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The psychotherapeutic framing of psychedelic drug administration

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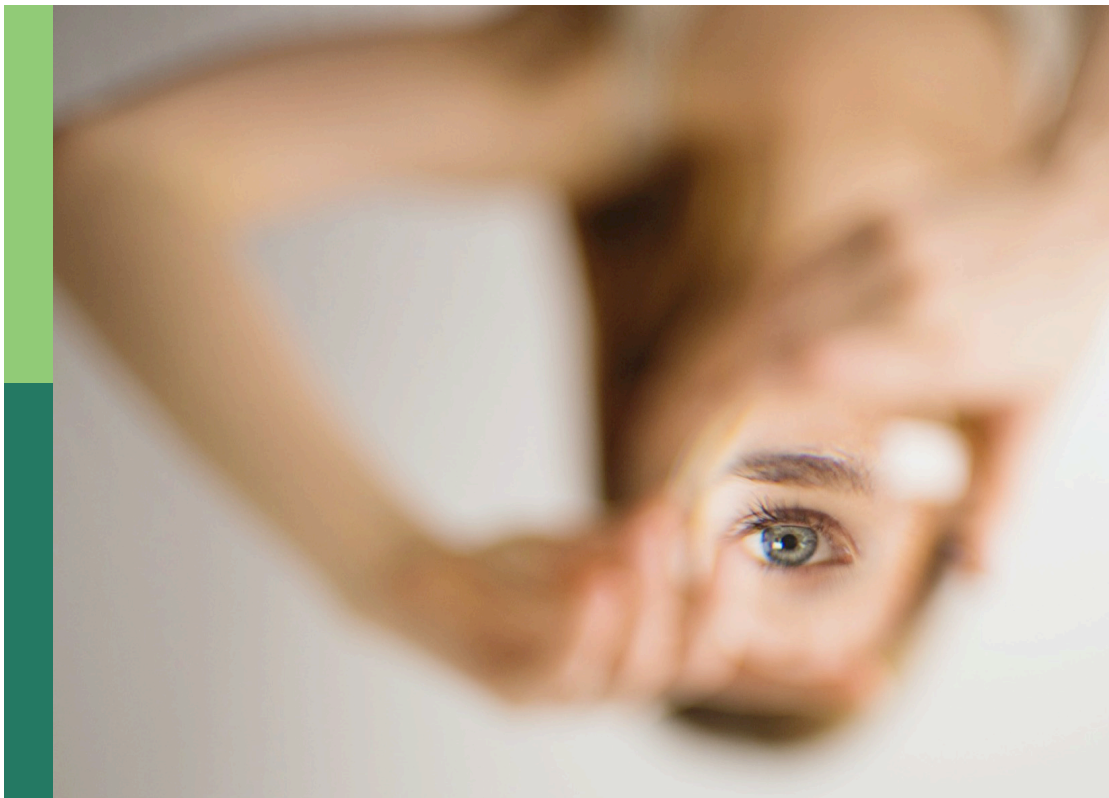
Published in
Frontiers in Psychology



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ISSN 1664-8714
ISBN 978-2-83251-627-0
DOI 10.3389/978-2-83251-627-0

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The psychotherapeutic framing of psychedelic drug administration

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Citation

Stenbæk, D. S., Poulsen, S., Doss, M., Beckman, M., eds. (2023). *The psychotherapeutic framing of psychedelic drug administration*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-627-0

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frontiers | Frontiers in Psychology

TYPE Editorial
PUBLISHED 23 January 2023
DOI 10.3389/fpsyg.2023.1121234

Check for updates

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

RECEIVED 11 December 2022
ACCEPTED 06 January 2023
PUBLISHED 23 January 2023

CITATION
Beckman M, Poulsen S, Doss M and Stenbæk DS (2023) Editorial: The psychotherapeutic framing of psychedelic drug administration. *Front. Psychol.* 14:1121234. doi: 10.3389/fpsyg.2023.1121234

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Editorial: The psychotherapeutic framing of psychedelic drug administration

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KEYWORDS

psychedelics, psychedelic-assisted psychotherapy, psychedelic assisted therapy, set and setting, psychotherapy, therapy, integration

Editorial on the Research Topic
The psychotherapeutic framing of psychedelic drug administration

Research on psychedelics as treatment for psychiatric disorders have gained renewed momentum. The focus during this psychedelic resurgence has mainly been on refuting the claim that these drugs have no medical use as stated under the Controlled Substances Act (1970), by providing evidence of clinical efficacy (Horton et al., 2021), pharmacological properties (Nichols, 2016), and neurobiological effects (Madsen et al., 2019; Doss et al., 2022). Although this endeavor is well-justified, it is important to also emphasize the interdisciplinary setting required (i.e., medical and psychotherapeutic) for the clinical administration of these substances (Johnson et al., 2008). This is particularly important since both the therapeutic relationship and subjective aspects of the psychedelic experience are hypothesized as mechanisms of treatment effects (Kaelen et al., 2018; Murphy et al., 2021; Yaden and Griffiths, 2021).

Due to the profound effects of psychedelic drugs on consciousness (Mcmillan and Jordens, 2022), and since physiological risks have proven rare (Studerus et al., 2011), the main tasks of health care professionals during treatments are to alleviate psychological distress (e.g., anxiety), and facilitate beneficial effects (Johnson et al., 2008). Early psychedelic research demonstrated the importance of mindset and context, also called *set and setting,* for safe administration (Hartogsohn, 2016, 2017). With the application of set and setting protocols (i.e., psychological support protocols), or more elaborated psychotherapy models of administration, the rate of adverse responses in modern psychedelic-assisted psychotherapy (PAP) controlled trials have dropped significantly (Schlag et al., 2022). However, it is still unclear which PAP models should be considered best practice, and thus considerable heterogeneity in the psychological protocols used in clinical trials (Thal et al., 2022). Some researchers have suggested added elements of evidence-based, condition-specific psychotherapies (e.g., Sloshower et al., 2020; Horton et al., 2021). While this may lead to increased therapeutic effects, there are also arguments for more integrative approaches that take into account the unique medical and therapeutic contribution these treatments may offer.

This Research Topic brought together researchers from the psychedelic field to explore psychological models of psychedelic drug administration. The included papers span at least three levels in their approach to the topic: (1) Scoping reviews and conceptual analyses;

(2) Comprehensive approaches to PAP; and (3) Specific PAP components and practices. At the first level, Cavarra et al. conducted a systematic review in which 55 papers were identified and organized according to whether the psychotherapeutic models were originally devised for psychedelics, or for traditional psychotherapeutic settings and later adopted for PAP. Common principles and differences between models and future directions are highlighted and discussed. Additionally, Bathje et al. conducted the first extensive review and concept analysis of psychedelic integration, including four models primarily based on psychotherapy, and six more spiritual/holistic models directed outside clinical settings. They also reviewed a large number of additional integration practices and activities, and incorporated the ten included models into a synthesized model of integration.

At the second level, after describing several historical and sociological influences on current psychedelic administration, Yaden et al. argued that cognitive behavioral approaches have the largest evidence-base for safety and efficacy, and therefore also the strongest rationale as the default PAP paradigm. In line with this, Mathai et al. described an acceptance and commitment therapy model for administration of esketamine, and Pots and Chakhssi presented a psilocybin-assisted compassion focused therapy for depression. However, after briefly reviewing strengths and limitations of current PAP models, Brennan and Belser argued that most of them lack adequate attention to the ethical concerns and embodied and relational elements that these treatments involve. To address this, the authors then introduced a transdiagnostic, trans-drug PAP framework.

At the third level, González et al. presented a meaning-making restorative retelling technique to process and integrate psychedelic experiences into autobiographical memory, and Sekula et al. suggested virtual reality as a possible PAP tool in their paper. Additionally, Messell et al. described a method of guided imagery and music for psychedelic interventions, and Søndergaard et al. provided evidence in favor of mindfulness-based interventions as part of future default PAP models.

Taken together, these articles make an important contribution to the present knowledge of psychotherapeutic framing of psychedelic drug administration. However, we suggest that, for a better understanding of the clinical efficacy of PAP, future trials should be designed to systematically evaluate the set and setting components of treatment, and provide detailed descriptions of all elements of the psychotherapeutic framing, including relational aspects and training of therapists.

Author contributions

MB and DS contributed to conception and writing. All authors contributed to the editorial and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Psychology

CONCEPTUAL ANALYSIS
published: 04 March 2022
doi: 10.3389/fpsyg.2022.813746

Virtual Reality as a Moderator of Psychedelic-Assisted Psychotherapy

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Psychotherapy with the use of psychedelic substances, including psilocybin, lysergic acid diethylamide (LSD), ketamine, and 3,4-methylenedioxymethamphetamine (MDMA), has demonstrated promise in treatment of post-traumatic stress disorder (PTSD), anxiety, addiction, and treatment-resistant depression. Psychedelic-assisted psychotherapy (PP) represents a unique psychopharmacological model that leverages the profound effects of the psychedelic experience. That experience is characterized by strong dependency on two key factors: participant mindset and the therapeutic environment. As such, therapeutic models that utilize psychedelics reflect the need for careful design that promotes an open, flexible, trusting mindset and a supportive setting. To meet this need, the PP model is increasingly supplemented by auxiliary methods, including meditation, relaxation, visualization or spiritual practices. We suggest virtual reality (VR) as a full-spectrum tool able to capitalize on and catalyze the innately therapeutic aspects of the psychedelic experience, such as detachment from familiar reality, alteration of self-experience, augmentation of sensory perception and induction of mystical-type experiences. This is facilitated by VR's evidenced capacity to: aid relaxation and reduce anxiety; buffer from external stimuli; promote a mindful presence; train the mind to achieve altered states of consciousness (ASC); evoke mystical states; enhance therapeutic alliance and encourage self-efficacy. While these unique VR features appear promising, VR's potential role in PP remains speculative due to lack of empirical evidence on the combined use of VR and PP. Given the increased commercial interest in this synergy there is an urgent need to evaluate this approach. We suggest specific VR models and their role within PP protocols to inspire future direction in scientific research, and provide a list of potential disadvantages, side effects and limitations that need to be carefully considered. These include sensory overstimulation, cyber-sickness, triggering memories of past traumatic events as well as distracting from the inner experience or strongly influencing its contents. A balanced, evidence-based approach may provide continuity across all phases of treatment, support transition into and out of an ASC, deepen acute ASC experiences including mystical states and enrich the psychotherapeutic process of integration. We conclude that the potential application of VR in modulating psychedelic-assisted psychotherapy demands further exploration and an evidence-based approach to both design and implementation.

Keywords: altered state of consciousness, MDMA, psilocybin, set and setting, integration, psychedelics, virtual reality, psychotherapy

OPEN ACCESS

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *12 November 2021*
Accepted: *11 February 2022*
Published: *04 March 2022*

Citation:
Sekula AD, Downey L and Puspanathan P (2022) Virtual Reality as a Moderator of Psychedelic-Assisted Psychotherapy. Front. Psychol. 13:813746. doi: 10.3389/fpsyg.2022.813746

INTRODUCTION

Treatment Using Psychedelics

Classic psychedelics, such as psilocybin, *N,N*-dimethyltryptamine (DMT) or lysergic acid-*N,N*-diethylamide (LSD), and psychedelic-like substances, such as 3,4-methylenedioxymethamphetamine (MDMA) or ketamine, have a long history of medicinal use (Carod-Artal, 2015; Nichols, 2016). The past 10-years has seen a resurgence in the use of and research into the potential therapeutic benefits of psychedelic compounds (Carhart-Harris and Goodwin, 2017). Psychedelics have primarily been examined as aids to psychotherapy in the treatment of post-traumatic stress disorder (Mithoefer et al., 2019), treatment-resistant depression (Carhart-Harris et al., 2021), and substance dependence (DiVito and Leger, 2020). Controlled administration of psychedelics can be a tool for facilitating psycho-behavioral change (Garcia-Romeu et al., 2014, 2016; Barrett and Griffiths, 2017) and lead to marked, rapid, and enduring benefits in both healthy volunteers and patient populations, particularly when accompanied by a supportive context (e.g., psychological support; Luoma et al., 2020).

The impact of psychedelics upon aspects of mental health and well-being have been attributed to the phenomenological features of the psychedelic experience, in particular peak or mystical states (Griffiths et al., 2006). Those phenomenological features as well as the depth of the mystical experience (ME) are affected by the type of psychedelic drug, dosage, the environment in which it is administered, and participant's individual predispositions, in particular their openness to the experience (Carhart-Harris et al., 2018). These features, along with the degree to which the psychedelic experience is integrated into the participant's psyche, are thought to regulate the therapeutic outcomes and emergence of any persisting, positive changes in attitudes and behavior (Haijen et al., 2018).

Limitations of Psychedelic-Assisted Psychotherapy

Studies on Psychedelic-Assisted Psychotherapy (PP) are yet to systematically evaluate the role of context. Whilst it remains unclear what the most favorable contextual elements are, both personal consumption and psychedelic retreats favor nature-immersion models (Kettner et al., 2021; Ruffell et al., 2021), that were promoted by early researchers in the field (Hofmann and Ott, 1980), in contrast to clinical settings in use today. Nature-immersion models aim to maintain a continuous, relaxed, multi-sensory engagement throughout the psychedelic journey (Shanon, 2002; Winkelman, 2021). The clinical approach, largely due to logistical limitations, departed from this model, resulting in segmentation into distinct, separate phases of treatment (preparation, dosing, and integration), which could impede a fluid transition throughout PP. Moreover, although study methods in clinical or research settings are carefully designed in accordance with principles of the *set* and *setting* protocol (Johnson et al., 2008; Hartogsohn, 2017), there is often a lack of congruence between the dosing session, and the preparation and integration sessions (Griffiths et al., 2016). Within individual trials, preparation and integration phases may be based on diverse psycho-therapeutic frameworks, including the change of the role of the therapist from that of supporting facilitator to that of psychotherapy provider (Johnson et al., 2014) or the involvement of different therapists (Fuentes et al., 2020). This discontinuity is further perpetuated by different phases taking place in different environments (e.g., Griffiths et al., 2016) and the variable use of diverse aids, particularly music, which plays a critical role throughout the dosing session but is not always formally utilized during integration sessions (Kaelen et al., 2018). Moreover, profound psychedelic experiences present challenges for the process of integration, due to their ineffable nature (Neitzke-Spruill, 2019), impaired perception of time (Wittmann et al., 2007; Wackermann et al., 2008; Yanakieva et al., 2019), the vast number of thoughts experienced (Carhart-Harris et al., 2016), overwhelming emotions (Gouzoulis-Mayfrank et al., 1998) and impaired recall even shortly after (Barrett et al., 2018; Doss et al., 2018b). This recall may be further impacted by an internal resistance to reliving challenging or highly emotionally loaded experiences in the absence of the psychoactive substance. It is also recognized that traditional psychotherapeutic approaches may not be best suited to therapeutic modalities that depend on intentional induction of a psychedelic-like state. Previously auxiliary practices such as somatic therapy, breathwork or mindfulness, are increasingly moved to the forefront of the therapeutic process (Payne et al., 2021).

Considering that each phase of treatment impacts the course and the outcome of PP, the lack of congruence throughout treatment (e.g., Carhart-Harris et al., 2018), could be postulated as a causative factor in reported psychological side effects such as paranoia or violent urges (e.g., Studerus et al., 2011; Johnstad, 2021) and waning of positive outcomes with time (e.g., Bogenschutz et al., 2015). It is argued that adopting a more unified structure, ensuring perceived continuity across all phases of treatment, could minimize psychological side effects and sustain positive outcomes of PP for longer. A more congruent design is also expected to encourage an overlooked phase of the psychedelic journey, which may follow the integration phase: *self-practice*. A clear, uninterrupted structure of PP paves the path for participants to continue integration privately, at their own pace, for as long as it is of benefit to them.

Virtual Reality Therapy

The psychedelic state is characterized by a non-ordinary experience of consciousness, which involves subjective changes of attention, awareness and/or affect. Therapeutic applications of non-ordinary states that are similar to those induced pharmacologically with psychedelic drugs, can also be evoked physically (e.g., through shamanic dance; Lee et al., 2016), psychologically (e.g., through meditation; Hanley et al., 2018), or through sensory stimulation (e.g., light flicker; Bartossek et al., 2021). Virtual Reality (VR) has also emerged in recent times as having the capacity to disrupt the rigidity of typical conscious experience (Glowacki et al., 2020). Typically, this involves providing specifically designed visual content, viewed by a participant through a head-mounted display, which may also include auditory components and less frequently other

sensory input such as haptic feedback (Repetto et al., 2009; Le May et al., 2021). In this way, VR can be used to alter the sensory experience of users, including evoking particular mental states and emotional responses, for example the sense of awe (Stepanova et al., 2019). It is also possible to simulate visual hallucinatory experiences (Suzuki et al., 2017). VR's capacity to transiently alter a participant's perspective and disrupt the rigid patterns of mental experience has also found application in the treatment of a variety of mood disorders, often alongside traditional therapies (Fernández-Caballero et al., 2017).

Virtual reality experiences are characterized by several distinct features, which have been evidenced to confer substantial benefits to patients undergoing various forms of psychotherapy (e.g., Boeldt et al., 2019), including augmentation of the sense of presence in exposure treatment (e.g., Rothbaum et al., 2001) and acute stress relief in treatment of anxiety (Tarrant et al., 2018; Donnelly et al., 2021). VR's capacity to distract from external cues has been utilized in pain reduction, both as an adjunct to pharmacotherapy, most commonly with opioids (Das et al., 2005), and as its replacement (Schmitt et al., 2011). VR exposure therapy has also been explored in combination with other pharmaceuticals, including cortisol in treatment of acrophobia (Dominique et al., 2011), cognitive enhancers (yohimbine hydrochloride) in treatment of aerophobia (Meyerbroeker et al., 2012) and antidepressants (paroxetine or venlafaxine) in treatment of agoraphobia (Castro et al., 2014).

Whilst these two different therapeutic approaches have developed separately, but in parallel, consideration has recently been given to a composite approach in order to enhance efficacy (Moroz and Carhart-Harris, 2018). For example, it has been suggested that VR might be used to optimize the environment in psychedelic sessions (Aday et al., 2020). Despite the growing interest in combining VR and psychedelics, which is emerging predominantly within the commercial industry, there are no experimental studies to date which investigate this combined approach. Nonetheless, a large body of research on VR and the growing body of research on therapeutic application of psychedelics allow for a theoretical, speculative investigation of the features of VR that are relevant to an altered state of consciousness associated with psychedelic use. Here, unique features of VR and their functional relationship with psychedelics are discussed, followed by a theoretical exploration of the range of synergistic outcomes that could be expected from simultaneous application of VR therapy and PP. To encourage an empirical exploration, we provide specific examples of VR models that could be integrated into various PP protocols, considering potential advantages against substantial limitations and possible disadvantages of this synergistic approach.

FEATURES OF VIRTUAL REALITY RELEVANT TO PSYCHEDELICS

Relaxation

Treatments of affective disorders (e.g., PTSD, obsessive-compulsive disorder, addiction) frequently involve relaxation methods for their significant benefits in reducing anxiety and depression symptoms (León-Pizarro et al., 2007; Manzoni et al., 2008), improving physiological markers of the stress response (Esch et al., 2003) and decreasing physical discomfort (León-Pizarro et al., 2007). Relaxation techniques have also been observed to increase patients' willingness to continue treatment (Pasyar et al., 2015; Ream et al., 2021) and to ensure extension of treatment benefits long term (Libo and Arnold, 1983).

A state of relaxation before psychedelic drug administration is one of the main predictors of positive self-dissolution (Dittrich, 1998), underscoring the importance of methods and environments that promote a relaxed mindset before and during psychedelic treatment. Despite the common use of mindfulness, breathwork or visualization techniques during PP (Watts and Luoma, 2020), stress and anxiety before or during dosing remain one of the most commonly reported undesired effects associated with psychedelic use in recreational and therapeutic settings (Griffiths et al., 2006; Studerus et al., 2011; Bienemann et al., 2020). This points to the need for more reliable relaxation methods for PP.

A recent meta-analysis showed that a wide range of VR interventions, in particular when using nature-based audio-visual stimuli, reliably facilitate a state of relaxation (Riches et al., 2021), highlighting VR's potential for use in conjunction with psychedelic therapy, which can be viewed as challenging by some clients. Although sustained, long term effects of VR relaxation interventions are yet to be ascertained (Riches et al., 2021), VR-based relaxation sessions commonly precede VR exposure treatment (Repetto et al., 2013; Son et al., 2015) due to recognized benefits of VR in acutely reducing distress symptoms associated with anticipation of a stressful or emotionally challenging event (Maples-Keller et al., 2017). VR has also been shown to outperform a diverse range of control conditions as a stress relief intervention in acute settings, including desktop-based relaxation interventions (Liszio et al., 2018), guided meditation and progressive relaxation exercises (Veling et al., 2021). Those results indicate that VR may be suitable to promote the state of relaxation during psychedelic treatment if applied prior to psychedelic exposure, and to relieve stress acutely if it arises during the session.

Buffering

The efficacy of VR as a mental health treatment modality can be partially attributed to its capacity to act as an "immersive distractor" (Le May et al., 2021). This ability to detach the participant from other sensory experiences could explain, for example, why VR leads to significant alleviation of pain in acute (Hoffman et al., 2008; Maani et al., 2011) and chronic conditions (Schmitt et al., 2011). Therefore, whilst VR is recognized predominantly for its ability to provide sensory stimulation, its therapeutic utility appears to be equally dependent on its ability to subtract it.

