field of psychedelic research, including the role of the 'inner-healer', therapeutic alliance, mysticality, standardized reporting and methodological limitations of the PAP study design.

Future research designs should conduct high-quality comparative investigations on different psychotherapeutic models of PAP in depression, alongside neurobiological and clinical assessments to determine the optimal framework from a personalized approach. This line of work will contribute to the development of best practice guidelines to inform clinical care for individuals with depression. Adaptive frameworks, such as EMBARK, have already been developed as a transdiagnostic, trans-drug PAP model based on principles of both basic support and evidenced-based therapy approaches and could be refined for unipolar and bipolar depression.²⁵ The psychotherapy component of PAP has arguably been a historically neglected component of psychedelic therapy research when compared to psychedelic dosing, yet may represent a significant driver of psychological change.

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