Psychedelic-assisted psychotherapy relies strongly on maintaining an appropriate balance between sensory enrichment and sensory deprivation (Carhart-Harris et al., 2018). For example, application of blindfolds in combination with music, and occasional use of visual cues like nature books, are used to modulate the sensory input (e.g., Johnson et al., 2014),

although blindfolds only allow limited, binary control over environmental stimuli (no visual stimuli vs. complete visual stimuli). Moreover, despite recognition of the importance of environmental design in curating the psychedelic experience, studies that utilize psychedelic substances rarely exploit the potential of using the environment to create a distinction between the day-to-day and the ethereal (Fuentes et al., 2020). Clinical and retreat environments are filled with familiar, even domestic cues, which may keep the attention rooted in the mundane, hijacking the experience instead of inspiring deeper emotional processes (Hartogsohn, 2017). What is more, those cues are likely to be perceived differently by the therapist and the patient who is under the effects of a psychedelic, forming a wedge in perceptual congruence and in turn perhaps, a barrier to therapeutic alliance. Finally, current approaches to setting design have not seen major innovation since the earliest psychedelic trials (Grinspoon and Bakalar, 1979).

In contrast to the current binary approach, VR allows fine control over the context and richness of stimuli that is provided. The virtual world can reduce distraction from the real world by replacing familiar cues with unfamiliar, fantastical objects and symbols (Quesnel and Riecke, 2018), that are conducive of deep immersion into the psychedelic experience (Glowacki et al., 2020). VR can therefore be used to transport the user out of the treatment environment and into an alternate reality, acting as a buffer zone, which is equally novel for both therapist and participant, facilitating awareness of the immediate experience in a more mindful way.

Mindful Presence

The intensity of the psychedelic experience, especially the experience of ego dissolution, can sometimes prove difficult and patients may resist the effects or attempt to temper them, for example by using engagement with the therapist as a distraction (Bourzat and Hunter, 2019). On the other hand, staying engaged despite the discomfort and surrendering to experiences that are challenging seems to have a beneficial impact on therapeutic outcomes (Johnstad, 2021). The capacity to stay engaged with a challenging sensation may be strengthened by learning to deepen the sense of presence without judgment, a skill that is commonly practiced by mindfulness meditators (Baer, 2015).

Mindfulness meditation is a technique that aims to expand the sense of awareness of diverse physiological and psychological sensations, without assessment or attachment to any of them (Kabat-Zinn, 2009). When used in combination with psilocybin, mindfulness practice has led to a deepening of the acute psychedelic experience, in particular a stronger sense of unity, bliss and spirituality (Smigielski et al., 2019a) and facilitated lasting therapeutic outcomes, including positive changes in psycho-social functioning (Griffiths et al., 2018; Smigielski et al., 2019b). Nonetheless, mindfulness is a challenging practice that requires time and commitment, and clients may still be unsuccessful in reaching the mindful state even when both are abundant (Hunt et al., 2020).

Mindfulness interventions are gaining increasing popularity among psychedelic practitioners (Payne et al., 2021) and VR has proven successful in helping people engage with mindfulness as well as reach the meditative state (Perhakaran et al., 2016; Seabrook et al., 2020). VR-based meditation interventions lead to a deep state of mindfulness, that has been reflected in changes of EEG patterns indicative of a relaxed, meditative state. Those changes, for example a shift of high to low beta frequencies and reduced beta activity in anterior cingulate cortex (Tarrant et al., 2018), were not observed in control conditions such as guided audio meditation (Yildirim and O'Grady, 2020). Significant increase in state mindfulness and positive affect have also been observed following VR mindfulness sessions in both clinical (Navarro-Haro et al., 2019) and non-clinical settings, making it suitable for all types of therapeutic environments that employ psychedelic substances. Technology could help mitigate the main barriers to drawing benefits from a mindful attitude in psychedelic treatment, predominantly the discouragement caused by uncertainty of achieving sufficient depth of mindfulness, and the need for often unrealistically lengthy, challenging training.

Augmenting Peak States

In approaching the psychedelic experience, a relaxed, mindful mindset has been observed to reduce the likelihood of adverse psychological events (Johnson et al., 2008) and is conducive to producing a mystical experience (Smigielski et al., 2019a). The depth of the ME, commonly measured by the mystical experiences questionnaire (MEQ30), is one of the key predictors of positive outcomes following psychedelic psychotherapy (e.g., Garcia-Romeu et al., 2014), including a decrease of clinical symptoms and lasting improvements in well-being (Haijen et al., 2018). Although the nature of the ME remains enigmatic, researchers have managed to identify certain phenomenological characteristics, or dimensions, of those experiences that resonate with the majority of participants (Barrett and Griffiths, 2017). These include: the sense of awe, unity and sacredness; timelessness and spacelessness; ineffability; as well as a sense of authenticity and validity of the reality that is being witnessed, despite its unrecognizable, sometimes even bizarre makeup (Hood, 2001; MacLean et al., 2012).

Highly immersive VR experiences also demonstrate some of those same, unique characteristics. The loss of sense of space, time and even connection to one's body is a commonly reported phenomenon (Seabrook et al., 2020). Patients tend to lose points of reference with reality, which seems to engage them in the process of contemplation and introspection (Seabrook et al., 2020). The resultant absorption into VR can counteract reality-testing mechanisms, tricking our senses into making a surreal scenario appear real (Suzuki et al., 2017). Witnessing and believing this alternative reality can lead to a sense of surrender (Seabrook et al., 2020), resulting in a level of engagement with VR scenarios, which can be stronger than that with the real world (Kotler and Wheal, 2017). Additionally, the experience of an alternative reality can also be ineffable (Glowacki et al., 2020).

Virtual reality-induced awe also appears to share functional characteristics with psychedelic mechanisms (Hendricks, 2018). Recent findings on phenomenological aspects of awe distinguished between the immediately available but less impactful "quick boiled awe," and the deeper, if more difficult

to achieve, "slow simmer awe" (Chirico and Gaggioli, 2018). VR-based experiential approach allows for eliciting the latter, more intense form (Gallagher et al., 2015; Chirico et al., 2016, 2017), which has also been proposed as a putative mechanism of psychedelic effects (Hendricks, 2018). VR, in evoking the challenging, destabilizing and deep sensations associated with awe, could act as a medium for a self-transcendental experience (Chirico and Gaggioli, 2018).

Although psychedelic compounds have been used historically and in the present to successfully evoke MEs (Griffiths et al., 2006) and emerging evidence shows that VR can also be successful in eliciting such mystical-type experiences (Glowacki et al., 2020), little empirical work has been performed on joint application of both methods acting synergistically to deepen the mystical state. Psychedelics have previously been combined with a range of other state altering methods, in order to deepen the ME, for example *via* the use of LSD with sensory deprivation (Lilly, 1990), psilocybin with meditation (Smigielski et al., 2019a,b), or hallucinogenic Datura plant with trance inducing dance practices (Du Toit, 1977). Results of those studies suggest that combining different ego-dissolving or awe-inspiring practices may lead to an augmented, cumulative effect in producing a more "complete mystical experience" or "complete ego dissolution," which are known to play an important role in the healing process (Haijen et al., 2018). Given the wide range of shared properties that are relevant to evoking a ME, the pairing of VR and psychedelics presents itself as a promising candidate for further exploration of this capacity for augmentation.

Altered States of Consciousness Priming

MEs are preceded and facilitated by unique changes in consciousness that are often referred to in literature as altered states of consciousness (ASC; Vaitl et al., 2005). An ASC is a phenomenological experience characterized by changes in perception of time, space and even oneself, accompanied by a non-ordinary range of attention, awareness and emotion (Ludwig, 1966). Here we refer to ASCs that are subjectively experienced as a form of expansion or transcendence of normal, wakeful consciousness, and are purposefully induced by a consumption of a psychedelic compound (Metzner, 1994), and also, although less reliably, through meditation (Shapiro, 2009; Stapleton et al., 2020), trance (Glicksohn and Ohana, 2011), or practices that induce flow states (Csikszentmihalyi and Nakamura, 2018), among others.

Interestingly, evidence suggests that the ability to achieve an altered state of consciousness can be improved through practice (Kotler and Wheal, 2017). Brain imaging outcomes revealed that experienced meditators exhibit better control over their attentional resources (Farb et al., 2007; Hasenkamp and Barsalou, 2012). This has been attributed to lasting changes in functional connectivity between brain regions responsible for attention and self-awareness (e.g., between the right insula and the prefrontal cortex) that seem to be the result of mindfulness practice (Farb et al., 2007; Hasenkamp and Barsalou, 2012). More experienced meditators are also more likely to experience ego dissolution, which is a hallmark of high dose psychedelic experiences (Hölzel and Ott, 2006; MacLean et al., 2012). What is more, practicing the ability to attain an ASC seems to be translational across different techniques. This is exploited, for example, in the training of American Navy SEALs, who practice common ASC methods (meditation, sensory deprivation, or trance) to optimize their ability to enter a state of flow during missions (Kotler and Wheal, 2017). In a similar way, prior mindfulness meditation practice significantly increases the depth of the ME induced by psilocybin, particularly the dimensions of introvertive mysticism and oceanic boundlessness (Smigielski et al., 2019a), and increases positive emotions associated with psilocybin-occasioned ego-dissolution. Finally, the incidence and the intensity of ME have been shown to be influenced by a clear intention for a mystical or a spiritual experience; this intention can be strengthened with practice (MacLean et al., 2011; Haijen et al., 2018).

The previously presented evidence suggests that practicing the ability to achieve an ASC using one method may increase the capacity for achieving it with other methods. Since early on in its inception, VR has been recognized as a tool capable of eliciting ASCs (Glicksohn and Avnon, 1997), and has been used extensively in the entertainment industry to produce an entire range of ASCs (Weinel, 2018). Moreover, VR has already been highly successful in facilitating other therapies that entail the production of ASC, for example meditation (Perhakaran et al., 2016; Seabrook et al., 2020). Research has also shown that VR can be used to induce visual alterations that closely resemble those brought on by classical psychedelics (Suzuki et al., 2017). It has been suggested that using VR to prepare clients for perceptual alterations induced by psychedelics may have beneficial effects on their expectation of hallucination effects and on pre-trip anxiety (Aday et al., 2020). By providing a comfortable, reliable and potent rehearsal space, VR can equip clients with a sense of awareness of initiating and engaging with an ASC, encouraging a more complete surrender to and exploration of the psychedelic state.

Therapeutic Alliance

A comfortable and productive relationship between the client and the therapist, known as positive therapeutic alliance, can account for as much as 30% of the positive outcomes of psychotherapy (Hubble et al., 1999). Its value may be even higher for treatments that use psychedelics, due to the palpable impact that setting (including the therapist) has on the hallucinogenic experience (Johnson et al., 2008). Current manuals for psychedelic practitioners agree that establishing successful rapport is the therapist's primary responsibility (Guss et al., 2020). Moreover, it is essential for that rapport to be established collaboratively (Greer and Tolbert, 1998). Conversely, inadequate therapeutic alliance has been suggested as one of the important factors in participants' poor response to psychedelic-based treatment (Nielson and Guss, 2018) and may increase the likelihood of adverse psychological reactions during the dosing session (Johnson et al., 2008).

Despite the common argument that use of technology in therapy can reduce the human connection (Przeworski and Newman, 2012), VR therapies are reported to have one of the highest therapeutic alliance rates (e.g., Garcia-Palacios et al., 2007; Meyerbröker and Emmelkamp,

2008) and satisfaction rates (Beck et al., 2007; Baños et al., 2009) across various therapeutic approaches. Relaxing VR environments reinforce patient involvement in treatment and increase positive rapport (Boeldt et al., 2019). VR is especially effective in facilitating a sense of safety and trust among the most traumatized or apprehensive patients, who tend to choose VR over talking to a counselor in person in order to work through their traumatic experiences (Garcia-Palacios et al., 2007; Wilson et al., 2008). Lastly, VR scenarios can be designed, by way of interactivity, to give patients an element of control and ownership over their surroundings, and as a result a sense of agency within the experience (Ewalt, 2018). The resultant collaborative exploration of this alternative world may be able to foster a better sense of equality by disrupting the therapist-patient hierarchy (Wrzesien et al., 2011).

Self-Efficacy

One of the key roles of preparation sessions in PP is to promote a non-avoidant attitude, particularly to challenging components of the psychedelic experience (Mithoefer et al., 2008; Davis et al., 2020). A mindset that welcomes challenging thoughts and emotions, rather than avoiding them, determines the depth of the psychedelic experience and subsequently its therapeutic impact (Studerus et al., 2011; Carbonaro et al., 2016; Haijen et al., 2018; Roseman et al., 2018).

VR has been shown to help patients overcome the fear of sharing their deepest, most disturbing thoughts, even when they are unwilling to discuss them directly with their therapist (Maples-Keller et al., 2017; Prudenzi et al., 2019). Following a single VR thought-defusion session, clients reported significant improvement in negativity, conviction and discomfort related to a patient-specific disturbing thought (Prudenzi et al., 2019). VR therapies are also thought to facilitate an increase in self-efficacy and a decrease in negative self-statements (Meyerbröker and Emmelkamp, 2008), giving patients a sense of agency in coping with negative self-referential thoughts. As such, VR can be used during the preparation phase to strengthen self-efficacy in confronting difficult thoughts or emotions (Premkumar et al., 2021), thus promoting the ability to surrender to challenging experiences as they occur.

MODELS OF INCORPORATING VIRTUAL REALITY INTO PSYCHEDELIC-ASSISTED PSYCHOTHERAPY

Based on the presented parallels in functional properties of VR and psychedelics, we suggest potential methods of VR application in a PP protocol, which fall into four categories: expansion, transition, cohesion and rescue.

Expansion

The outcomes of PP capitalize on the combined effectiveness of all its elements, from preparation, through dosing, to integration and beyond; VR is suitable for incorporation into any of these phases.

Firstly, adequate preparation preceding the psychedelic experience is necessary to solidify intention for the upcoming psychedelic journey and prepare clients for unusual psycho-emotional or bodily sensations that may occur (Carhart-Harris et al., 2018). While those sensations are often discussed during preparation sessions, current protocols have limited means of meeting the need for experiential exploration (Guss et al., 2020). To bridge this gap, VR scenarios can be used to practice an ability to achieve an ASC and promote a sense of ease around obtaining and experiencing those states, including but not limited to perceptual alterations (Suzuki et al., 2017). Additionally, VR has been shown to be highly effective in optimizing psycho-emotional processes that also play a role in the phenomenology of the psychedelic state, such as psychological flexibility (Davis et al., 2020; Pinilla et al., 2020; Watts and Luoma, 2020), for example *via* challenging participants to control their impulsivity and sustain attention in gaming environments (Blandón et al., 2016) or by introducing positive changes in the VR's storyline in response to positive changes in participants' affect (Cavazza et al., 2014). By repeatedly inducing meditative-like or psychedelic-like states during the preparation phase, for example with hypnotic audiovisual elements or a visually engaging guided meditation program, VR can be utilized to prime occurrences of expanded states of consciousness prior to dosing. After a more relaxed, contemplative or non-ordinary state is reached, VR scenarios can facilitate psychological flexibility training, for example by defusing abstract thought representations of patient-identified barriers, such as loss of control, that could obstruct complete surrender into the psychedelic experience. In turn, this may encourage greater openness in approaching unfamiliar, psychedelic-induced psycho-emotional experiences.

Secondly, the depth and the content of the acute psychedelic experience during the dosing session is of particular importance to the outcomes of therapy (Studerus et al., 2011). When profoundly meaningful, those experiences have been reported to be one of the most or the single most influential experience of one's life (Griffiths et al., 2006), and have been proposed to have the potential to lead to pivotal changes in one's feelings, attitudes, behaviors and even personality traits (Brouwer and Carhart-Harris, 2021). Given that psychedelic effects display a remarkable response to external triggers (Kaelen et al., 2018), a supportive, spiritual, or inspiring setting is far more likely to encourage a ME than clinical or laboratory environments (Strassman, 2000; Hartogsohn, 2017). Sensory stimulation with music has also been shown to be capable of evoking meaningful therapeutic experiences during dosing (Kaelen, 2017). The most effective auditory stimuli during the peak phase of the psychedelic experience have been described as homogeneous, with static dynamics, unrecognizable instruments, with regular and consistent phase structure and mostly cyclical compositional form (Barrett et al., 2017). Given the ability of VR to create any environment that can be imagined (Quesnel and Riecke, 2018), its application has unsurprisingly been uniquely

successful at creating immersive mystical, spiritual or awe-evoking scenarios (Gallagher et al., 2015). Such models could be harnessed while drug effects last, to construct an optimal setting that increases the chances of inducing a mystical-type experience. On the other hand, any setting provided for the participant during the dosing session may detract from the innately derived healing pathway or even highjack the experience. VR may be best introduced in protocols that already rely on a form of engagement with the external world during dosing, for example protocols that involve nature immersion or group interaction. Within such therapeutic frameworks, VR's unlimited potential for setting design could be leveraged to provide unique, awe-evoking models, for example, of deep space or unreachable natural landscapes. These could be paired with appropriate auditory stimuli, such as solar system sonification (Tomlinson et al., 2017) or a recording of ocean waves (Erich, 2006), thus unifying the visual and auditory stimuli into a congruent whole. Other designs may include personally meaningful links to tribal or spiritual practices or places of worship, paired with, for example, ritualistic shamanic drumming (Bensimon et al., 2008).

Lastly, the noetic quality of ASC experiences is often at odds with the familiar sensations characteristic of the normal, wakeful consciousness, and is therefore difficult to assimilate into daily life (Kotler and Wheal, 2017), posing a challenge for integration (Guss et al., 2020; Callon et al., 2021). During acute drug effects, communication, especially verbal, can be unappealing, lacking a cohesive narrative, or functionally impossible (Neitzke-Spruill, 2019). Insights that appear obvious and profound during the psychedelic state can also become less clear even shortly after the experience concludes. The ineffable nature of the psychedelic experience may explain why current integration procedures, where recall is based largely on verbal exchange with the therapist (White, 2007), find themselves limited. Instead, the evidence of beneficial outcomes of meditation and spiritual practices on outcomes of PP points to an important role of non-verbal practices in mediating integration (Cohen, 2017; Smigielski et al., 2019a). VR presents as a uniquely suited medium to reliably initiate ASC experiences during the integration process, thus allowing exploitation of their beneficial characteristics, such as broadened awareness or mindful presence (McPeake et al., 1991; Vaitl et al., 2005). If continuity is maintained between VR models used in conjunction with the psychedelic substance and those applied during the integration process, VR may also be able to facilitate greater recall of psychedelic experiences. For example, if a specific natural landscape accompanied by appropriately paired musical sounds (Barrett et al., 2017) is applied during the dosing session, introduction of that same scenario during integration may bring back memories, emotions or insights that were present during the psychedelic experience. Unfortunately, not all reinforcement of memories is beneficial (Doss et al., 2018a, 2020) and any stimulus that is used to trigger recall of the psychedelic experience puts the participant in danger of having false or negative memories reinforced. Additionally, whilst VR's capacity to increase recall can be advantageous, it also means that extra care is necessary around its application during integration, to minimize the risk of inducing a vulnerable, challenging or anxious mindset.

Transition

The effects of most psychedelic drugs do not emerge nor dissipate rapidly, but rather follow parabolic-like changes in intensity (Majić et al., 2015), starting with a slow onset (*pre-peak phase),* followed by the core of the experience (*peak phase*), and ending with a gradual resolution (*post-peak phase*; (Fox et al., 2018). A latency period follows consumption of a psychedelic substance, after which subjective effects begin to appear, including changes in arousal and perception (Hollister, 1984; Carhart-Harris et al., 2012). Those initial changes may be stressful or anxiety provoking (Hollister, 1984), prompting participants to consciously oppose or subconsciously disengage from deeper immersion into the psychedelic state. This stressful response, together with disruptions in thought that emerge during the pre-peak phase, may also lead to loss of cognitive focus on the intention, which is often essential to reaping full benefit from the remaining part of the experience (MacLean et al., 2011; Haijen et al., 2018). It can be argued that with appropriately designed environments, cues or symbols, VR can gently nudge the attention back to the intention, for example by offering a model that centers around a personalized, patient-designed totem. Such totems can be constructed as a multi-sensory experience, combining visual and auditory elements that are personally significant in an attempt to activate or intensify emotions, thoughts and memories. The audiovisual content may be created to represent a sense of journey, expanding on one of the primary utilities of music in PP, the provision of a sense of guidance (Kaelen, 2017). This process of personalization would play a critical role in accounting for the inter-person variability in individual intentions and in avoiding misdirecting the experience. Nonetheless, such explicit representations may still be inadequate for a construct as ineffable as intention. Therefore, the use of VR during the pre-peak phase may be best reserved for those struggling to utilize their intention as guidance, for example participants who resist the effects of the psychedelic substance or get lost in a cognitive loop. In such cases, VR also offers mild stimulation to maintain alertness and keep focus on the present moment (Seabrook et al., 2020) whilst displacing familiar cues from the treatment setting, that may be distracting or negatively triggering, thus supporting the state of relaxation (Seabrook et al., 2020). Thereby, application of VR during the onset of an ASC can reinforce the intention and encourage a deeper immersion into the psychedelic experience among participants who have previously displayed difficulty in this regard.

When the effects of the psychedelic substance begin to wane, during the so called "resolution period," psychedelic experiences still echo vividly whilst patients slowly begin to reconnect with the external world (Fox et al., 2018). They may begin to vocalize the contents of their antecedent psychedelic experience in the process referred to as "the first narrative" (Guss et al., 2020), which is often disordered but revelatory for patients. In some models of psychotherapy, the first narrative is explored freely, without explicit guidance from the therapist (Mithoefer et al.,

2008; Guss et al., 2020). While holding an open dialogue around the psychedelic experience may present a challenge for therapists (Johnson et al., 2008), a large number of patients naturally gravitate toward VR for its comfortable and less confrontational nature than face to face therapy (Garrett et al., 2017; Riva et al., 2019). What is more, VR provides a wide range of expressive tools to communicate with the therapist, without having to rely on language (Hacmun et al., 2018; Kaimal et al., 2020). Compared to traditional, two-dimensional art, creative expression such as painting, modeling or designing is less inhibited in VR, challenges familiar modes of perception and activates full sensory engagement (Kaimal et al., 2019; King et al., 2019). As such, VR allows a space that can be used to explore and consolidate psychedelic experiences before they need to be shared, for example *via* creating representations of thoughts, insights or emotions with expressive art tools, personalized spatial design of the VR model, or intentional use of symbolism. VR could serve as a physical representation of a memory library, where any information which seems of importance during the resolution period is recorded visually or verbally or both. Such VR models should be personalized and interactive, allow a large degree of flexibility, and ideally be built up over numerous sessions. VR may serve as a blank canvas, with a multitude of available elements that can be used to build personally meaningful contexts. Audio input could be adapted to channel appropriate emotional sentiment, for example grief or hope, drawing on music's capacity to increase therapeutic engagement by reflecting autobiographical and personally significant content (Kaelen, 2017). Such individually designed models can then be utilized during the integration process, to further explore and discuss the elements that were already established, while adding new insights or actionables, expanding and reconfiguring the memory library throughout the integration phase. However, any tools used to deepen the memory of an experience can affect the process of memory formation and introduce the risk of consolidating a false narrative (Doss et al., 2018b). Other concerns include the following: VR may prove overly stimulating and act as a distractor rather than an aid in recounting or interpreting the ineffable experience; the virtual aesthetic may be at odds with the internal experience and therefore impair the process of self-discovery; predetermined VR input may disengage the participant and deprive the participant of a sense of agency. To mitigate this, VR scenarios used at this point in the dosing sessions should be characterized by a large degree of flexibility and responsiveness, to allow for a participant-driven process of assembling the VR model from within the VR space. VR may best be treated as an advanced tool for self-expression, with the immersive world created by the participant instead of for the participant.

Cohesion

Therapeutic sessions that revolve around the novel and impactful nature of the psychedelic experience require a clear and receptive mindset, that is in contrast to the occupied and distracted character of day to day cognitive functioning (Davis et al., 2020). Thanks to its unique ability to act as a buffering tool and promote the state of relaxation and mindful presence, VR can aid the process of transition from daily life to the therapeutic setting (Chandrasiri et al., 2020; Seabrook et al., 2020; Riches et al., 2021). Immersive and deeply engaging VR environments isolate one from the distractions of the external world, promote detachment from familiar temporal and spatial reference points, and ground the attention in the here and now (Seabrook et al., 2020). Additionally, contextually rich models that are created in VR can be reapplied in precisely the same manner each time (Maples-Keller et al., 2017), including nuanced factors such as time of day and natural lighting conditions, that cannot be accounted for in real-life environments. Through such repeated use, the sense of presence and relaxation becomes more pronounced and easier to achieve with each session (PeÒate et al., 2008). Scenarios that promote relaxation, mindful presence and buffering often use serene man-made spaces (Järvelä et al., 2021), nature immersion (Liszio et al., 2018), or outer space models (Chirico et al., 2016). These examples are predominantly non-directive, characterized by low to medium intensity stimuli, with wide focal points that require minimal focus. Perceived continuity across phases may be achieved not only by repeated use of the same scenario, but also by the way of a continuous theme (e.g., a forest), repetition of a key object (e.g., a noticeable large oak tree), or the participant playing a familiar role in each experience (e.g., going on a walk in the landscape). These familiar, reliable cues can be returned to at any time (Repetto et al., 2013), also between formal integration sessions (for example during challenging moments when the therapist is not immediately available) or once the integration process concludes, in order to prolong treatment effects *via* self-practice. Ideally, VR scenarios used for self-practice should maintain continuity with VR models used during dosing, whilst building on the goals of therapy. For example the same scenery that was applied during dosing, such as a model of a personally meaningful natural scenery, could be used as a backdrop for an interactive training program that targets a desired behavioral change such as attention training (Li et al., 2020). Interestingly, VR therapies have one of the highest compliance rates (Thielbar et al., 2020) and can significantly improve adherence to other treatments when used as an adjunct to therapy (Navarro-Haro et al., 2019), suggesting that incorporating VR into PP protocols may make participants more willing to continue integration in the form of self-practice. What is more, VR's capacity to reduce physical discomfort and pain (Hoffman et al., 2011; Garrett et al., 2017), and to distract from unwanted symptoms, for example addiction withdrawal (Goldenhersch et al., 2020), makes it particularly promising for clients who experience challenging psychedelic episodes, which may discourage them from revisiting these during the integration and self-practice sessions. Lastly, the process of self-practice does not need to be restricted to the laboratory, clinical or retreat environments (Bell et al., 2020), allowing a continued integration to take place at a local VR studio, VR clinic, or even at home, thanks to increasingly affordable technological advancements in the field.

Rescue

Challenging experiences seem to play an important role in the psychedelic experience (Johnstad, 2021). Immersing in them instead of avoiding them seems to be the most effective way to diminish the anxiety or panic that they may otherwise

cause and to extract the maximum benefit from the integration process (Carbonaro et al., 2016). Conversely, resisting the difficult experience could obstruct the therapy's beneficial effects, impact the resolution of the issue and catalyze the progression from a challenging experience to an adverse effect (Vollenweider and Kometer, 2010). Therapists face difficulty in distinguishing when they should encourage leaning into that challenge, and when it may become detrimental to the participant and/or the therapist (Carbonaro et al., 2016). Currently, no tool exists that would be capable of terminating a potentially adverse progression both rapidly and transiently. One technique utilized, taking blindfolds off and performing relaxation exercises or similar, is a transient but not a reliable method. On the other hand, pharmacological interventions, like benzodiazepines, put an end or create an irreversible disruption to the experience and as a result, any therapeutic effects (Rey et al., 1999; Lerner et al., 2003; Bounds and Nelson, 2020).

In situations that impose acute emotional strain, VR is significantly more reliable at overriding stress responses than current alternative methods, including two-dimensional visual displays of similar scenarios (e.g., Riches et al., 2021). When applied during an acutely stressful situation, VR has already been shown to lead to immediate and significant lowering of stress levels, marked by changes in heart rate variability and cortisol levels, as well as significant improvements in subjective measures of anxiety and affect (Liszio et al., 2018). The strongly absorbing nature of immersive VR environments that are designed to act as an immediate anxiety relief (Valtchanov, 2010; Yu et al., 2020), offer a competing stimulus (Wiederhold et al., 2014; Nordgård and Låg, 2021) and may act as a sobering tool during an over-challenging or otherwise psychologically detrimental psychedelic experience. Even when not utilized, the knowledge that VR is available as an immediate rescue tool may act as a safety net for the participant, aiding the sense of relaxation, trust and surrender into the experience.

To act as a rescue tool, the VR scenario needs to compete with the strongly engaging inner experience. Therefore, a rescue VR tool should be characterized by a very rich contextual design; immersive sensory stimuli; dynamic, attention-demanding content and an interactive component, closely resembling a typical gaming environment. To act in opposition to the emotionally engaging therapeutic process, the audio content of a rescue VR scenario should also contrast any musical input applied up to that point. VR will thus act as a purposeful distractor from the internal experience, possibly changing the quality of the experience dramatically and irrevocably. Therefore, it is critical that the decision to use it is not made lightly.

LIMITATIONS OF VIRTUAL REALITY AND GUIDELINES FOR SAFETY

Over-Stimulation

Virtual reality allows a wide range of design alternatives, with an abundance of lights, colors, shapes, motion features and interactivity options to select from Ewalt (2018). Some designs can be strongly stimulating, even to the point of visual discomfort (Saredakis et al., 2020), and the potential risk of over-stimulation (and in extreme cases, seizures) has been raised by VR providers (Oculus, 2020). Care needs to be taken around combining any powerful, external stimulus with the already intense sensory experiences brought on by a psychedelic substance. VR content provided to participants should avoid sudden changes in visual patterns, extremes of saturation or brilliance and spatial disorientation. Additionally, although adverse events of VR that involve seizures have not been documented, even in people with known photosensitive epilepsy (Tychsen and Thio, 2020), protocols that combine the use of VR and psychedelics should exclude individuals that may be at risk of epilepsy, until there is greater understanding of this potential adverse effect.

Accidental Exposure

A traumatic response can be triggered unexpectedly by any relevant cue (Van der Kolk, 1998). Highly immersive VR environments can easily act as a trigger, if their content is directly related to the traumatic experience (Difede, 2016; Rizzo et al., 2017), particularly during the vulnerable state induced by psychedelic substances (Carhart-Harris et al., 2018). Unless exposure is the intention of treatment, the VR content needs to be examined for presence of any cues that have personal resonance or could be associated with traumatic experiences, both at a generic and individual level. Generically, this should be achieved by considering and maintaining care around common triggers, for example heights, dark spaces, narrow or enclosed spaces, scenarios in or under water, etc. At an individual level, key triggers need to be discussed with the participant during preparation and, if possible, the VR scenario should first be examined when sober, if it is later to be used when under the influence of the psychedelic substance.

Leading

The expectancy effects associated with psychedelics mean that selection of VR environments will have a strong impact on the psychedelic journey (as do environments in the real world; Carhart-Harris et al., 2018). Therefore, introducing any VR input, especially immediately prior to dosing or during the pre-peak or peak phases, must be treated with utmost care. A delicate balance needs to be struck between providing mild stimuli to block distraction from mundane external realities and maintaining focus on the intention (guiding), whilst avoiding hijacking of the experience and dictating its content (leading). The use of symbols and cues, for example to strengthen the intention, if necessary, needs to be carefully weighed against the risk of overtaking/dictating the experience completely. As such, VR may be best avoided as the first line of guidance in the particularly vulnerable parts of the journey (pre-peak and peak); instead, being better suited for patients who received psychedelic treatment previously, but gained little benefits from it, or relapsed. Limited response to PP may be caused by avoidance, anxiety or lack of clarity around intention (Carbonaro et al., 2016; Davis et al., 2020), which are the areas of care that VR may be able to assist with.

Distraction

In many PP protocols, external stimulation during the dosing session is kept to minimum, and the participant is encouraged to focus their attention inward, as any sensory input may cause disruption to the unfolding internal narrative. Therefore, potential benefits of utilizing VR during dosing, including peak and post-peak phases, have to be carefully weighed against potential disadvantages. There is currently no evidence to suggest that VR may be of added benefit during the peak phase. VR may be best reserved for the post-peak phase of the experience, when most of that internal narrative has unfolded. Nonetheless, it is critical to avoid overly leading this process as an active engagement with VR may lead to some participants feeling urged to verbalize their experience before they are ready to do so. This may lead to vague or even misguided conclusions therefore the process of recall and sense making should not be rushed. Additionally, explicit imagery or journey-based scenarios may replace the internal insights. The use of personalized, patient-driven design is therefore critical. Lastly, as outlined in the rescue scenario, interactive VR content is likely to compete with the effects of the drug and should only be used as a rescue function. Otherwise, cognitive interaction, for example *via* task-oriented activities (da Costa et al., 2021) or physical interaction, for example *via* the use of controllers or real-life movement (Lee et al., 2015), may be best avoided during dosing, as these may be particularly impactful in distracting from attention to the internal state. Even in the case of intentional use of VR as a distracting stimulus, it should not be hastily applied to "rescue" participants during challenging psychedelic experiences but should be reserved for when the therapist assessment is of impending progression to an adverse experience.

Cyber-Sickness and Physical Discomfort

The physical comfort of the patient needs to be considered. VR stimulus can lead to simulator sickness symptoms, most commonly fatigue, headache and nausea, (Akiduki et al., 2003; Norman, 2018), which may be caused by poor coordination between the visual VR stimulus and the real life movement, creating the so called "sensory conflict" (Dużmańska et al., 2018; Weech et al., 2019). Although most simulator sickness symptoms are mild and resolve quickly (Nichols and Patel, 2002), they may be exacerbated by the simultaneous occurrence of gastrointestinal effects of psychedelics (Johnson et al., 2012; Reiff et al., 2020). Cyber-sickness symptoms can be mitigated with careful consideration of VR design specifications, for example: avoiding controller-based movements, minimizing gaming content in favor of scenic or minimalistic content (Saredakis et al., 2020), or maintaining an appropriate exposure time (Dużmańska et al., 2018). Finally, the head mounted visual display, technical glitches or poor visual quality of the VR model may cause some discomfort (Norman, 2018), which may be of particular relevance when under the influence of a psychedelic substance, when senses are heightened and uncomfortable bodily sensations may already be present (Reiff et al., 2020). Therefore, attention needs to be devoted to using the highest quality content and equipment as well as adjusting the VR set-up for maximum comfort of the participant, including for participants who wear glasses. Individuals with severe visual impairment or who wear large glasses that cannot be fitted into the VR headset may need to be excluded from treatment.

Resource Limitation

Introduction of VR technology into therapy requires the development of novel protocols and procedures as well as training of practitioners (McMahon and Boeldt, 2021). Therapists would be required to upskill to take advantage of VR's unique features and, more importantly, to ensure that any VR-related technological malfunctions or psychological adverse reactions are mitigated. Additionally, VR becomes a new variable that the therapist needs to control, potentially distracting them from being fully present for the patient. A large dose of comfort, familiarity and control over the VR software and hardware is required before it can be employed by the practitioner, which puts additional demand on training time and resources.

Commercial Interests

Virtual reality is currently predominantly used as entertainment technology (Cipresso et al., 2018). Its use in therapy is largely unregulated and numerous VR products that target therapeutic, or well-being applications have not been scientifically tested or validated. Such validation is of particular importance when technology is used in combination with psychoactive substances that can alter processing of external and internal stimuli as profoundly as psychedelic compounds. An increasing interest in introducing VR into PP calls for an urgent need for careful evaluation, ideally *via* a scientific, peer-reviewed process. Additionally, VR models should always be supplied with robust protocols that consider application, timing, technical requirements, mitigation of potential side effects and response to adverse events, among others.

SUMMARY

Psychedelic-assisted psychotherapy presents itself as a promising and attractive alternative to established psychiatric treatments (Nichols, 2016; Belouin and Henningfield, 2018). The recent revival in research on therapies that use psychedelics highlights a unique set of benefits, along with a unique set of challenges and limitations of this approach (Wheeler and Dyer, 2020; Williams et al., 2021). In parallel, VR is reportedly one of the most enjoyable and comfortable forms of therapy (Garrett et al., 2017), having one of the highest compliance rates and best therapeutic alliance across all forms of treatments (Meyerbröker and Emmelkamp, 2008; Wilson et al., 2008), even among individuals resistant to other treatments (Riva et al., 2019). It can be used to provide the most favorable environmental stimulus with a high level of control and thus reinforce PP with properties in which current protocols may be inadequate.

In supporting treatments that use psychedelics, VR can be utilized for its ability to:

1. Mitigate psychological side effects through enhancing the state of relaxation,

2. Help participants sustain their focus on intention by removing familiar cues that keep them tethered to their external world,
3. Encourage entering the inner world of experience by inducing a mindful presence,
4. Deepen the intensity of acute psychological and emotional states *via* simultaneous targeting of ME-evoking pathways,
5. Prime the capacity to achieve an ASC through familiarization and comfort with the ASC experience,
6. Enhance and maintain a hierarchy-free therapeutic alliance that is consistent throughout treatment,
7. Strengthen resilience and a sense of agency around facing challenging experiences.

To maximize potential benefits from profound ASC experiences, including ME, VR can be used to prime occurrences of those states by training the capacity to enter them during preparation; augment their depth and facilitate their profound emotional impact during dosing; and enhance therapeutic utility by aiding revisiting of these states during integration. When working in synergy with changing features of the psychedelic experience, VR scenarios can offer gentle guidance during the delicate process of transition from normal to altered consciousness and from altered to normal consciousness (Fox et al., 2018). When used repeatedly across multiple, different PP sessions, VR can provide continuity to the experience of treatment, from preparation to dosing, from dosing to integration and from integration to self-practice. Further, VR may extend the benefits of PP by enabling and encouraging deeper exploration of insights that emerged during integration, and inspire continued, self-paced practice of beneficial activities, for example meditation or relaxation (Mithoefer et al., 2008). Last but not least, the VR world is a safe, comfortable and intuitive intervention that, when needed, can temporarily distract from an overly challenging or adverse experience, or disrupt the process of being stuck in an experiential loop without terminating treatment.

Finally, it is noted that special care needs to be taken when using VR as a part of psychedelic psychotherapy, particularly around not introducing potentially disturbing or traumatic triggers, distracting from the inner experience, leading the narrative of the psychedelic experience or providing overstimulating or cyber-sickness inducing content. We recommend that any VR scenario that may be introduced into PP is developed in accordance with a robust protocol, both of which are scientifically validated and accompanied by thorough training of any practitioners involved in therapy.

CONCLUSION

We described features of VR that make it a promising candidate as a complementary moderator of therapies that utilize psychedelic substances. Whilst these features are yet to be empirically explored in relation to psychedelics, we propose a range of potential synergistic applications of VR and PP and evaluate their individual advantages and disadvantages aiming to inspire an informed research practice in this emerging field. We suggest that a comfortable, adaptable, and reliable VR setting may support treatment with psychedelics *via* mitigating adverse psychological states, catalyzing the effects of each phase of the psychedelic experience and building a cohesive trajectory for the entire PP. Further research could explore the potential application of VR to: expand and deepen mystical and peak experiences; guide transition into and out of an altered state of consciousness; promote a continuous, multi-sensory experience through the entire psychedelic journey; and offer a non-invasive mitigation of adverse events. These potential synergistic applications need to be empirically validated in the view of potential limitations prior to commercial application.

AUTHOR CONTRIBUTIONS

AS was in charge of overall direction and planning of the manuscript, collected, analyzed, and synthesized the evidence, created the first and main conceptual themes of the manuscript, and drafted the first version of the manuscript, that was then further re-examined conceptually together with PP, as new evidence was explored. AS and PP explored those conceptual themes and prepared the manuscript outline. PP refined the manuscript and the language. LD was responsible for supervising the process and critical revision of the manuscript. All authors contributed and approved the final version of the manuscript.

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Conflict of Interest: AS and PP are co-founders of Enosis Therapeutics Pty. Ltd., a self-funded commercial venture that specializes in the design of VR environments for the psychedelic experience.

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frontiers in Psychology

HYPOTHESIS AND THEORY
published: 25 March 2022
doi: 10.3389/fpsyg.2022.868103

Toward Synergies of Ketamine and Psychotherapy

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Ketamine is a dissociative drug that has been used medically since the 1970s primarily as an anesthetic agent but also for various psychiatric applications. Anecdotal reports and clinical research suggest substantial potential for ketamine as a treatment in conjunction with psychological interventions. Here, we review historical and modern approaches to the use of ketamine with psychotherapy, discuss the clinical relevance of ketamine's acute psychoactive effects, propose a unique model for using esketamine (one isomeric form of ketamine) with Acceptance and Commitment Therapy (ACT), and suggest considerations for moving medication-assisted psychotherapy forward as a field.

Keywords: ketamine, esketamine, therapy, psychotherapy, psychedelic, dissociation, ACT

OPEN ACCESS

Edited by:
Maria Beckman,
Karolinska Institutet (KI), Sweden

Reviewed by:
Ämma Tangen,
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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *02 February 2022*
Accepted: *25 February 2022*
Published: *25 March 2022*

Citation:
Mathai DS, Mora V and Garcia-Romeu A (2022) Toward Synergies of Ketamine and Psychotherapy. Front. Psychol. 13:868103. doi: 10.3389/fpsyg.2022.868103

INTRODUCTION

Ketamine emerged from the study of phencyclidine (PCP) derivatives suitable for anesthetic use in humans, and its discovery in 1962 is attributed to Parke-Davis Labs and Dr. Calvin Lee Stevens, a professor of organic chemistry at Wayne State University (Domino et al., 1965). Early clinicians recognized ketamine's dreamlike and hallucinogenic properties, experienced by patients as feeling "disconnected" from their environment, and leading to its classification as a "dissociative anesthetic" (Domino et al., 1965; Reier, 1971). The subjective effects associated with ketamine were observed to be "pleasant" (Domino et al., 1965), and investigators soon began to consider its broader value as an antidepressant and psychotherapeutic agent (Yensen, 1973; Fontana and Loschi, 1974; Sofia and Harakal, 1975). The drug has since been explored for a growing number of psychiatric applications both as a standalone medication and in combination with supportive interventions.

A compelling and transdiagnostic body of clinical research has emphasized the use of ketamine in combination with psychotherapy for mental health conditions. While psychotherapy is not easily defined, it has been reasonably described as an interpersonal intervention that relies on repeated encounters, a healing relationship, and a particular explanatory model, all within a structured therapeutic frame (Greenway et al., 2020). Psychotherapy may be simplified even further, to denote any "communication between patients and therapists that is intended to help people (American Psychological Association, 2017)." These definitions will be used hereafter to discuss a range of psychotherapeutic modalities involving ketamine administration.

The idea of harnessing psychotherapy with pharmacotherapy has been considered before. The additive and synergistic effects of combining conventional antidepressants and psychotherapy, for example, are well-established (Cuijpers et al., 2014; Dunlop, 2016). Some precedent even exists for the approval of drug-therapy combinations by regulatory bodies such as the U.S. Food and Drug Administration [FDA; 21 CFR 201.57 (c)(2)(i)(A), 2022]. Medications such as

naltrexone extended-release injectable suspension for alcohol and opioid dependence, bupropion hydrochloride extended-release for smoking cessation, and buprenorphine sublingual tablets for opioid dependence are all labeled for use in conjunction with therapy. This is also expected to be the case if psilocybin and MDMA are approved as psychiatric treatments for major depression and post-traumatic stress disorder (PTSD), respectively (Yazar-Klosinski and Mithoefer, 2017; Johnson et al., 2018).

Combination strategies serve a variety of purposes, driven largely by the limitations of single-modality interventions. These strategies serve to address treatment non-response, residual symptoms, and relapse and recurrence involving psychiatric illness (Dunlop, 2016). Others have further emphasized that approaches to pharmacotherapy that include psychotherapy have the potential to improve psychological flexibility, quality of life, and overall functioning, beyond symptom reduction, in ways that are valuable to patients (Kamenov et al., 2017; Watts and Luoma, 2020). Integrated approaches may also promote drug safety and tolerability. For instance, a therapy-oriented approach to psilocybin administration in research settings is thought to mitigate the psychological risks that are possible with treatment (Johnson et al., 2008). The use of psychotherapy with ketamine could similarly address treatment risks, for example, by allowing for drug-sparing treatment paradigms that are of public interest and decrease the likelihood of tachyphylaxis (Mathai et al., 2020, 2021).

What is perhaps most unique to the use of ketamine as a therapeutic adjunct is its status as a highly psychoactive, medically legal, and reliably perplexing agent. Here, we review historical and modern approaches to the use of ketamine with psychotherapy, discuss the clinical relevance of ketamine's acute psychoactive effects, propose a unique model for working with esketamine (the S-enantiomer of ketamine), and make suggestions for moving forward as a field. We emphasize a conceptual understanding of ketamine and psychotherapy, rather than the specific parameters of treatment administration.

A BRIEF HISTORY

The first known uses of ketamine as a therapeutic adjunct date back to the early 1970s, soon after its approval as an anesthetic agent. In Mexico, the psychiatrist Salvador Roquet discovered that subanesthetic doses of the drug occasioned mental states that could be combined with psychoanalytical techniques and indigenous healing practices in an approach he called "psychosynthesis" (Yensen, 1973; Wolfson, 2014). His pioneering and controversial work incorporated the use of multiple psychedelic substances and "sensory overload" in group treatment settings with the goal of producing, and then processing, extreme psychological experiences. Through this method, Roquet believed that patients could confront existing psychological conflicts and achieve emotional catharsis.

Around the same time, physicians in Southern Iran were exploring similar qualities of ketamine in the individual treatment of hospitalized psychiatric patients (Khorramzadeh and Lotfy, 1973). Enayat Khorramzadeh and Atta Ollah Lofty observed that ketamine facilitated patients' ability to engage in an "abreactive" psychotherapy process involving the recollection and processing of traumatic memories, which was ultimately associated with enduring relief of depression, anxiety, and other psychiatric symptoms (see **Table 1** for characteristics of this and other research trials involving ketamine and psychotherapy). They later conducted a follow-up study examining how dimensions of personality contributed to the psychoactive effects of ketamine and found that elements of "extraversion," "neuroticism," and "psychoticism" could reliably predict drug experiences, suggesting the importance of nonpharmacological factors in treatment (Khorramzadeh and Lotfy, 1976).

Several other significant explorations of ketamine as a therapeutic agent occurred through the 1970s and 1980s (Lilly, 1972, 1978; Fontana and Loschi, 1974; Sappington et al., 1979; Grof, 1980; Golechha et al., 1985), though the single most comprehensive body of clinical research in this area can be credited to the Russian physician, Evgeny Krupitsky. Krupitsky first used ketamine in a form of behavioral psychotherapy in the former Soviet Union in 1985 (Kolp et al., 2014). In his earliest studies, ketamine was combined with other agents to induce unpleasant psychedelic experiences that were associatively linked with alcohol toward the goal of decreasing alcohol use (Krupitsky et al., 1992; Sivolap and Savchenkov, 1994). Krupitsky eventually realized that patients benefited similarly from positive, transcendent experiences while on ketamine and shifted from a model of aversive conditioning to one informed by existential and transpersonal psychology. This model has been described as Ketamine Psychedelic Psychotherapy (KPP) or Ketamine Psychedelic Therapy (KPT), and was used successfully in the treatment of alcohol and opioid use disorders (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002, 2007). Moreover, these studies indicated that ketamine could be combined with psychotherapeutic interventions to produce meaningful and enduring changes in psychological attitudes, concepts of self, and overall functioning. Krupitsky's research was ultimately shuttered by the rescheduling of ketamine in Russia amidst growing concerns around its recreational use (Kolp et al., 2014).

MODERN APPROACHES

Widespread psychiatric interest in ketamine accelerated with positive findings from the first randomized controlled trial (RCT; Berman et al., 2000) and a larger replication study (Zarate et al., 2006) of ketamine as a standalone treatment for depression. These and most subsequent academic investigations have assumed a "biochemical paradigm" (Bennett, 2019), wherein the therapeutic benefits of ketamine are attributed to a pharmacologic effect independent of perceived psychoactivity or supporting interventions. This paradigm is, for example, evident in current FDA-approved uses of esketamine as an antidepressive and antisuicidal agent (McIntyre et al., 2021).

However, in the mid-2000s, it became apparent that some community practitioners were continuing to work with ketamine as had been done historically, using it as a tool to facilitate psychological exploration and healing (Kolp et al., 2006, 2007;

TABLE 1 | Characteristics of studies reviewed using ketamine and psychotherapy.

Study	N	Design	Treatment population	Drug parameters	Psychotherapy parameters
Adams et al. (2017)	1	Case study	Refractory obsessive compulsive disorder	50 mg IN ketamine; twice weekly for 4 weeks	16-week program of inpatient/outpatient ERP; for inpatient weeks 3–6, therapy was accompanied by twice-weekly administration of ketamine; unclear timing of therapy relative to ketamine administrations
Azhari et al. (2021)	8	Uncontrolled trial	Cannabis use disorder	1–2 IV ketamine infusions over 4 weeks; Infusion 1: (0.71 mg/kg over 52 min) on week 2; Infusion 2 (non-responders): (1.41 mg/kg over 92 min) on week 4	6-week program of MET and MBRP with therapy occurring outside of ketamine administrations (i.e., MET therapy on the day before the infusion and the afternoon of the infusion)
Dakwar et al. (2019)	55	Randomized controlled trial	Cocaine use disorder	Treatment group: Single IV ketamine infusion (0.5 mg/kg over 40 min); Control group: Single IV midazolam infusion (0.025 mg/kg over 40 min); infusions on day 2	5-week inpatient/outpatient program of MBRP; 1 MBPR session daily during first 5 days; followed by 8 sessions of MBRP outpatient (twice-weekly for 4 weeks); Patients received IV infusion on day 2 of inpatient stay; therapy occurred outside of ketamine/ midazolam administration (i.e., MBRP 2 h post-infusion)
Dakwar et al. (2020)	40	Randomized controlled trial	Alcohol use disorder	Treatment group: Single IV ketamine infusion (0.71 mg/kg over 52 min); Control group: Single IV midazolam infusion (0.025 mg/kg over 52 min); infusions on week 2	5-week outpatient program of MET; 6 sessions of MET over 5 weeks (1 session/ week); therapy occurred outside of ketamine/ midazolam administration (i.e., MET session provided 24 h after infusion)
Dames et al. (2022)	94	Observational study	Mixed	3 sessions of PO or IM ketamine (during weeks 4, 5, and 7): either PO or IM ketamine for session 1 (dose unspecified); IM ketamine (1–1.5 mg/kg) for sessions 2 and 3	12-week treatment program including group meetings and KaT with model of preparation, dosing, and integration; therapy occurred outside of ketamine administration (i.e., "initial sharing" began after 90 min, and post-KaT group integration sessions occurred within 36 h)
Dore et al. (2019)	235	Observational study	Mixed	SL, IM, (or both) ketamine; Average dose range was 200–250 mg SL, and 80–90 mg IM	Outpatient KAP with sessions typically 2 weeks apart, or more frequently depending on acuity; number of sessions ranged from 1–25, which were spread over variable time periods from initial session, to visit evaluation, to termination where applicable; therapy occurred before, during and after ketamine administrations
Grabski et al. (2022)	96	Randomized controlled trial	Alcohol use disorder	Treatment group: 3 weekly IV ketamine infusions (0.8 mg/kg over 40 min); Control group: 3 saline infusions; Infusions occurred at visits 2, 4, and 6 spaced 1–3 weeks apart	Treatment group: 7 sessions of MBRP; Control group: 7 sessions of AE; therapy began at visit 2 and continued for the subsequent six visits; therapy occurred outside of ketamine administration (i.e., infusion was always preceded by MBRP or AE and followed by another session about 24 h later)
Halstead et al. (2021)	1	Case study	Persistent depressive disorder and treatment-resistant post-traumatic stress disorder	SL ketamine (150 mg); 4 administrations over 13 days	13-day intensive outpatient therapy program consisting of MBCT and FAP; therapy occurred before, during and after ketamine administrations
Khorramzadeh and Lofty (1973)	100	Non-randomized controlled trial	Mixed	IV ketamine infusions in 3 dose ranges: (1) 0.2–0.3 mg/kg; (2) 0.4–0.6 mg/kg; (3) 0.7–1.0 mg/kg; unknown duration of infusion	"Abreactive" psychotherapy during drug administration
Krupitsky et al. (1992)	186	Randomized controlled trial	Alcohol use disorder	Treatment group: Single co-administration of aethimizol (1.5% 3 ml, IM), bemegride (0.5% 10 ml IV), and ketamine (3 mg/kg, IM); Control group: Conventional aversive therapy without ketamine administration	ACA method of alcoholism treatment with therapy occurring before, during, and after ketamine administration

(Continued)

TABLE 1 | Continued

Study	N	Design	Treatment population	Drug parameters	Psychotherapy parameters
Krupitsky and Grinenko (1997)	111	Non-randomized controlled trial	Alcohol use disorder	Treatment group: Single co-administration of aethimizol (1.5% 3 ml, IM), bemegride (0.5% 10 ml, IV), and ketamine (2.5 mg/kg IM); Control group: Conventional therapy for alcoholism without ketamine	KPT method of treatment with therapy occurring before, during, and after ketamine administration
Krupitsky et al. (2002)	70	Randomized controlled trial	Heroin use disorder	Treatment group: Single IM ketamine injection (2 mg/kg: hallucinogenic dose); Control group: Single IM ketamine injection (0.2 mg/kg: non-hallucinogenic dose)	KPT method of treatment with therapy occurring before, during, and after ketamine administration
Krupitsky et al. (2007)	59	Randomized controlled trial	Heroin use disorder	Treatment group: 3 IM ketamine injections (2 mg/kg); 1-month intervals between doses; Control group: Single IM ketamine injection (2 mg/kg)	Addiction counseling and KPT method of treatment with therapy occurring before, during, and after ketamine administration
Ocker et al. (2020)	1	Case study	Opioid medication dependence with opioid-induced hyperalgesia	5-day (inpatient) continuous IV infusion of ketamine in combination with a multimodal analgesia regimen; ketamine dose titrated throughout admission (0.09–0.59 mg/kg/h)	Outpatient CBT every 3–4 weeks after initial period of ketamine administration
Pradhan et al. (2018)	20	Randomized controlled trial	Treatment-refractory post-traumatic stress disorder	Treatment group: Single IV infusion of ketamine (0.5 mg/kg over 40 min); Control group: Single IV infusion of normal saline over 40 min	12 sessions of TIMBER; therapy occurred during and then after single ketamine administration
Ragnhildstveit et al. (2021)	1	Case study	Treatment-resistant bulimia nervosa	18 IV ketamine infusions (0.5 mg/kg IV over 40 min) over 3-month period	18 sessions of guided psychotherapy during ketamine administrations and preceded by 30 min of preparatory psychotherapy
Rodriguez et al. (2016)	10	Uncontrolled trial	Obsessive compulsive disorder	Single IV infusion of ketamine (0.5 mg/kg over 40 min)	10 sessions of ERP over 2-week period; therapy occurred outside of ketamine administration (i.e., after completion of single ketamine administration)
Sappington et al. (1979)	21	Randomized controlled trial	Healthy volunteers	Treatment group: IV ketamine infusion (0.1 mg/lb); Control groups: No ketamine	"Induced-anxiety" therapy focused on induction of negative affect prior to drug administrations, drug-induced relaxation, and processing with therapist
Shiroma et al. (2020)	12	Uncontrolled trial	Chronic, moderate post-traumatic stress disorder	3 IV infusions of ketamine (0.5 mg/kg over 40 min); once weekly for the first 3 weeks of treatment; unclear if IV infusions continued after week 3	10-week program of PE with therapy occurring during ketamine administrations
Wilkinson et al. (2017)	16	Uncontrolled trial	Major depressive disorder	4 IV infusions of ketamine (0.5 mg/kg over 40 min) over 2 weeks	10-week program of CBT with therapy occurring outside of ketamine administrations
Wilkinson et al. (2021)	41	Randomized controlled trial	Severe major depressive disorder and treatment-resistant depression	6 IV infusions of ketamine (0.5 mg/kg over 40 min) over 3 weeks	Treatment group: 14-week program of CBT; Control group: 14-week program of TAU; therapy occurred outside of ketamine administrations

ACA, affective contra-attribution; AE, alcohol education; CBT, cognitive behavioral therapy; ERP, exposure response prevention; FAP, functional analytic psychotherapy; IM, intramuscular; IN, intranasal; IV, intravenous; KaT, ketamine assisted therapy; KAP, ketamine assisted psychotherapy; kg, kilograms; KPT, ketamine assisted psychotherapy; lb, pounds; MBCT, mindfulness based cognitive behavioral therapy; MBRP, mindfulness based relapse prevention therapy; MET, motivational enhancement therapy; mg, milligrams; min, minutes; PO, per os; TAU, treatment as usual; TIMBER, trauma interventions using mindfulness based extinction and reconsolidation.

Early, 2014; Ring et al., 2016). A new wave of ketamine-assisted psychotherapy (KAP) began to emerge, attracting a growing network of clinicians and informed theoretically by principles of psychedelic therapy (Dore et al., 2019; Halstead et al., 2021; Ragnhildstveit et al., 2021; Dames et al., 2022). As with other psychedelic therapies, KAP emphasizes attention to "set and setting" (Dore et al., 2019) – a broad conceptualization of the nonpharmacological parameters that are thought to shape hallucinogenic drug response, such as the degree of preparation before, and the environment during, drug administrations (Hartogsohn, 2016). Administrations of ketamine within KAP follow "a dosage escalation strategy to achieve different levels of trance increasing to full out-of-body experiences" while holding central "that some degree of mind alteration is necessary for ketamine's effects (Dore et al., 2019)." This framework suggests the possibility of highly variable and dose-dependent states of consciousness induced by ketamine that represent different opportunities for therapeutic intervention (Kolp et al., 2014; Dore et al., 2019). For example, the KAP context would be compatible with both "psycholytic therapy," typically involving lower doses of psychoactive drug to facilitate the therapeutic and relational quality of ongoing psychotherapy during acute drug effects, and "psychedelic therapy," involving higher doses of drug to facilitate the occurrence and integration of profound, mystical- and peak-type experiences (Garcia-Romeu and Richards, 2018). KAP, along with early uses of ketamine in psychiatry, can then be classified as "experience-oriented" approaches to treatment, for which the subjective quality of drug effect is thought to have inherent value and be an integral part of the therapeutic process (Mathai et al., 2020). In this framework, the patient's experiences under drug effects can be considered meaningful and potentially insightful material, which can then be utilized in collaboration with the therapist to facilitate therapeutic progress.

Other recent and contrasting approaches have tended to use behavioral therapies largely outside of the period of acute drug effects (Rodriguez et al., 2016; Adams et al., 2017; Wilkinson et al., 2017, 2021; Dakwar et al., 2019, 2020; Ocker et al., 2020; Shiroma et al., 2020; Azhari et al., 2021; Philipp-Muller et al., 2021; Grabski et al., 2022). This strategy presumes that, beyond the period of its immediate psychoactive function, ketamine produces a window of enhanced neuroplasticity and other neural adaptations that facilitate cognitive and behavioral interventions (Dakwar and Nunes, 2016; Wilkinson et al., 2019; Hasler, 2020). Theoretically, drug-facilitated psychotherapy could be optimized when delivered during "critical periods" of neural development, marked by exquisite sensitivity to environmental input and potentially conducive to learning (Lepow et al., 2021). It could be argued that this "plasticity-oriented" approach is rooted most in the function of ketamine as a "psychoplastogen" – a term used to describe small molecule neurotherapeutics that produce rapid and measurable changes in plasticity after a single administration that are thought to support relatively long-lasting changes in behavior (Olson, 2018). This logic suggests the possibility of ketamine-like psychoplastogens that might enhance psychotherapeutic processes in critical periods after drug administration without the need for marked mind-altering effects (Olson, 2021). Consistent with this understanding, predominantly plasticity-oriented approaches to ketamine as a therapeutic adjunct differ from KAP in how psychological support is allocated, with relatively less emphasis on or engagement with drug-induced experiences over the course of treatment (see **Figure 1** for illustration of these models).

The "experience-oriented" and "plasticity-oriented" uses of ketamine outlined above could overlap but may be seen as portrayals of two leading theories of treatment. Though not described here, other nuanced psychotherapeutic applications

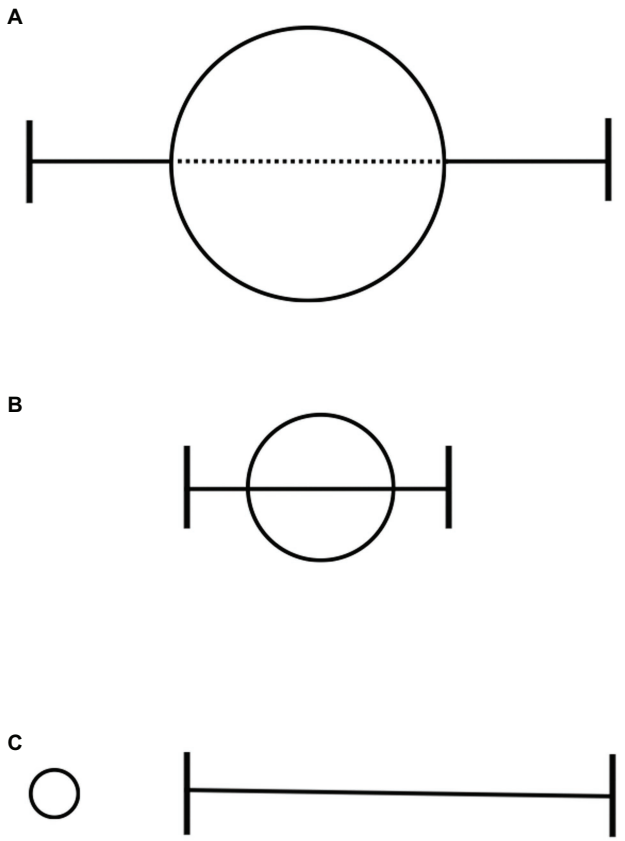

FIGURE 1 | Functional units for existing models combining ketamine with psychotherapy. Each circle indicates a single experience of ketamine, with circle size corresponding to relative theoretical emphasis on the nature of the experience. Bracketed lines are used to indicate optimal windows of psychotherapeutic intervention. **(A)** shows the strategy of high-dose "psychedelic therapy," involving significant preparation before and integration after a limited number of drug sessions, which themselves are largely inner-directed, rather than primarily relational, experiences. **(B)** shows the model of low-dose "psycholytic therapy," in which ongoing psychotherapy coincides with ketamine administration, making use of acute drug effects that are thought to facilitate the quality of therapy. The two former approaches are examples of "experience-oriented" frameworks, such as KAP. **(C)** is representative of "plasticity-oriented" strategies, wherein psychotherapy is delivered after the period of acute drug effects but within "critical periods" of neural adaptation that are thought to facilitate the uptake and efficacy of behavioral interventions.

of ketamine are emerging (Pradhan et al., 2018; Veen et al., 2018; Bottemanne et al., 2021; Bottemanne and Arnould, 2021; Muscat et al., 2021b), and novel ways of using the drug will continue to develop. For all approaches, there exist scientific questions that can engage key theoretical assumptions. For example, how do animal models of critical periods and adaptive learning inform the timing and nature of complex, idiosyncratic interventions using ketamine in humans? This research is still in its infancy. Additionally, and of particular relevance to clinicians, what is the role of the subjective ketamine experience in ketamine therapy? Current findings on this point are reviewed below.

THE RELEVANCE OF EXPERIENCE

It has been argued that no study to date has demonstrated a therapeutic effect for ketamine absent some degree of perceived psychoactivity (Dore et al., 2019). Several challenges are inherent to such an undertaking, including the experimental prospect of defining "psychoactivity," which would seemingly include experiences ranging from feeling "high," "relaxed," "connected," "happy" and "light" to the peak- and mystical-type phenomena that occur at sufficiently high doses of ketamine. A "critical test" of this question has been proposed (Yaden and Griffiths, 2021), wherein a psychedelic agent demonstrates full and lasting therapeutic efficacy when administered to individuals while unconscious and who subsequently report no memory of drug-related experience. In counterpoint, Olson (2021) draws attention to several interesting, albeit limited, studies suggesting that intraoperative ketamine may improve mood in surgical patients even when they are unconscious during drug administration (Kudoh et al., 2002; Jiang et al., 2016; Xu et al., 2017). Among issues with poor generalizability due to experimental design, it is unclear if the demonstrated effects from these studies meet criteria for "full and lasting therapeutic efficacy." More suitable investigations of the "critical test" are underway (Heifets, 2021), but in the meantime, other types of correlational data can provide insight into the relationship between subjective drug experience and therapeutic efficacy.

The acute ketamine effect for which there is the most data is "dissociation," as measured by the Clinician-Administered Dissociative States Scale (CADSS) and includes feelings such as detachment from oneself and one's environment and changes in sensory perception (Grabski et al., 2020). Several independent reviews have identified experimental evidence of a positive correlation between dissociation and antidepressant efficacy for ketamine, although this relationship has been inconsistent when examined across clinical trials (Ballard and Zarate, 2020; Grabski et al., 2020; Mathai et al., 2020). Another large post-hoc analysis of phase 3 clinical trial data found no mediating effect of dissociation on the antidepressant effects of esketamine (Chen et al., 2022). While these findings are difficult to interpret, it is notable that modern studies have classified dissociation primarily as an adverse event, suggesting that a major limitation in the predictive ability of the CADSS, and similarly utilized instruments, is prevailing research bias toward these psychoactive effects as undesirable. Most studies of ketamine have also not examined the relevance of dissociation in the context of psychotherapy.

It is nonetheless worth considering that dissociation, as a single metric and captured by the CADSS, may not be a useful predictor of the therapeutic efficacy of ketamine. Other subjective effects during drug administration, including ratings of "happiness" (Chen et al., 2020) or the sensation of "lightness" (Stocker et al., 2019) have also been associated with antidepressant benefit. Conversely, anxiety experienced during ketamine infusions appears to predict negative treatment response for depression (Aust et al., 2019). These findings require replication but together suggest that the affective quality of drug-induced experience may also be pertinent to therapeutic outcomes with ketamine. It is moreover possible that the benefits of certain subjective effects, such as drug-mediated increases in connectedness (Kolp et al., 2014; Griffiths et al., 2021; Mollaahmetoglu et al., 2021), are not fully realized in the absence of interpersonal therapeutic engagement.

Finally, it is valuable to recognize the similarities between ketamine and classic (serotonergic) psychedelics such as psilocybin and lysergic acid diethylamide (LSD), which produce overlapping subjective phenomena in spite of diverging pharmacological mechanisms of action (Bowdle et al., 1998; Studerus et al., 2010). For classic psychedelics, it is well-established that a subset of psychoactive effects, often referred to as mystical-type effects and characterized by a sense of unity, predict greater therapeutic response across a variety of conditions such as depression, existential distress, and substance use disorders (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Roseman et al., 2018). Interestingly, it has been hypothesized that the same mechanisms that drive the efficacy of these treatments may also be responsible for dose-dependent psychiatric risks, like that of psychosis (Haarsma et al., 2021). However, the relevant psychoactive effects of classic psychedelics appear to be optimized in careful experimental conditions that consider the benefit, safety, and tolerability of such (Johnson et al., 2008; dos Santos et al., 2018). While similar optimization has not been pursued for ketamine, increasing research suggests that mystical- and peak-type experiences, such as measured by the Hood Mysticism Scale (HMS) and 11D-ASC questionnaire, increase the likelihood of various therapeutic benefits (Dakwar et al., 2014, 2018; Mollaahmetoglu et al., 2021; Rothberg et al., 2021; Sumner et al., 2021). Regardless of whether these effects are essential to treatment, there is mounting support for a broader understanding of and attention to the spectrum of experiences induced by ketamine.

A SPECIFIC PROPOSAL

In light of existing knowledge gaps, the authors and colleagues have proposed a pilot investigation of esketamine with Acceptance and Commitment Therapy (ACT) for treatment-resistant depression that is currently in the planning stage. ACT has been recognized as a well-suited framework for psychedelic-assisted treatment (Walsh and Thiessen, 2018;

Sloshower et al., 2020; Wolff et al., 2020). ACT is a form of cognitive-behavioral therapy that emphasizes psychological flexibility (PF) and has been shown to be effective in the treatment of depressive symptoms (Bai et al., 2020). PF is a transdiagnostic construct that can be thought of as an individual's capacity to recognize and adapt to contextual demands, shift mindset or behaviors during individual and social experiences, maintain balance across important life domains, and to be aware of and committed to behaviors consistent with values (Kashdan, 2010). PF appears to predict outcomes of psychotherapy for treatment-resistant depression (Yasinski et al., 2020) and measurements of this construct, like The Acceptance and Action Questionnaire (AAQ-II), have been shown to mediate the relationship between acute psychedelic effects and subsequent decreases in depression and anxiety (Close et al., 2020; Davis et al., 2020). Importantly, it is also held that the quality and therapeutic value of relevant psychedelic effects are influenced by the specific treatment context for classic psychedelics (Johnson et al., 2008; Hartogsohn, 2016; Carhart-Harris et al., 2018; Garcia-Romeu and Richards, 2018), although this has not been adequately explored with ketamine. Taken together, these data indicate that PF-oriented models may be key to supporting processes of change when psychotherapy and psychedelic experience are combined (Watts and Luoma, 2020).

While several published studies indicate the value of psychotherapy alongside ketamine administration, none of these investigations have utilized an ACT-based approach. Furthermore, to our knowledge no studies have examined the combination of esketamine and concurrent psychotherapy. In this pilot study we propose to examine three research questions: (1) will an augmented esketamine treatment protocol (AET) involving preparatory counseling and ongoing ACT during esketamine administration yield greater or more durable antidepressant-type effects than treatment as usual (TAU) esketamine dosing? (2) will the AET treatment context produce significantly different subjective (e.g., dissociative-type) effects than TAU esketamine dosing? and (3) Are esketamine-induced subjective effects within either treatment context associated with antidepressant efficacy?

The study will randomly assign patients initiating esketamine for treatment-resistant depression to either the TAU or AET arm beginning with the first dose and throughout the duration of the 4-week induction phase (see **Figure 2**). The fact that the FDA requires a two-hour monitoring window after esketamine dosing provides a unique opportunity for psychotherapy that coincides with the period of acute drug effects. ACT sessions will be conducted approximately 1 h after drug administration, and we expect that standard dosages of esketamine will facilitate a "psycholytic" and relational model of therapy. Participant treatment response will be tracked using standard measures of depression from baseline through the end of the 4-week maintenance period, and again at a 3-month follow-up. Subjective effects will be assessed throughout esketamine dosing using a battery of psychometric questionnaires. Other measurements of interest include psychological flexibility, therapeutic alliance, and need for maintenance treatment that may differ between treatment arms. These data will provide needed empirical observations regarding the impact of psychotherapeutic intervention in conjunction with esketamine, and the mediating role of subjective and contextually determined drug effects.

DISCUSSION

Ongoing study will help clarify the uses of ketamine as a therapeutic adjunct. Notably, in contrast to pharmacotherapy development, no formal approval process exists for specific psychotherapies, which are ultimately defined as "evidence-based" when research

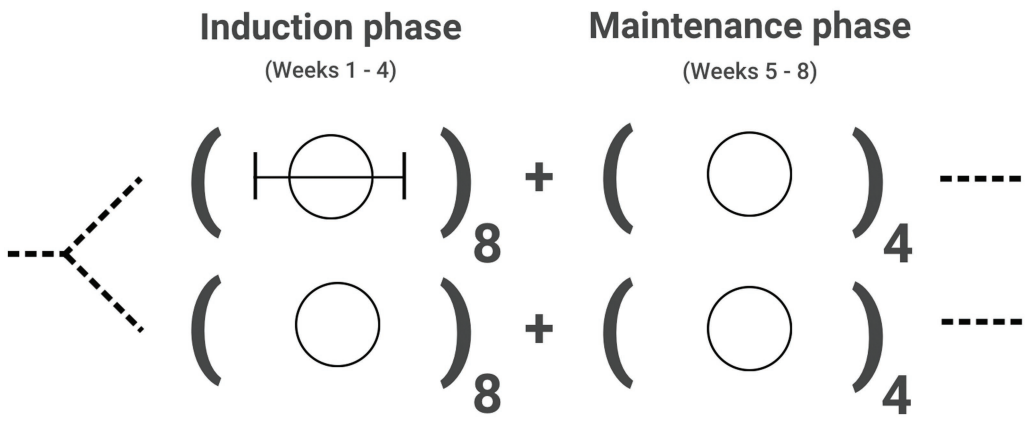

FIGURE 2 | Proposed design for a pilot investigation of esketamine with Acceptance and Commitment Therapy (ACT) for treatment-resistant depression. Current esketamine dosing protocols call for twice weekly dosing during a 4-week induction phase, followed by weekly dosing during a maintenance phase in weeks 5 through 8. Patients receive an initial dose of 56 mg, followed by repeated doses of 56 mg or 84 mg based on treatment response (i.e., efficacy and tolerability). After initial study procedures, participants will be randomized to receive treatment as usual (plain circle) or esketamine in conjunction with ACT (circle with bracketed line) during the induction phase of treatment. Both study arms will follow the same clinical procedures for maintenance treatment and subsequent follow-up.

involving a substantial number of patients has provided evidence of treatment effect (National Institute of Mental Health, 2021). However, these lines of inquiry are unlikely to attract the funding of pharmaceutical companies and will thus depend heavily on the support of public agencies (Migone, 2017). Furthermore, with the need for time-consuming and complex factorial study designs to adequately compare drug x therapy interactions (Grabski et al., 2022), standards of care for combinations of ketamine and psychotherapy are expected to develop slowly.

For the time being, there is value to considering existing and independent medical and psychological standards. Prescribing of ketamine, particularly for off-label uses that may have therapeutic utility, should be based on "firm scientific rationale and on sound medical evidence" (U.S. Food and Drug Administration, 1998), such as effectiveness data collected from controlled trials or documented in clinical settings (Radley et al., 2006). Best psychological practice is informed not only by existing research but also "clinical expertise in the context of patient characteristics, culture and preferences (American Psychological Association, 2008)." Additional parameters are expected to be relevant to the interactions of ketamine and therapy, including variables such as medication dosage and the timing of psychological interventions, as described here, along with other factors, such as the normative claims of treatment, and provider training in specific therapeutic modalities.

Different paradigms for ketamine can coexist – the "experience-oriented," "plasticity-oriented," and others still. Even guidelines for strictly pharmacological uses of ketamine and esketamine emphasize the importance of "a comfortable and adaptable environment" for patients given that drug administration "may amplify sensory experiences and/or result in dissociation or psychotomimetic effects (McIntyre et al., 2021)." An integrated approach to ketamine therapy, considering both historical perspectives on subjective experience and modern advances in neuroscience, may ultimately lead to a better understanding of relevant drug effects, improved treatment protocols, and multiple dimensions of benefit (Muscat et al., 2021a; Walsh et al., 2021). Much like the "abreactive" interventions of old, ongoing applications of ketamine are expected to reflect the prevailing psychological zeitgeist. However, while the mechanics, contexts, and explanations for our interventions may shift, the therapeutic endeavor is the same as it has always been – toward the vision of a better life for patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DM, VM, and AG-R made substantial contributions to the conception, design, and drafting of the manuscript. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

FUNDING

Funding for this research was made possible by the Johns Hopkins Center for Psychedelic and Consciousness Research and provided by Tim Ferriss, Matt Mullenweg, Blake Mycoskie, Craig Nerenberg, and the Steven and Alexandra Cohen Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Conflict of Interest: AG-R receives support from the Heffter Research Institute and serves as a scientific advisor to ETHA Natural Botanicals and NeonMind Biosciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Psychology

HYPOTHESIS AND THEORY
published: 25 March 2022
doi: 10.3389/fpsyg.2022.812930

Psilocybin-Assisted Compassion Focused Therapy for Depression

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Psilocybin-assisted psychotherapy, i.e., psilocybin treatment with psychological support, has demonstrated the efficacy of psilocybin to reduce depressive symptoms. However, in clinical trials, the structure of psilocybin-assisted psychotherapy is primarily based on preparation, navigation (support during dosing sessions), and integration. For psychotherapeutic guidance, the application of this structure is favored over the usage of theoretical models. The applied psychotherapeutic models may be of critical importance if the effects are augmented due to the psychologically insightful experiences during the navigation and integration sessions. One of the important next steps is to provide therapists with guidance on how to provide psilocybin-assisted psychotherapy. We present an integrated protocol for psilocybin-assisted psychotherapy for depression based on the theoretical model and psychotherapeutic framework of Compassion Focused Therapy (CFT). We hypothesize that CFT can provide the theoretical model and compassion practices that will reinforce the experiences during the navigation and follow-up therapy sessions. In this paper, we describe the rationale for selecting CFT, the compatibility of CFT and psilocybin-therapy, an overview of the psilocybin-assisted CFT protocol, the study protocol, and limitations to this approach.

Keywords: psilocybin, psychotherapy, treatment protocol, compassion focused therapy (CFT), depression, psilocybin-assisted psychotherapy

OPEN ACCESS

Edited by:
Stig Poulsen,
University of Copenhagen, Denmark

Reviewed by:
Paul Gilbert,
NHS England, United Kingdom
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University of Derby, United Kingdom

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *10 November 2021*
Accepted: *21 February 2022*
Published: *25 March 2022*

Citation:
Pots WTM and Chakhssi F (2022) Psilocybin-Assisted Compassion Focused Therapy for Depression. Front. Psychol. 13:812930. doi: 10.3389/fpsyg.2022.812930

INTRODUCTION

Major depression is a prevalent disorder that has a large impact on quality of life and is associated with high rates of comorbidity and increased mortality (Vigo et al., 2016). Current treatment approaches for depression, including psychotherapies and pharmacotherapies, are effective but leave significant room for improvement since remission is only achieved for less than half of the treated patients (Cuijpers et al., 2020).

More recently, psilocybin has gained attention as a new paradigm in the treatment of depression. Psilocybin, a classic hallucinogen, effects glutamate levels in key areas of the brain, including the medial prefrontal cortex and hippocampus that are associated with positive changes in self-experience and increased feelings of unity with others and one's surroundings (Nour and Carhart-Harris, 2017; Mason et al., 2020). Distortions of self-experience may be an important mechanism to target in the treatment of depression (Carhart-Harris and Goodwin, 2017).

Several studies have demonstrated the efficacy of psilocybin with moderate to large effect sizes in patients with life-threatening cancer and depressive symptoms (Griffiths et al., 2016; Ross et al., 2016), and in patients with major depressive disorder (Carhart-Harris et al., 2016; Davis et al., 2021). These findings also show promising tolerability data, eliciting head-to-head comparative

efficacy studies with current treatments (e.g., current pharmacotherapies). Furthermore, psilocybin has a lower risk for addiction and harmful neurological effects compared to other novel interventions such as ketamine (Morgan et al., 2012; Fond et al., 2014; Johnson et al., 2018; Mcintyre et al., 2020).

Psilocybin treatment with psychological support, structured in preparation-, navigation- and integration sessions, has shown to act rapidly and to have long-lasting effects on depression (Carhart-Harris et al., 2016; Agin-Liebes and Davis, 2021; Davis et al., 2021). A recent review of psychotherapeutic components in psilocybin-assisted psychotherapy found that psychotherapy was primarily given in the preparation and integration sessions, and that psychotherapy mostly consisted of a non-directive approach and music therapy (Horton et al., 2021). The core elements of supportive psychotherapy are calmness, empathy, personal support, and reassurance (Johnson et al., 2008). Some studies have combined psilocybin with Cognitive Behavioral Treatment (CBT) for smoking cessation (Johnson et al., 2017), Acceptance and Commitment Therapy (ACT) for treatment-resistant depression (Sloshower et al., 2020; Watts and Luoma, 2020), or Motivational Enhancement Therapy (MET) for alcohol dependence (Bogenschutz et al., 2015). In most studies, the therapeutic content is often neither reported nor examined. Therefore, it remains unclear how psychotherapy affects the patient's experience. However, it has been suggested that the offered psychotherapeutic model enhances the personal and meaningful experiences, and thereby the antidepressant effects, of psilocybin-assisted treatment (Griffiths et al., 2006, 2011). One of the important next steps is to provide therapists with guidance on how to provide psilocybin-assisted psychotherapy (Nutt and Carhart-Harris, 2021), including the development of treatment protocols (Sloshower, 2018; Gorman et al., 2021), and support that with research into the possible added value of psychotherapy or psychological support to the effect of psilocybin for depression.

A recently developed therapeutic approach that is of particular interest for psilocybin-assisted therapy is Compassion-Focused Therapy (CFT; Gilbert, 2014). CFT provides patients with a rationale and practices that might enhance the effects of psilocybin-assisted therapy by increasing connectedness, compassion for self, and compassion for others. CFT is based on evolutionary psychology and attachment theory and stimulates the affiliative or "rest and digest" system (Gilbert, 2014). It enables insight into the interplay of the lack of care and compassion, especially early in life, and underlying mental health problems, and shows how developing compassion can act as a psychotherapeutic process and promote social connection and social safeness (Weng et al., 2013; Gilbert, 2020). Previous studies suggest that certain substances, including psilocybin, can produce similar increases in self-compassion and reductions in self-criticism as compassionate practices (Kamboj et al., 2015; Watts et al., 2017). Likewise, research shows that psilocybin-assisted psychotherapy may decrease negative affect and the neural correlates of negative affect (Davis et al., 2021) and increase connection and acceptance (Watts et al., 2017), similar to the proposed working of the affiliative system within CFT. We believe that CFT may be a relevant psychotherapeutic model to help to improve the understanding of the experiences during administration or navigation and integration sessions, while at the same time providing meaningful practices that help the integrative process.

Therefore, the aim of the current article is to provide a CFT framework in which psilocybin-assisted psychotherapy can be embedded.

COMPASSION FOCUSED THERAPY

Compassion focused therapy is specifically developed for and aimed at individuals who have a compromised capacity for experiencing and expressing affiliative motives and emotion to self and others (Gilbert, 2010). It is particularly suited for individuals characterized by the tendency to negatively evaluate and judge aspects of the self, such as patients with depression. Several meta-analyses demonstrate efficacy for compassion-based interventions in various (non)-clinical populations with moderate to large effects on depression and well-being (Leaviss and Uttley, 2015; Kirby et al., 2017; Wakelin et al., 2021).

Compassion focused therapy was developed as a transdiagnostic model by Paul Gilbert (Gilbert, 2005) in response to the observation that many of his chronic depressed clients, in particular those high in shame and self-criticism, did not benefit from traditional therapy. Although these clients were able to engage in cognitive and behavioral exercises, they weren't able to generate a self-compassionate inner voice. Gilbert (2014) proposed a framework for the biological mechanisms underpinning compassion that is based on evolutionary biology. CFT takes an evolutionary functional view to emotion—especially the affiliative emotions and their competencies—and focuses on three major emotion regulation systems: (1) the threat protection system which responds to threat with defense strategies; (2) the drive- and resource-seeking system which links to achievement and acquiring of resources and rewards; and (3) the soothing and affiliation system which enables individuals to soothe, calm, and content themselves (Gilbert, 2014). The three major emotion regulation systems are displayed in **Figure 1**. Compassion is thus understood as an evolved motivational system designed to regulate negative emotions through attuning to the feelings of self and others, and expressing and communicating feelings of affiliation, warmth, and safeness (e.g., Gilbert, 1989; Spikins et al., 2010). Within the framework of treating depression, harmonizing the emotion regulation system is essential as studies show that emotion regulation affects depressive symptoms *via* increasing rumination and decreasing reappraisal (Joormann and Stanton, 2016).

Gilbert's (1989) evolutionary model suggests that the potential for compassion evolved with the affiliative system that is linked to the attachment system. CFT is underpinned by social mentality theory (SMT), which states that different mental states not only organize our minds but also shape our relationships (Gilbert, 1989, 2000, 2005). Both care seeking and care giving social mentalities are activated when one is relating to others (e.g., a crying child and a comforting mother), but can also be activated when relating to the self. Compassion, as a social mentality, can "flow" in three directions. First, there is the compassion

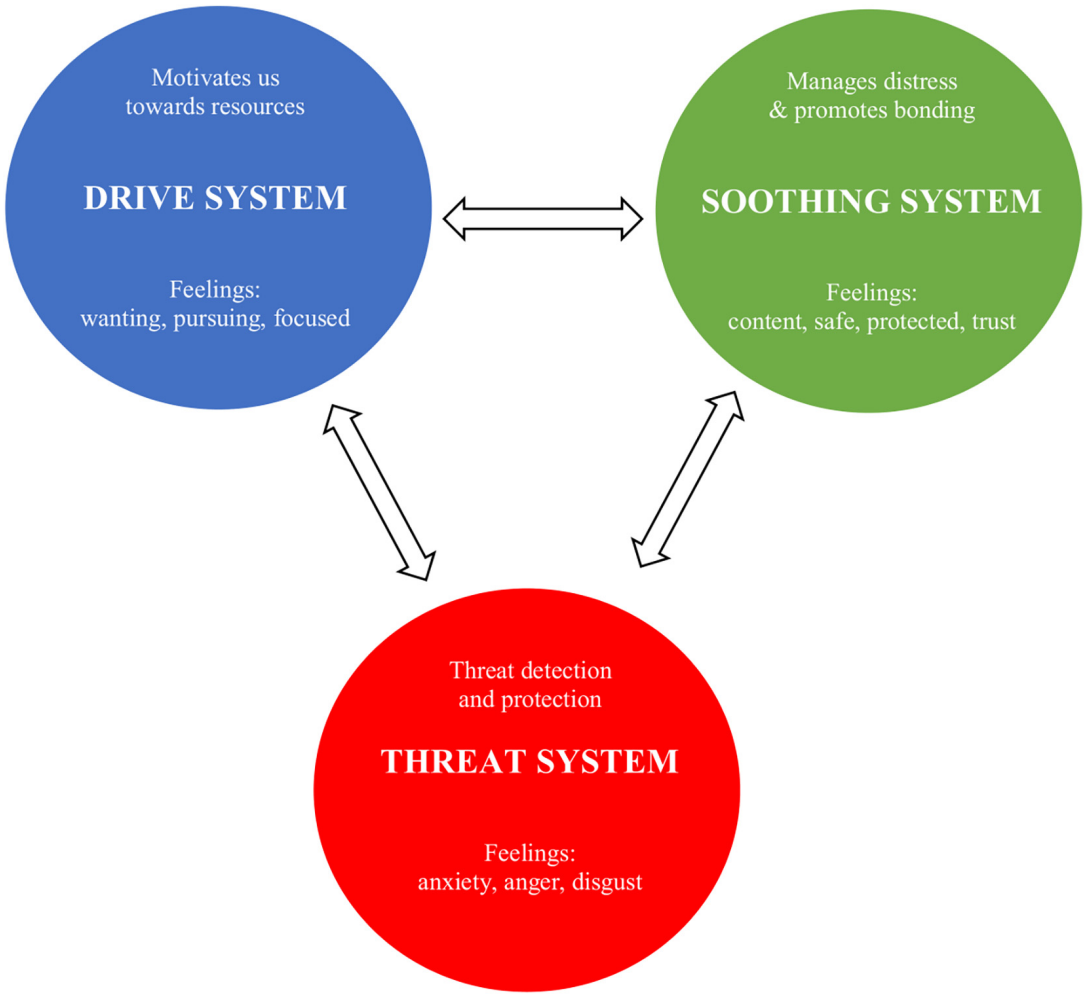

FIGURE 1 | Three types of CFT emotion regulation systems.

we can feel for others; second, there is the compassion we can feel coming from others to ourselves, and thirdly there is the compassion we can direct to ourselves which is defined as self-compassion. Each of these can be a focus in CFT. Research shows that the quality of care and affection received in childhood lays the foundation for being caring and compassionate as an adult (Gillath et al., 2005). Imagining being cared for and receiving compassion has the same effects, as it stimulates the soothing system, helping individuals feel safe and calm. CFT emphasizes the significance of our affiliative system in reducing the activity in the threat-based protection system by allowing us to feel cared for and to be able to offer care to both ourselves and others (Gilbert, 2014). Accordingly, CFT targets both the psychological and the biological processes underpinning care and compassion. When combined these processes help to down-regulate the threat system and stimulate positive affect and a sense of social safeness.

The primary aim of CFT is to help clients develop these caring processes and create a better sense of social connectedness to understand and respond to their distress from the perspective of a compassionate mind. Through the incorporation of a range of compassion-based skills, attributes, and qualities, clients become more distress aware and insightful, learning how to develop empathy and distress tolerance and how to take wise and compassionate action to address distress. Thus, in this model, the skill of giving or receiving compassion can be enhanced through therapy and generate experiences of being cared for and socially connected to (a) caring other(s).

RATIONALE FOR COMPASSION FOCUSED THERAPY AS A THERAPEUTIC MODEL IN PSILOCYBIN-ASSISTED PSYCHOTHERAPY

Conventional Cognitive Behavioral Therapy (CBT) approaches to depression primarily target signs and symptoms of depression, but do not impact emotional, psychological and spiritual wellbeing as much as more recent approaches such as CFT

(Van Agteren et al., 2021). CFT focuses more on the persons' relationship to thought and emotion rather than on their content, and uses techniques and concepts derived from mindfulness, emotion focused therapy, psychodynamic therapy, and attachment theory (Gilbert, 2020). More specifically, CFT targets compassion as a psychotherapeutic process and effectively increases social connection and social safeness (Leaviss and Uttley, 2015; Kirby et al., 2017; Craig et al., 2020). Weng et al. (2013) showed that compassion can be cultivated through training compassion meditation and imagery, boosting the brain's resilience to suffering. This is important because part of the reason that compassion can be helpful is that it is activating particular physiological systems linked to caring, social connections, and feeling cared for Gilbert (2020), Holze et al. (2021), and Steffen et al. (2021).

Similar to CFT, psilocybin-assisted psychotherapy is aimed to increase openness and acceptance by creating space for people to tolerate and allow internal and external discomfort and enhancing compassion for self and others. Indeed, a study by Barrett et al. (2020) showed that psilocybin may decrease negative affect and the neural correlates of negative affect. One-month post-psilocybin administration, positive affect remained elevated and trait anxiety was reduced (Barrett et al., 2020). They hypothesized that the reduction of negative affect may undermine ruminative processes that contribute to the development and maintenance of mood disorders. Further studies provide evidence that psilocybin has a significant effect on social connection, attachment, and feeling more connected to self, others, and nature/the world (Watts et al., 2017; Forstmann et al., 2020), similar to the proposed working of the soothing system within CFT (as described above). Furthermore, several authors (e.g., Watts et al., 2017) have recommended that social connection as flows (from self, others, and the world), should be examined in future studies as they appear to form a central theme of patient's experiences. This also adds further rationale to the use of CFT as it facilitates the flow of compassion.

As people with depression tend to operate from their threat system by having a negative affect and thoughts, providing psilocybin within the framework of CFT will stimulate the affiliative system and provide a positive and supposedly healing context of thoughts, feelings, and behaviors.

PSILOCYBIN-ASSISTED COMPASSION FOCUSED THERAPY PROTOCOL

The current therapy protocol was constructed based on the basic structure of other psychedelic-assisted psychotherapy protocols (Johnson et al., 2014; Mithoefer, 2015; Guss et al., 2020; Watts, 2021). The included interventions and exercises were devised in conjunction with the CFT model. The psilocybin-assisted CFT protocol consists of 13 sessions (see **Table 1**). In the protocol, each session includes instructions for the therapist to guide the treatment session. Also, each session includes psychoeducation (e.g., the conceptualization of depression) followed by an in-session experiential exercise (e.g., soothing rhythm breathing; see below for an explanation), which participants are also asked to practice on their own between sessions (2 h per week). Compliance with the homework sessions is assessed at the start of each session.

Compassion Focused Therapy-Based Preparatory Sessions

Within the psilocybin-assisted CFT protocol, CFT is the framework to provide the understanding of the nature of depression and its thoughts, feelings, and behaviors, as well as the psychedelic experiences. The goal of the preparatory sessions is for the therapists to help participants understand and respond to their distress from the perspective of a compassionate mind, generating an understanding that comes from an evolutionary perspective of the mind. Therefore, in the preparatory sessions (1–3), therapists will frame the conceptualization of depression based on the affiliative motives and emotions of the participant, and explain the concept of the so called "Tricky Brain." This tricky brain encompasses the notion that all human beings find themselves with an evolved brain and influential environments that we didn't choose but shaped our responses and behaviors. Within CFT, the concept of the tricky brain is used as a way to de-shame participants: "*it is not our fault that we have this highly evolved brain that can create these fear states, nor is it our fault that we are born in these particular circumstances that gave us these learning behaviors*." This concept of the tricky brain will be explored, as well as the fear of compassion. Therapists will explain the evolved functions of emotions by using the three circles model: the threat system, the drive system, and the soothing system, drawing them with examples from the life of the participant (see **Figure 2** for a case example).

Soothing rhythm breathing (i.e., a breathing technique with a style and rhythm of breathing that feels calming and soothing) and compassion focused body practices (i.e., exercises aimed at improving and utilizing body awareness to support a compassionate mindset) are taught in the sessions together with the therapist and are given as homework. During the first three preparatory sessions, the therapist pays close attention to the way the participant perceives him or herself, being attentive to the different emotional states that may lie underneath different affiliative motives and emotions, and to thoughts and feelings about the psychedelic experience. Exercises focusing on building a compassionate self and working with multiple "selves" or "parts" will be explored to give context to the daily life struggles of the participant. Within CFT, working with those parts is a therapeutic technique that helps people access and relate to the different emotional states they experience in their daily life from the perspective of the compassionate self. For example, while tuning into the thoughts, bodily feelings, action tendencies, memories, and needs of a particular part (i.e., anxious, sad, or angry) that comes up, the therapist can ask: "*From the wisdom of the compassionate self, what is your view of that* [anxious, sad, angry, . . .] *part of you? What do you think it wants, and what do you think it fears? How would you like to relate to that part of you?*" The compassionate self can relate to that particular self that is explored from the qualities of wisdom, strength, and commitment. At the end of the third preparatory

TABLE 1 | Overview of CFT-based psilocybin-assisted psychotherapy sessions in treatment protocol.

Session information	Week	Session number	Duration hours (h)	Session goals and CFT components
Preparatory session	1	1	1.5	Establishing a therapeutic alliance. Psychoeducation CFT model and psilocybin experience. Practicing mindful breathing. Compassionate motivation.
Preparatory session	2	2	1.5	Tricky brain and Emotion regulation systems. Practicing compassion focused body practices. Practicing compassionate flow. Case conceptualization.
Preparatory session	3	3	1.5	Compassionate self. Multiple selves. Intention setting medication session 1.
Psilocybin navigation session	4	4	7–8	Therapists gather information for CFT based case conceptualization. Therapeutic stance is largely non-directive, allowing the individual's own healing intelligence determine what will happen and following the participants lead. Working with parts is appropriate when participants spontaneously bring them up.
Integration session	4, 1 day after session 4	5	1.5	Debriefing of medication session and reconstruction of narrative of experience. Identify and explore association of core experiences with CFT principles. Practicing compassionate skills and compassionate reframing.
Integration session	5	6	1.5	Deepening of compassionate self and compassionate skills. Practicing relating compassionate self to multiple selves and applying compassionate skills in daily life.
Integration session	6	7	1.5	Deepening of compassionate self and compassionate skills. Practicing relating compassionate self to multiple selves and applying compassionate skills in daily life.
Preparatory session	7	8	1.5	Adapting case conceptualization with recent information from previous sessions. Practice compassionate skills. Intention setting medication session 2.
Psilocybin navigation session	7	9	7–8	Therapists gather information for CFT based case conceptualization. Therapeutic stance is largely non-directive, allowing the individual's own healing intelligence determine what will happen and following the participants lead. Working with parts is appropriate when participants spontaneously bring them up.
Integration session	7, 1 day after session 9	10	1.5	Debriefing of medication session and reconstruction of narrative of experience. Identify and explore association of core experiences with CFT principles. Recap self-compassion in the body. Compassionate letter writing.
Integration session	8	11	1.5	Deepening of compassionate self and compassionate skills. Practicing relating compassionate self to multiple selves and applying compassionate skills in daily life. Practice problem solving and daily living with a compassionate mind.
Integration session	9	12	1.5	Deepening of compassionate self and compassionate skills. Practicing relating compassionate self to multiple selves and applying compassionate skills in daily life. Practice values-based living.
Follow-up session	10	13	1.5	Exploration of insights gained from medication sessions and integration sessions. Reinforce CFT concepts and encourage corrective behavioral changes. Review CFT skills and create a progress and contingency plan.

session, the result of these explorations will be translated into an intention for the first psilocybin navigation session. The preparation for the second psilocybin navigation session will integrate the explorations with the insights and/or learnings from the first psilocybin navigation session.

Compassion Focused Therapy-Based Navigation Sessions

The psilocybin navigation sessions are guided by a non-directive approach. The non-directive approach has been a core principle of psychedelic-assisted therapies as it enables a patient to adopt an uncritical approach concerning their own psychedelic experience(s) and engage in self-directed insight-finding and meaning-making processes (Gorman et al., 2021). It allows the client to reconcile unconscious material in the order and nature in which it comes to the surface for healing. The navigation sessions will be guided with music generated by the therapist or curated psychedelic therapy playlists that are freely available (e.g., by Mendel Kaelen[1]). Within the context of inner healing during the navigation session, one or multiple parts can come up. When the participant is being burdened or hindered by that particular self, the therapist will encourage the participant to look into their own inner experience for insights and guide him or her to go into the experience with their inner healing intelligence (Mithoefer, 2015; Clare, 2018; Phelps, 2019). The experience of the participant can be further guided from the understanding of CFT and working with different parts. The participant can be guided toward bringing in the compassionate self and relating to the different parts from the position of the compassionate self as explained above. The CFT case conceptualization is consistently held as a temporary framework of understanding and used

[1]psychedelicstoday.com/music-resources/

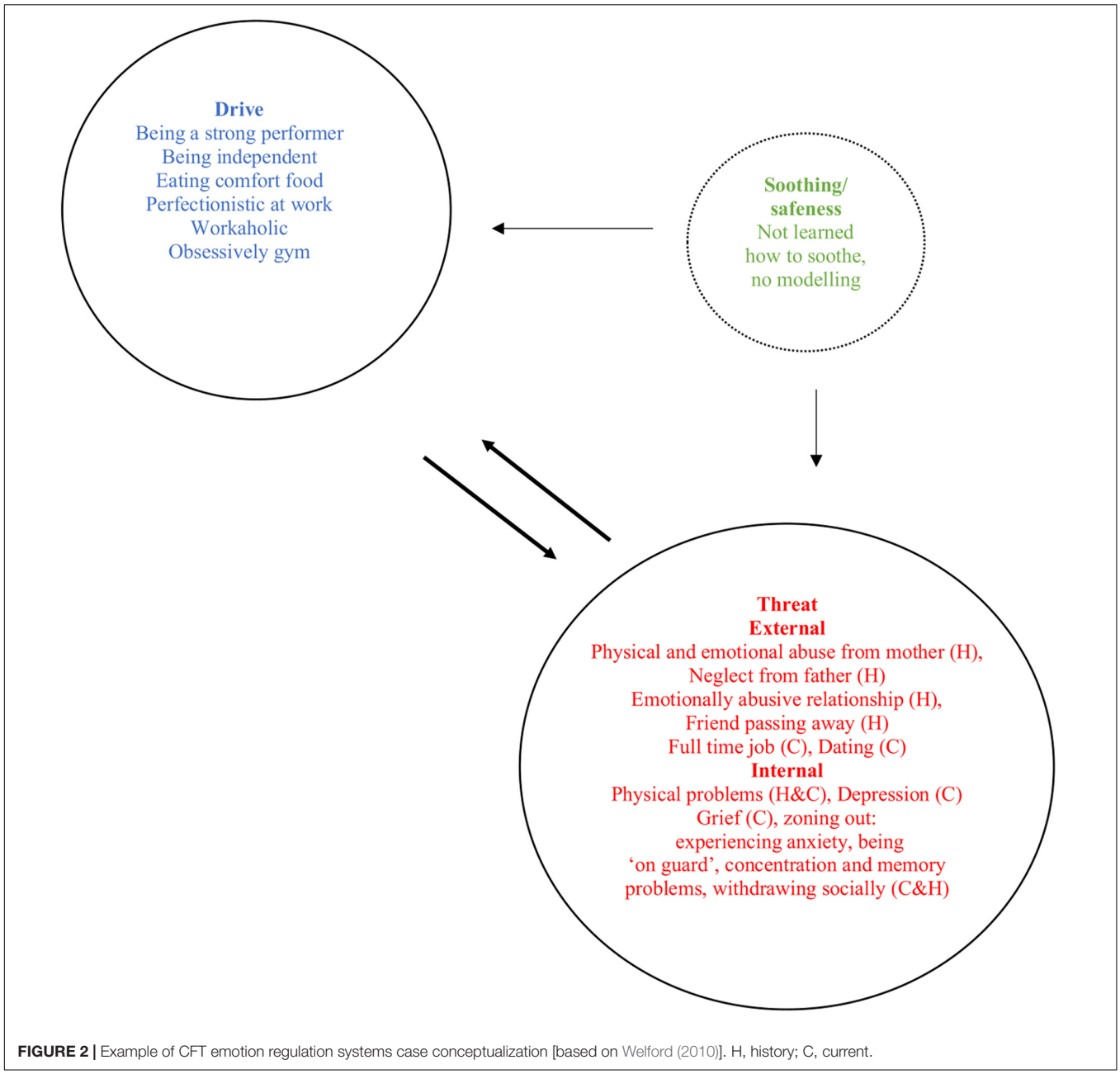

FIGURE 2 | Example of CFT emotion regulation systems case conceptualization [based on Welford (2010)]. H, history; C, current.

iteratively as it occurs throughout all therapeutic encounters. Thus, the case conceptualization will continuously be updated by information from the navigation sessions.

Compassion Focused Therapy-Based Integration Sessions

Integration sessions are partly debriefing of the psychedelic experiences of the psilocybin navigation session, and partly psychotherapeutic CFT integration sessions. The debriefing focuses on recollecting the experiences of the psilocybin navigation session and the accompanying feelings. All psychotherapeutic sessions focus on deepening the compassionate self and applying compassionate skills in daily life. Participants are taught how to engage with themselves and others with compassion, teaching them the skills to develop the key aspects of compassion. For example, practices of compassionate attention help to refocus attention to positive attributes or skills, such as courage, kindness, or gratitude; practices of compassionate behavior focus on practicing new behavior with an encouraging, warm tone in their mind; and compassionate imagery practices focus on exploring the image of a compassionate self, including facial expressions, body postures, and voice tones. Exercises are done in sessions and given as homework: compassionate thought challenging records, as a way to reframe thoughts and feelings from the compassionate mind;

compassionate letter writing, where participants will write about painful events from a compassionate reframing; worksheets that address the inner critic.

Compassion Focused Therapy Therapeutic Stance

Although all psychotherapy sessions are didactic, all sessions are equally experiential as they contain exercises of CFT. The therapeutic stance of CFT is to offer a safe therapeutic setting that will allow the participant to freely and safely explore the psychedelic realm and the therapeutic relationship, to tolerate the distress that accompanies a participant's journey and therapy, and to be non-judgmental and approach inner-criticism with kindness.

STUDY PROTOCOL AND THERAPIST TRAINING

Overall, research indicates that psilocybin-assisted psychotherapy shows promising results regarding the acceptability and effectiveness for patients with depression. However, it is currently not clear what psychotherapy or even standard psychological support adds to the effect of psilocybin for depression. This question could be addressed in a three-armed randomized clinical trial (RCT), comparing psilocybin-assisted CFT to psilocybin-assisted psychotherapy with non-directive psychological support (see Griffiths et al., 2016) and psilocybin-assisted psychotherapy with minimal support (psilocybin-only condition). In the psilocybin-only condition, because of potential adverse effects such as crying, sadness, or grief (Davis et al., 2021), some additional safety measures should be implemented. Before and during psilocybin administration trained research assistants guide participants and intervene when participants are in distress by providing verbal or physical reassurance (see Griffiths et al., 2016). We hypothesize that both the psilocybin-CFT condition and the psilocybin-standard condition would have more favorable changes, compared to the psilocybin-only control condition, and that psilocybin-assisted CFT would result in a larger effect than psilocybin-assisted psychotherapy with non-directive psychological support.

An alternative to a three-armed RCT for settings where group designs are challenging or costly to perform would be a single case experimental design (SCED). SCEDs are designs that do not require large groups while permitting to draw scientifically valid inferences about the effects of an intervention and their theoretical mechanisms (Kazdin, 2019). In particular, a single case multiple baseline design (which is a variant of a SCED) would be a feasible and appropriate design to measure the efficacy of the psilocybin-assisted CFT protocol for depression. In a multiple baseline design, data is repeatedly collected during a baseline phase on outcomes of interest (e.g., well-being or depression) to describe the level of functioning. After assuring that the functioning is stable in the baseline phase, the intervention will be introduced to the participant. Data collection is continued during the intervention, and if the intervention is effective, changes are expected in the outcomes of interest. This suggests that the intervention was responsible for the changes in the outcomes. By varying the length of the baseline for the participants (i.e., one participant will start after 2 weeks, whereas another participant after 3 weeks of gathering baseline data), the influence of other factors (such as time effects) is unlikely. The repeated change in outcomes in response to the introduction of the intervention demonstrates its efficacy (Kazdin, 2019). In other words, if changes in the participant's functioning occurred during or after the psilocybin-assisted CFT intervention, these changes are seen as evidence of the effectiveness of the specific intervention.

The proposed primary outcome measure is the Hamilton Depression Rating Scale (GRID-HAMD), in line with Davis et al. (2021). Secondary outcome measures could be the Mental Health Continuum-Short Form (MHC-SF; focuses on emotional, psychological, and social well-being), Compassion Engagement and Action Scales (CEAS), the Types of Positive Affect Scale (TPAS; subscale Safe Positive Affect), and the Fears of Compassion Scales (FCS). Physiological assessment is measured with HRV assessment of resting state and activity state (Steffen et al., 2017; Caldwell and Steffen, 2018). All outcomes could be administered at baseline, before psilocybin sessions at week 4, and week 7, and at a follow-up session at week 10.

To examine the psilocybin-assisted CFT protocol in a study, we are devising a treatment manual and training for therapists based on recent CFT handbooks and/or manuals (Arnold et al., 2021; Cattani et al., 2022; Gilbert and Simos, 2022). The goal of the training is to introduce therapists to the core principles of psychedelics and CFT and to train them how to use the therapist manual.

DISCUSSION

In this paper, we provided a CFT framework for psilocybin-assisted psychotherapy for depression. We believe that such a framework is needed as it may enhance the efficacy of psilocybin-assisted psychotherapy for depression. Offering a psychedelic experience within the framework of CFT will provide the tools and practices for participants to understand and integrate their psychedelic experiences into their daily life. CFT as a modality is particularly helpful as CFT inherently enhances compassion for self, others, and the world, social connection, and social safeness. Additionally, we also provided an overview of a new treatment protocol for therapists to work with clients within the field of psychedelic psychotherapy.

The integrative approach of psilocybin-assisted CFT circumvents challenges that are associated with the current standard approaches for depression. In real world settings psychotherapies and pharmacotherapies are typically provided by different clinicians, sometimes even at different clinics. However, combining psychotherapy and pharmacotherapies in a collaborative manner is more effective than pharmacotherapy alone (Coventry et al., 2014). The current integrative approach opens the possibility to tailor, adjust, or change the intervention to meet the needs of participants, and thus potentially increase the responsiveness of the participants.

In the current protocol, we believe that CFT is a suitable psychotherapeutic framework for psilocybin treatment of depression. However, other approaches may also offer a relevant psychotherapeutic framework for psilocybin assisted-psychotherapy, such as CBT, ACT, or MET (Bogenschutz et al., 2015; Johnson et al., 2017; Sloshower et al., 2020; Watts and Luoma, 2020). For example, Acceptance and Commitment Therapy (ACT) has been suggested as a framework for major depressive disorders, wherein the focus of the therapy lies on increasing psychological flexibility (Sloshower et al., 2020). CFT as well as ACT focus on changing the relationship of the participants to their thoughts, sensations, and emotions. However, CFT focuses specifically on developing compassion and social connection as a mediator of change and this could be especially suitable for people who have a compromised capacity for experiencing and expressing affiliative motives and emotions, i.e., those with high levels of self-criticism and shame. Future research should examine different mechanisms of change in relation to participants' physiological characteristics and hopefully can give some guidelines on what treatment protocol best suits whom.

We further believe that particularly CFT is suitable as the psychotherapeutic framework for psilocybin-assisted psychotherapy as it focuses on stimulating motivational systems that evolved to support caring connections. As both CFT and psilocybin-assisted therapy are stimulating connectedness and social safeness, they can augment each other and provide a solid framework for the treatment of depression. Research indicates that some individuals have difficulties with developing compassion, particularly those who have an insecure attachment style and high self-criticism (Kamboj et al., 2015; Kirby, 2017; Steffen et al., 2021). They can experience negative impacts of compassionate imagery, partly because compassion can stimulate the caring system which may have trauma memories. Likewise, in a study by Rockliff et al. (2011) the authors studied the effects of intranasal oxytocin on compassion focused imagery (CFI). They found that participants higher in self-criticism, lower in self-reassurance, social safeness, and attachment security had fewer positive experiences of CFI under oxytocin than placebo, indicating that the effects of oxytocin on affiliation may depend on attachment and self-evaluative styles. It's possible that psilocybin-assisted psychotherapy can stimulate sadness in that particular group by relating to a deep interconnectedness through stimulating the 5-HT2A receptor pathways (Van De Kar et al., 2001; Holze et al., 2021). Offering an integrated approach of psilocybin-assisted CFT has the potential to break through some of the fears, blocks, and resistances to compassion that are common in therapy, and therefore improve people's capacity to experience a sense of caring, connectedness, and compassion. Future studies should research the degree in which offering an integrated approach is augmenting the effect of each modality by itself, especially for those who have an insecure attachment style and high self-criticism.

Limitations

The presented treatment protocol for psilocybin-assisted CFT holds promise, but some limitations also apply. First, it remains unclear if and how much therapeutic guidance is necessary for the effect of psilocybin on depression demonstrated in the recent clinical trials. The underlying assumption is that the navigation sessions (psilocybin administration) open a therapeutic window that disrupts the entrenched negative framework of thoughts, sensations, and emotions, allowing insights or experiential knowledge to arise, that—with psychotherapeutic guidance—can lead to an adjustment into a more balanced emotion regulation system. However, future research should examine the dosage-effect of psychotherapy in psychedelic-assisted psychotherapy (Horton et al., 2021). Now that psychotherapeutic treatment protocols are being published, different protocols could be compared in future studies to conditions were minimal (non-psychotherapeutic) guidance or only psilocybin is offered. Secondly, this protocol was specifically developed as psilocybin-assisted psychotherapy for depression. Generalization of this protocol to other symptoms is not recommended. Also, this treatment protocol should not be used with other psychedelics or medication. Third, we cannot make any claims about the specific competencies needed to administer a psilocybin-assisted protocol for depression. However, we believe, it is crucial for therapists to acquire training in the competencies that are regarded as essential for psychedelic-assisted psychotherapy (Phelps, 2017).

CONCLUSION AND FUTURE DIRECTIONS

This paper provides a psychotherapeutic framework for the psilocybin-assisted psychotherapy of depression. As treatment protocols have been scarce so far, the psilocybin-assisted CFT protocol not only fills a gap but also enhances the effectiveness of the psilocybin-assisted therapy. The efficacy of the protocol should be examined, and we have suggested a design that is feasible for interested researchers and/or clinicians.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

WP and FC conceived the presented idea. WP developed the theory and treatment protocol. FC designed the study protocol. Both authors contributed equally in writing the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 03 May 2022
doi: 10.3389/fpsyg.2022.832879

Restorative Retelling for Processing Psychedelic Experiences: Rationale and Case Study of Complicated Grief

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Rationale: Many psychedelic experiences are meaningful, but ineffable. Engaging in meaning-making regarding emerging symbolic content and changing previous schemas have been proposed as mechanisms of change in psychedelic therapy.

Objective: Firstly, we suggest the implementation of a Restorative Retelling (RR) technique to process and integrate the psychedelic experience into autobiographical memory, in a way that fosters meaning-making. We also show how ayahuasca has the potential to evoke key psychological content in survivors, during the process of grief adjustment following the death of a loved one.

Methods: The rationale for the implementation of RR to process psychedelic experiences and a case study of a woman suffering from Complicated Grief (CG) after her mother's suicide are presented.

Results: Evaluations conducted before the ayahuasca experience and after RR suggest the effectiveness of ayahuasca and RR in reducing symptoms of CG and psychopathology.

Conclusion: This case report illustrates an effective adaptation of the RR technique for processing the psychedelic experience. The significance of the study and its limitations are discussed.

Keywords: ayahuasca, grief, restorative retelling, integration, psychedelic therapy

OPEN ACCESS

Edited by:
Stig Poulsen, University of Copenhagen, Denmark

Reviewed by:
Harris Friedman, University of Florida, United States
Michael Crofton Mithoefer, Medical University of South Carolina, United States

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *10 December 2021*
Accepted: *08 April 2022*
Published: *03 May 2022*

Citation:
González D, Aixalà MB, Neimeyer RA, Cantillo J, Nicolson D and Farré M (2022) Restorative Retelling for Processing Psychedelic Experiences: Rationale and Case Study of Complicated Grief. Front. Psychol. 13:832879. doi: 10.3389/fpsyg.2022.832879

INTRODUCTION

Ayahuasca is an Amazonian brew used as traditional medicine by more than 70 different indigenous communities (Schultes and Hofmann, 1992), and as a sacrament by several religious groups including Santo Daime, União do Vegetal (UDV), and Barquinha (Labate and Araujo, 2004). "Ayahuasca" is a Quechua term derived from the words: *Aya* (dead, soul, or ancestor) and *Huasca* (rope or vine), translatable as "vine of the souls" or "vine of the dead" (Metzner, 2005). Clinical trials provide evidence that ayahuasca could be effective for treating depression (Osório et al., 2015; Palhano-Fontes et al., 2019). Preliminary scientific results also show

ayahuasca's potential in treating addiction (Thomas et al., 2013) and grief following the death of a loved one (González et al., 2019, 2020).

The main components of ayahuasca are *N,N*-Dimethyltryptamine (DMT), present in the shrub *Psychotria viridis*, and the alkaloids harmala, harmine, and harmaline, found in the vine *Banisteriopsis caapi* (Schultes and Hofmann, 1992). Ayahuasca's effects are dose-dependent (Riba et al., 2003) and the nature of an individual's psychedelic experience is determined by their mindset as well as by physical and cultural environmental influences (Hartogsohn, 2017). Effects begin around 30–40 min after oral intake and last up to 4 h. Psychological effects include changes in spatio-temporal perception, sensorial alterations, synesthesia, increased emotional arousal and emotional lability, increased introspection, reflections, biographical memories, associative thinking, insights, and changes in the sense of "self" (Riba et al., 2001, 2003). Particularly striking are the visions that occur mainly with closed eyes, which encompass a rich panorama ranging from geometric patterns to supernatural imagery and long conversations with an imagined "other" (Shanon, 2002, 2003). However, as under the effects of other psychedelics, participants may find it difficult to express their experience in words, both during the effects and *a posteriori* (Preller and Vollenweider, 2016). However, the ineffability of such experiences is not incompatible with their remarkable tendency to enhance perception of meaning (Winkelman, 2017; Hartogsohn, 2018).

One psychotherapeutic model attracting growing attention for treating grief from the death of a loved one is the constructivist approach, which views grieving as a process of reconstructing a world of meaning that has been challenged by loss (Neimeyer, 2015, 2019). Several studies have shown that meaning-making is a predictor of adaptative bereavement (Currier et al., 2006) and a potential mediator of bereavement adjustment (Milman et al., 2017, 2019). Given psychedelics' ability to enhance perception of meaning and that several qualitative studies have shown that ayahuasca naturally evokes new meaningful experiences related to the grief process in bereaved individuals (González et al., 2019, 2021), the process of "re-constructing a world of meaning" promoted by constructivist psychotherapy could be significantly enriched by new information that emerges during psychedelic experiences. Furthermore, since psychedelics act as non-specific amplifiers of psychological material (Grof, 1994), the techniques employed in psychotherapy may facilitate an appropriate mindset for the emergence of psychological content related to the grieving process during psychedelic experiences. In this way, the benefits derived from constructivist psychotherapy and ayahuasca ceremonies could complement and enhance one another within a framework of psychedelic-assisted psychotherapy. This therapeutic model favors the use of one or a few high doses of psychedelics to create an overwhelming and transcendent experience to catalyze the therapeutic process (Garcia-Romeu and Richards, 2018). The combination of drug administration embedded within talk therapy aims to facilitate processing the psychedelic experience and potentiate novel insights into the patient's condition (Pahnke et al., 1970).

The Rationale for Restorative Retelling for Processing Psychedelic Experiences

Narrative is the way by which and in which everyday experience is processed (Wigren, 1994). Encoding experience through language allows it to be integrated into semantic and episodic memory, facilitating retrieval and reflection (Irish and Piguet, 2013). The culturally shaped cognitive and linguistic processes that guide the self-telling of experiences allow us to structure perceptual experience, organize memory, and purpose-build the very "events" of an experience (Bruner, 1987). However, it is often challenging to craft a narrative about a psychedelic experience. Psychedelics modify neural hierarchies and the flow of information, reducing top-down control, and enhancing bottom-up information transfer (Carhart-Harris et al., 2012; Alonso et al., 2015). This allows information from sensory, emotional, and memory areas to emerge into consciousness without the constraints normally exerted by the prefrontal cortex based on previous knowledge and expectations. In addition, decreased activation of areas involved in language processing such as Broca's area (BA 44) has been observed during ayahuasca ingestion, while subjects were performing a classical verbal fluency task (Prado et al., 2009). All this is reflected in the access to a deeply internal world that is not easy to process semantically.

Similar to psychedelic experiences, trauma victims are often unable to form narratives of traumatic experiences (Wigren, 1994). On a neurocognitive level, traumatic experiences involve decreased activity in Broca's language-processing area and increased activity in areas that govern intense emotions and visual images, such as the amygdala and the right secondary visual cortex (Rauch et al., 1998). This leads to incoherence and disorganization of trauma narratives that correlate with trauma symptoms (Foa et al., 1995).

Schemas and concepts are central to the constructivist approach. A schema is a cognitive structure containing a concept and the relationships among its various attributes (Fiske, 2004). At a cognitive level, traumatic experiences are too alien and too discrepant from previous schemas to be automatically integrated (Wigren, 1994). Unexpected experiences that do not fit into previous existing mental schemas can become dissociated or forgotten. The creation and evolution of schemas occur through the dual processes of *assimilation* and *accommodation* (Furth, 1969). In the former, familiar experiences are categorized and incorporated into existing schemas, thereby strengthening them; in the latter, schemas are modified in order to account for novel experiences that cannot be categorized into existing schemas.

Lastly, as may happen with some psychedelic experiences, people affected by certain traumatic events may perceive the experience as too intimate to be told, fear the implications it may have on others, or fear being misunderstood or socially censured. On this relational level, traumatic experiences are typically only related as a highly "edited" or censored story to others, often resulting in a "silent story" that lives continuously in the traumatized person's own rumination (Neimeyer, 2019).

For these reasons, the constructivist model of grief intervention (Neimeyer, 1999, 2019, 2022; Gilbert, 2002; Shear et al., 2011) identifies narrative reconstructions of the trauma experience as central to the therapeutic process. This model involves integration

of sensory trauma memories by representing them linguistically as part of the healing process within the trauma narrative (Wigren, 1994; Peri and Gofman, 2014). In this narrative technique, traumatic experiences are assimilated and accommodated into previous schemas using questions like: *How do my religious or philosophical beliefs help me accommodate this experience* and *how are they changed by it in turn?* (Neimeyer and Thompson, 2014).

Based on the aforementioned similarities between traumatic and psychedelic experiences and the long-term benefits of meaning-making through narration, we suggest an adaptation and implementation of Restorative Retelling (RR) for semantically processing psychedelic experiences, including but not restricted to those related to a grief process. The adjustment of RR for the processing of ayahuasca experiences is described here through a detailed evidence-based case report.

Restorative Retelling

Restorative Retelling is a clinical procedure in which a trained mental health professional supports a bereaved client in closely reviewing and relating the story of a traumatic event, or in this case a psychedelic experience, under conditions of high safety and low avoidance (Rynearson, 2006; Salloum and Rynearson 2006; Neimeyer, 2012a, 2019; Neimeyer and Rynearson, 2022). Sometimes drawing is encouraged to externalize and illustrate any "hot spots" and facilitate their integration (Correa, 2016).

a. The **assimilation process** involves the following steps: First, grounding the client in personal, relational, or community sources of resilience. Second, inviting the client to vividly relive the experience, using the present tense to potentiate emotional engagement with the memory. Third, slowly panning the "camera" of attention over the details of each scene, noting emotionally significant material. Fourth, moving naturally among different narrative voices:

   - The *external narrative* is the account of what happened during experience. The key is to listen carefully, facilitating the development of a detailed sequential narrative.
   - The *internal narrative* is the story of what was happening inside the client as critical aspects of the experience were unfolding around them. The key is to allow clients to acknowledge the intimate impact of their story.
   - The *reflexive narrative* is the meaning-oriented story, which is often suggested by the therapist's implicit questions and the client's interpretations of the events being related. The goal is to trace and create space for the client to make fuller sense of the psychedelic experience.

The final step involves repeatedly reviewing any "hot spots" by regulating the upsurge of strong emotions through mindful breathing or visual distancing from the scene. Emotional processing is facilitated when the client is fully engaged with the memory but at the same time is grounded in the present and not emotionally overwhelmed (See Neimeyer, 2012b and Neimeyer and Rynearson, 2022 for a broader review).

The process of assimilating the experience may take several sessions. When this occurs, the narrative should be punctuated in closed chapters that allow the client to go home feeling safe, avoiding rumination about the experience. Importantly, sufficient time should be allowed for processing the experience, where the therapist and client discuss any insights that the client may have gained from it.

b. The **accommodation process** focusses on a reflective assessment and reorganization of the internal world. Our inner world can be understood in terms of schemas that act as a cognitive-emotional guide for perceiving ourselves, people, and events, and effectively planning and acting in our world (Epstein, 1990). Given that the assimilation of psychedelic experiences has a powerful capacity for mediating major shifts in perspective (Forstmann et al., 2020; Timmermann et al., 2021), the goal of this procedure is to prompt a psychological increase, expansion, or development in cognitive-emotional understandings of themselves, others, and the world.

Useful questions to evoke a reflective assessment of the patient's belief system are as: *Who am I in light of this experience? How does it fit into my existential sense of how the world operates?* (based on Neimeyer and Thompson, 2014). In psychedelic therapy, it can be useful to redirect questions to any specific issues on which clients feel blocked during a psychotherapy process. Special attention must be taken to nurture the reflective process until the client formulates an adaptive meaning-making of their belief system. Three routes have been described to foster posttraumatic growth: strength through suffering, including self-discovery and new self-perception produced over the course of coping and adaptation; the creation of value triggered by a perception of human fragility; and greater complexity and structural growth (Janoff-Bulman, 2014).

Objective

In this paper, we present a case study describing the adaptation of Restorative Retelling for the integration of an ayahuasca experience with a client suffering from complicated grief (CG). The client drank ayahuasca as part of a pilot study for the design of a psychotherapeutic intervention to prevent prolonged grief disorder. We show the changes following the intervention, as measured before the ayahuasca experience and after the Restorative Retelling procedure. We hypothesized that the combined effects of the ayahuasca experience and the Restorative Retelling procedure would lead to an improvement in CG symptoms. The ayahuasca experience narratives were recorded and are shown here in the form of vignettes. The description of the process has a 2-fold objective: to exemplify the use of the Restorative Retelling technique and to show how ayahuasca can naturally evoke key psychological content in the process of grief adjustment.

MATERIALS AND METHODS

Setting

Ayahuasca sessions were conducted in groups of seven participants supported by four facilitators in a private clinic

in Barcelona. Participants were allowed to sit or lie on mattresses while listening to a playlist of selected music while blindfolded with a mask.

The Participant

A.O. was a 29-year-old queer woman and the elder of two children. A.O's mother completed suicide at home by throwing herself off the balcony, leaving A.O. and her younger brother alone in their house aged 4 and 2, respectively. However, A.O was not present in the room when her mother died by suicide and has hardly any memory of her. A.O. lived her whole life believing the story her family told her about how her mother died in an accident. At the time, she gave her consent to participate in the pilot study, A.O's aunt had confessed to her the truth about her mother's suicide story. These provoked overwhelming feelings of grief and rejection toward her family for having felt cheated throughout her life, especially by her father. She also complained of having trouble moving forward with her life due to an intense longing for her mother and a family she could trust. She scored 51 on the Inventory of Complicated Grief (ICG) at the baseline assessment, meeting the criteria for complicated grief (Prigerson et al., 1995).

Procedure

The course of the pilot study involved 14 weekly psychotherapeutic sessions and three ayahuasca experiences. The ayahuasca sessions were carried out in groups of four participants supported by five facilitators. Consistent with Greer and Tolbert (1998), facilitators created a setting of safety and support trying to limit their interventions to the explicit requirements of the patient. The sessions were accompanied by a curated soundtrack with alternating periods of silence. Participants followed a schedule, meeting at the clinic at 9 am. After explaining the program of the session, participants' weights were measured in order to calculate the exact dose for each one. At 10 am, different techniques were carried out to encourage communication among participants and to anchor the topic of grief in their mindsets (Hedtke, 2012; Rollo-Carlson, 2015; Chow and Chu, 2016). At 11 am, the ayahuasca session began, lasting 4 h. After the ayahuasca session, participants were offered a vegetarian meal. At 4 pm, art materials were offered so that participants could express their experience on a visual artistic level. At 5 pm, a sharing circle was held in which participants could share their experience with the other members of the group. During this dynamic, participants were encouraged to cultivate active listening and not give any type of feedback on the experiences of their peers. At 7 pm, the specific questionnaires were distributed to assess the psychological state of each participant. The sessions of retelling the narrative of the ayahuasca experience were conducted individually by the psychologist in the same clinic from 3 to 5 days after the ayahuasca experience. Each narrative reconstruction session lasted approximately 90 min.

The psychological content that emerged during the first ayahuasca session in this case study was not directly related to the grief process. Immediately following the second ayahuasca session, A.O. unexpectedly relived the traumatic event of her mother's suicide, visualizing details of the scene she never witnessed. The Restorative Retelling of the second experience brought some posttraumatic growth, *via* the route of "strength through suffering." The narrative of the third ayahuasca experience is described in Qualitative Outcomes.

Measures

Inventory of Complicated Grief

The ICG (Prigerson et al., 1995) is a self-report questionnaire that assesses indicators of pathological grief in 19 Likert-type items scored from 0 to 4. Higher scores imply higher severity of grief, with a score of ≥30 indicating complicated grief (Shear et al., 2005).

The Symptom Check-List-90-Revised

The Symptom Check-List-90-Revised (SCL-90-R; Derogatis, 1994) is a self-report questionnaire that uses 90 Likert-type items scored from 0 to 4 to assess nine psychopathological symptomatic dimensions: Somatization (SOM), Obsessive–Compulsive (O–C), Interpersonal Sensitivity (I–S), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), and Psychoticism (PSY). In each scale, higher scores imply worse symptomatology.

Ayahuasca Analyses and Dose

The ayahuasca was provided by the Santo Daime church, Estrela D'Alva (Barcelona). The ayahuasca was prepared by boiling the stems of *Banisteriopsis caapi* and *Psychotria viridis*. Analyses were carried out by Energy Control[1] using liquid chromatography-mass spectrometry (LC–MS). Ayahuasca contained 0.5 mg/ml DMT, 0.03 mg/ml tetrahydroharmine, 0.08 mg/ml harmaline, and 1.4 mg/ml harmine.

Two doses were administered in each ayahuasca session: a first standard dose for all participants of 40 ml and, 35 min later, a second dose of 97 ml in the case of this participant (2 ml/kg body weight). Measurement of the second dose was consistent with previous literature, which establishes 1.0 mg DMT/kg body weight as a high ayahuasca dose (Riba et al., 2001). This dosing schedule was based on the estimated metabolization time for monoamine oxidase inhibitors (MAOIs) to achieve second-dose complete absorption of DMT (Riba et al., 2003).

Statistical Analyses

The Reliable Change Index (RCI) for ICG and SCL-90-R was computed according to Jacobson and Truax (1991) and Bauer et al. (2004), using previous data sets to obtain the SD and a coefficient for each measure (Prigerson et al., 1995; Sánchez et al., 2002; Tomioka et al., 2008; Parro-Jiménez et al., 2021). In this study, values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS for Windows, version 20).

[1]energycontrol-international.org

RESULTS

Qualitative Outcomes: Restorative Retelling of the Third Ayahuasca Session

Assimilation

Given that a therapeutic alliance already existed between A.O. and the therapist, the session began directly with body-awareness and relaxation exercises. Next, A.O. was invited to close her eyes and remember what happened during the ayahuasca ceremony. She was asked to identify the most emotionally charged fragments of her experience and organize them into a coherent narrative. When she felt ready, she began to retell the experience in detail, dividing it into two parts.

First Part

A.O. describes how she went "*to another place, suddenly with a jolt*" and began to have "*loads of visions: of animals, shapes, colors, junk*," with feelings of a "*panic I'd never felt before, like in a dream*." She was afraid of "*losing control*" and "*being alone*." She felt that in this other place "*nobody could help me*."

> *Participant: They were like a figure, one on top of the other… they turned into a totem pole, the totem was a mask, with like, aggressive faces… like sneering demons sticking out their tongues, long tongues. They were in front of me, they came for me and grabbed at me… it was like… fuck! Where the hell has this come from? It's so real!… This actually exists in some place, and I'm in that place…*
>
> *Therapist: Do these figures mean anything to you?*
>
> *Participant: The figures? (shakes her head) …no… well, yeah, they do kinda but I would not know how to describe it.*
>
> *Therapist: What do these figures suggest to you?*
>
> *Participant: I do not know if I've been conditioned from seeing Mexican art… but now that I think about it, it was like they were guardians, entities, and spirits.*
>
> *Therapist: Why do you think they appeared at that moment? What role could they be playing?*
>
> *Participant: … they were there to make me understand… or to make me aware of other states. They appeared in order to show themselves. So that I could "see."*

In this vignette, the therapist intervenes in the narrative, evoking a reflective process about the meaning of the images that the participant considers to be "real." The result was the construction of positive meaning around a phenomenon that did not previously make sense and produced feelings of panic during the experience.

A.O. continues describing her experience: "*In all that mad situation, since I saw that no one on earth could help me, I asked for my mother*."

Second Part

Mother and God

Next, the participant describes how, as she was laying on her mattress during the session, she felt her mother sitting on the edge of the mattress beside her and began to feel in a "*more defined place, with an aura that was, like… heavenly! Like, transparent, as if I was surrounded by a kind of fabric, like a sheen… and this gave me a lot of calm*."

> *Participant: And I remember that there was also a guide, like an entity or something … that gave me the feeling of this… 'Everything', you know?*
>
> *Therapist: this 'Everything'?*
>
> *Participant: Well, I got the feeling that it's what people call God, you know? A god… like God is Everything. It was an energy that was like, unearthly. And it… this energy brought me to my mum. It had a really strong bond with my mother.*
>
> *Therapist: How do you feel when you are with your mum and this energy that's 'like god'?*
>
> *Participant: Well, the way I feel it, it's like how love is unconditional, but love like… (she hunches over and thinks) like love is the be-all and end-all. It's the meaning of life.*

After being asked about the internal narrative, the participant recovers memories stored in her episodic memory, and, reflecting on them, she constructs a new metaphysical meaning of reality, with great potential for reorganizing and making sense of her life.

Mother and Relatives

The participant describes how her mother went in and out of the scenes, showing different situations to her. In the next scene, mother and daughter are watching a family meal from outside. During this scene, the mother communicates to the participant a need "*to have a kind of alliance with me, admitting that things had been tough (family dynamics after the suicide), that she understood that my relationship with my father was difficult … with my uncles… but that I had to understand it all from their point of view*."

Therapist: She wanted you to understand your family?

Participant: Yeah, that she'd left behind a really difficult situation for everyone… and that they all had their own crosses to bear, their own stuff to deal with and they could not have dealt with things any differently, same as I could not have… She wanted me to see beyond the surface of things.

Therapist: So that dialog with your mother allowed you to understand your relatives from another point of view?

Participant: Yeah.

Therapist: And what did you feel, being able to understand them differently?

Participant: I felt, like, unconditional love. And at the same time I felt so sorry, like, a deep sense of pity… because they had lost a sister, and the way they lost her… and my father was her partner. Perhaps my father is a waste of space, who's maybe never done anything right, never helped me to get better, but that's not… not the whole picture.

By carefully integrating the external and internal narratives of the ayahuasca experience, the participant is able to assimilate this new information about her family and can also accommodate previous schemas that had perpetuated difficult family relationships, in order to adopt a more compassionate attitude.

Mother Asks for Forgiveness

In the next scene, the participant and her mother meet each other in private "*and she just broke down… she begged me for forgiveness, and she accepted responsibility for the way things had turned out. It was as if she had not been able to cure herself in life, she was never able to see what I was seeing….*"

After the therapist digs a little into the meaning of this conversation, the participant explains, "*I've always had this need to have a talk with my mother that I could never have, and nobody could take her place*." This fragment clearly demonstrates a potential resolution of "unfinished business."

Mother During the Coma State

A.O. continues explaining the next scene of her experience.

Participant: Then I'm in another situation where it's like I'm there, as if I was her, in the hospital bed, and I'm, like, not completely dead yet… I think she must've felt so bad in that moment. I do not know if it's just my projection because it's something I've thought about so many times…

Therapist: … what exactly did you experience in that moment?

Participant: I was lying on the bed like this (she lies down), and suddenly, I do not know how, I lifted my hands (she crosses her hands across her chest) …and in that moment… bam!… I experienced being in a coma. Then I got hit by this huge wave of sadness, that was the same sorrow that she was going through in that state, my mum. And then I became aware of, like, fuck, I've gone and thrown myself off the balcony, I've left my two children in the house, this has really happened, I'm here… and so much sorrow, so, so much sorrow (she buries her face in her hands).

In this vignette, the therapist refocuses the participant's story, eliciting the external voice of the experience to redirect the narrative toward what happened during the experience, in order to preserve the narrative thread and continue with the assimilation of the experience.

In this case, we see how copying certain body positions that she had while under the effects of ayahuasca helped the participant to evoke clearer memories of her experience.

Funeral

A.O. describes how in the following scene she becomes a participant in a new funeral for her mother, since she was not allowed to attend the real funeral.

Participant: …and the funeral, well it's happy. I mean, like, not super happy… it's emotional. As if everything I was experiencing with all this energy (the "Everything" or "God") was being projected onto all of us, and the family was soaking it all up, you know?…

Therapist: What emotions were there?

Participant: like, a feeling of community… of being at peace with the process of death. Like, understanding that death has some kind of meaning.

Therapist: What meaning does death have, for you?

Participant: …that everything's not like it seems… that there are laws that move things that have a deeper consequence, that we cannot see right now, and maybe we'll never see in this life. If we could see it in levels, like… this happens here, but also there (she gestures with raised

hands), what's happening is something else. So then you say… ah, right! (death) is just another collateral damage, nothing more. But you only see someone who's sad, who's suffering, who leaves her kids in a flat, taking her own life… it's wild.

Following the natural course of the narrative, eliciting the reflexive inner voice, the participant constructs a richer and more complex hierarchy of beliefs, which allow her to accommodate her previous schemas regarding death.

Accommodation

The accommodation process of the ayahuasca experience centered on the schemas that the participant previously held regarding her mother, her relatives, the world, and herself. Here, we look at the accommodation process regarding the schema of her mother.

Therapist: Okay…, thank you for sharing your experience. If you wish, you can open your eyes when you are ready (Leaving enough time for her to sit up and open her eyes) …How do you feel?

Participant: (smiling) Good.

Therapist: Now, let me ask you a few questions about your experience. Do you think that this experience has changed the impression you had about your mother, in any way? Is there any kind of knowledge or information you have now, that you did not have before?

Participant: Yes, the only thing is, like… the reality of everyday life makes you… (she sighs) I dunno. But it's definitely left its mark; something has changed. There's a bit of it that will not be the same as before, but I do not know if it's specifically about how I see my mother… Like, after the experience, I get the feeling that I even see her differently in the photos.

Therapist: Differently? Can you tell me about those changes in the photos?

Participant: It's still her, but her attitude has changed… she seems more calm, more serene… like she had this dark, heavy energy before… but now it's like I look at the photo and I remember that second part (of the experience), that language… then, I look at the photo in a different way, I explain it to myself differently, and I see her in a different way.

Therapist: And has all this promoted any change in how you relate with her?

Participant: Yes, because I think that now she's… closer, more… accessible! …it used to be so disturbing because she's someone who disappeared and just… she was gone, there was nothing. Nothing! And now I have my little place (clasping her hands across her chest) where, if I want, I can find her. There's a space here where we can find each other. Not in the human and material way that I want, but now she's closer and more within reach. I have more tools and resources, because I've seen it and experienced it, so I know that if I want, and if I make the effort—because I see it as an effort—I can access her. I can ask her to be there, and she'll be there.

In this case, concrete questions about the experience's impact on schemas that play a key role in the grief process facilitate reflection and a reconstructed bond of connection with her mother in the present moment.

Quantitative Outcomes: Assessment

Complicated grief symptoms and psychopathology were assessed before taking ayahuasca (third session) and after the restorative procedure (**Table 1**). The participant did not meet the criteria for CG in the post-assessment. Depressive symptomatology was also significantly reduced at the post-test ($p < 0.001$).

DISCUSSION

Restorative Retelling for Processing the Ayahuasca Experience

This case report shows an adaptation of Restorative Retelling—an approach originally developed to construct narratives around traumatic death (Rynearson, 2006)—for processing psychedelic experiences. The results provide preliminary support for Restorative Retelling's effectiveness following psychedelic experiences, showing a clinically significant decrease in

TABLE 1 | ICG and SCL-90-R subscales before ayahuasca ingestion and after Restorative Retelling (RR).

	Score		
	Before	**After**	**RCI**
ICG	34.00	7.00	−3.59***
SCL-90-R			
Somatization	0.42	0.25	−1.31
Obsessive–compulsive	0.20	0.20	0.00
Interpersonal sensitivity	0.44	0.22	−1.12
Depression	1.38	0.62	−3.88***
Anxiety	0.10	0.10	0.00
Hostility	0.33	0.17	−0.58
Phobic anxiety	0.14	0.14	0.00
Paranoid ideation	0.83	0.33	−1.91
Psychoticism	0.60	0.40	−1.20

***$p \leq 0.001$. RCI: Reliable change index was calculated according to Jacobson and Truax (1991) using the formula of Bauer et al. (2004).

psychopathology levels as measured before the ayahuasca experiences and after the retelling process. This improvement in ICG symptoms and GSI was consistent with studies showing a link between organized, coherent narratives and a general decrease in psychopathology (Greenberg and Angus, 2004), PTSD symptoms (Foa et al., 1995; Jelinek et al., 2009), depression (Nelson and Horowitz, 2001), and grief (Barbosa et al., 2014).

Retelling the narrative of an event is a technique which can reduce Prolonged Grief Disorder symptoms (PGD; Boelen et al., 2007; Simon, 2013; Peri et al., 2016). However, our adaptation of this technique includes some novel characteristics. Dividing the process into two sections—one focused on assimilation and the other on accommodation—is not indicated in the original technique, where both are covered naturally during dialog between patient and therapist. In our adaptation of this technique for psychedelic experiences, we have established that the accommodation of schemas also emerges naturally during the assimilation phase, especially when the reflexive narrative is evoked. Nevertheless, given that psychedelic experiences have a powerful capacity for mediating major shifts in perspective (Timmermann et al., 2021), we considered it may be relevant to dedicate a section focused specifically on the accommodation of key schemas in the patient's therapeutic process. This not only encourages assimilation and meaning-making of content that emerged during the psychedelic experience, but also facilitates the reconstruction of a richer and more complex reality. When changes to previous schemas are particularly profound, we consider it appropriate that patients receive ongoing support from the therapist during their adaptation to this new reality. In this way, the health professional can maximize long-term therapeutic potential and minimize any risks derived from carrying out major changes that could affect third parties.

Changing previous schemas and meaning-making of emerging symbolic content may be mechanisms of change in psychedelic therapy (Meikle et al., 2020; Hearn, 2021; Nayak and Johnson, 2021). Restorative Retelling fosters both processes, facilitating the integration of the experience into autobiographical memory and promoting its long-term benefits. Moreover, it is consistent with the inner-directed approach used in psychedelic therapy, where the therapist encourages the client to look into their inner experience for insights (Mithoefer, 2017; Phelps, 2019). We hope this technique may complement other techniques for psychedelic experience integration such as psychedelic-assisted psychotherapy practices, somatic techniques, and mindfulness based-modalities (Gorman et al., 2021).

Therapeutic Potential of Ayahuasca With Grief

This case report highlights ayahuasca's potential for evoking the emergence of key psychological content in the adaptation of grief processes. In this experience with ayahuasca, the participant connects with the presence of her mother, and together they go through a series of different scenarios. This particular experience was evoked by ingesting ayahuasca, but between 50 and 80% of bereaved people experience a "sense of presence" of the deceased person, either in daily life or in vivid dreams, without the use of psychedelics (Steffen and Coyle, 2010). These experiences of a "sense of presence" are no longer considered to be symptoms of an underlying mental health condition nor a sign of pathology (Hayes and Leudar, 2016). Although in some cases, these experiences can cause distress, most bereaved individuals report feeling reduced loneliness, less intense pain from the loss, a helpful sense of connection and comfort, and receiving guidance or encouragement from the deceased (Hayes and Leudar, 2016; Jahn and Spencer-Thomas, 2018). These experiences can help create a framework for meaning-making following the death of a loved one, facilitating increased coping and growth, benefit-finding, and identity-change processes that can lead to posttraumatic growth (Steffen and Coyle, 2010).

We want to emphasize that, from our perspective, the most relevant aspect in our participant's adaptation of grief was a significant shift in her schema or "internal working model" of her mother, facilitated by the experience of "contact" with the presence of her mother. In this case, a new image of her mother, serene and calm, replaced the dark and tragic representation of her that the participant had previously harbored. Schemas or "internal working models" provide a connection with attachment figures, even in their physical absence, and the quality of this schema determines the attachment style with the loved one (Bowlby, 1982; Bartholomew and Horowitz, 1991). This implies that the transformation in the participant's internal representation of her mother has the potential to transform the style of bond she has with her, probably moving from an insecure or anxious style to a secure bond. The new paradigm in the adaptation of grief centers on continuing the bond with the deceased after death, rather than detachment and "moving on" in a linear way (Klass et al., 2014). For this reason, fostering a secure attachment with the deceased is the objective of various contemporary techniques employed in grief therapy (Neimeyer, 2012b, 2016, 2022; Kosminsky and Jordan, 2016). This is because secure relationships with attachment figures facilitate biological regulatory responses such as affective, attentional, and motivational processes (Shear and Shair, 2005). During the grief process, having a healthy, ongoing bond with the deceased can facilitate post-loss emotional processing, worldview reframing, and growth (Currier et al., 2015). Surprisingly, the impact of this change in the schema or internal representation of the mother was so powerful that it was even projected into the participant's perception of the outside world as she looked at the photograph of her mother. To the best of our knowledge, the therapeutic potential of grief adaptation caused by the transformation of the internal working model of the deceased has not yet been specifically studied. This may be because the concept of internal working models is vague and untestable, and they are considered to be fixed, non-changing long-term representations. Future research is needed, focusing on equivalent and testable concepts such as cognitive schemas (Bosmans, 2009).

A similar process happened for the participant regarding the rest of her family, especially with her father, where the "conversation" with her mother helped her to reinterpret her family situation in a way that alters its meaning and changes its emotional impact. This cognitive reappraisal of the family grief processes led the client to regulate her emotions, transforming her anger into

compassion. A follow-up would be necessary in this case to observe the long-term impact on the quality of family relationships.

Another aspect that emerged naturally during the ayahuasca experience is the resolution of "unfinished business." "Unfinished business" is defined as any incomplete, unexpressed, or unresolved relationship issues with the deceased and has been considered a risk factor for chronic and severe grief reactions (Klingspon et al., 2015). Given that the participant longed to have an explanation of why her mother killed herself, the ayahuasca experience allowed her to understand that her mother was not able to cure herself in life. This information may not have been new for the participant, but it seemed important for her to receive it "directly" from her mother.

The elaboration of a narrative from the psychological content that emerged spontaneously, like love as the ultimate goal of existence, God as an "everything," and the different levels of reality between life and death, implies the elaboration of superordinate or core features of a personal meaning system. These evoked superordinate constructs reflect central existential themes of meaning and purpose to a greater extent than subordinate constructs like personal or intellectual constructs (Neimeyer et al., 2001). Constructs functioning at this level of superordination are of fundamental importance for constructing the schemas of the self, others, and the world, which guide our behavior (Hinkle, 1965).

Limitations

While this case report presents preliminary support for Restorative Retelling for processing psychedelic experiences, further validation in studies using larger samples is needed. Additionally, the lack of assessment after the ayahuasca experience and before Restorative Retelling procedure limits the differentiation of the potential contribution of the ayahuasca experience itself to the reduction of symptoms. Follow-up could determine whether changes observed during this procedure are stable for longer periods afterward. An additional limitation of our study is that this adaptation of the technique is composed of the assimilation and the accommodation processes, but the unique contribution of each could not be differentiated here. Only larger scale studies to assess each component will help to clarify this question. However, even after considering these limitations, this case report suggests that Restorative Retelling may be useful for processing and meaning-making of psychological content that emerges during psychedelic experiences.

CONCLUSION

This study offers preliminary findings in support of Restorative Retelling as an effective technique for emotionally processing psychedelic experiences, fostering meaning-making in the life of the patients. Furthermore, this study shows how ayahuasca can evoke experiences that have a therapeutic potential in grief adjustment difficult to achieve with the classical therapeutic tools used in psychotherapy. Further research is needed to elucidate the therapeutic value of psychedelics by themselves from the contribution of the Restorative Retelling technique in the long-term relief of psychopathological symptoms and personal growth.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CEIC-Parc de Salut Mar, Barcelona, Spain. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DG conceptualized the study design. DG and MBA collected the data and performed the intervention. JC analyzed the data. DG, RN, DN, and MF wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was financially supported by the Riverstyx Foundation (United States) and the Verein Unfolding Light (Switzerland).

ACKNOWLEDGMENTS

The authors wish to thank all the volunteers for their participation and contributions to our understanding in this field. Especially, thanks to Pep Cunyat for his guidance and the Riverstyx Foundation for its support in the development of the pilot study.

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REVIEW
published: 23 May 2022
doi: 10.3389/fpsyg.2022.873279

Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default

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The acute subjective effects of psychedelics are responsive to users' expectations and surroundings (i.e., "set and setting"). Accordingly, a great deal of thought has gone into designing the psychosocial context of psychedelic administration in clinical settings. But what theoretical paradigms inform these considerations about set and setting? Here, we describe several historical, sociological influences on current psychedelic administration in mainstream European and American clinical research settings, including: indigenous practices, new age spirituality from the 1960s, psychodynamic/psychoanalytic approaches, and cognitive-behavioral approaches. We consider each of these paradigms and determine that cognitive-behavioral therapies, including newer branches such as acceptance and commitment therapy (ACT), have the strongest rationale for psychedelic-assisted psychotherapy going forward. Our primary reasons for advocating for cognitive-behavioral approaches include, (1) they avoid issues of cultural insensitivity, (2) they make minimal speculative assumptions about the nature of the mind and reality, (3) they have the largest base of empirical support for their safety and effectiveness outside of psychedelic therapy. We then propose several concepts from cognitive-behavioral therapies such as CBT, DBT, and ACT that can usefully inform the preparation, session, and integration phases of psychedelic psychotherapy. Overall, while there are many sources from which psychedelic psychotherapy could draw, we argue that current gold-standard, evidence-based psychotherapeutic paradigms provide the best starting point in terms of safety and efficacy.

Keywords: psychedelics, psilocybin, LSD, psychedelic assisted therapy, cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), acceptance and commitment therapy (ACT), psychedelic assisted psychotherapy

OPEN ACCESS

Edited by:
Dea Siggaard Stenbaek, University of Copenhagen, Denmark

Reviewed by:
Daniela Flores Mosri, Universidad Intercontinental, Mexico
Steven C. Hayes, University of Nevada, Reno, United States

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *10 February 2022*
Accepted: *14 March 2022*
Published: *23 May 2022*

Citation:
Yaden DB, Earp D, Graziosi M, Friedman-Wheeler D, Luoma JB and Johnson MW (2022) Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default. Front. Psychol. 13:873279. doi: 10.3389/fpsyg.2022.873279

INTRODUCTION

Classic psychedelics, such as 5-HT2a partial agonist psilocybin, are being tested for their potential therapeutic effects. Psilocybin is well-tolerated in clinical settings in which precautions have been taken to screen out participants who might have medical or psychological contraindications and where clinicians are available to provide support (Johnson et al., 2008). In general, the risks of toxicity and addiction are comparatively low with psilocybin compared to other recreational

psychoactive substances (Johnson et al., 2008; Nichols, 2016), though there are risks to psychedelic use in general which are increased in recreational settings (Carbonaro et al., 2016). Clinical trials have demonstrated the therapeutic potential of psilocybin on both mood (Carhart-Harris et al., 2016, 2021; Griffiths et al., 2016; Ross et al., 2016; Davis et al., 2021) and substance use disorders (Johnson et al., 2014; Bogenschutz et al., 2015). Further safety and effectiveness trials are needed (Yaden et al., 2021d), but it is possible that psilocybin (and perhaps other classic psychedelics) will be approved for clinical use in the next few years. While current psychotherapeutic and pharmacological treatments are effective, additional treatment options are needed for those suffering from mood and substance use disorders.

Classic psychedelics present a number of challenges and opportunities in terms of their clinical application. Importantly, the acute subjective effects of classic psychedelics such as psilocybin are highly responsive to one's expectations and physical/social surroundings (referred to as "set and setting"; Hartogsohn, 2016). This raises the question—-what psychotherapeutic paradigm(s) should most inform the administration of classic psychedelics such as psilocybin?

In this article, we review several historical, sociological influences on the development of contemporary classic psychedelic administration in mainstream healthcare and clinical research settings in European and American cultural contexts. Specifically, we briefly review indigenous practices, new age spirituality, psychodynamic/psychoanalytic approaches, and cognitive-behavioral approaches. After succinctly evaluating each of these and pointing to several issues with each (although extensive analyses of these paradigms goes beyond the scope of the present article), we focus on cognitive-behavioral therapy (CBT) approaches in more detail (also see Walsh and Thiessen, 2018; Luoma et al., 2019) and suggest that these approaches have the most evidence and rationale for serving as a default therapeutic paradigm to combine with psychedelic treatments in contemporary healthcare contexts. While much of what we discuss will apply to other psychoactive substances (e.g., MDMA, ketamine, DMT, etc.), we focus our discussion on classic psychedelics such as LSD and psilocybin. Lastly, we provide a sampling of concepts from CBT approaches, particularly from so-called "third wave" CBT, that we think can usefully inform the preparation, session, and integration phases of psychedelic-assisted psychotherapy.

INDIGENOUS PRACTICES

Historically, psychedelics appear to have been ingested in a number of regions across a wide range of cultures for hundreds or even thousands of years (Schultes, 1969; Miller, 2019). The available archeological and anthropological evidence suggests that psychedelics have often been used in ritual settings (and they still are, as discussed below), generally accompanied by the invocation of a society's religious worldviews by a religious leader (e.g., see Miller, 2019). We refer to this approach as "indigenous practices" as this is the term that has been used most by others in contemporary discourse, although we acknowledge that some may object to the use of the term indigenous term in this context. There are a number of contemporary religious traditions, such as the Peyote Church, in which psychedelic substances are ritually ingested. People who engage in these religious practices have a history of being oppressed by colonialists and in more recent eras by prohibition (e.g., see George et al., 2020).

Some have called for more integration of indigenous practices in contemporary, mainstream psychotherapeutic settings using psychedelics (e.g., Winkelman, 2007). The rationale for this view is that some religious practices may have been honed for many decades in order to maximize the beneficial effects of psychedelics. Proponents of this view might suggest that we ignore practices that have been developed over generations at our peril, as such practices could perhaps benefit participants and patients in contemporary healthcare settings.

We agree that such indigenous contexts should be studied, but we see problems with the view that such practices should be incorporated in secular clinical settings. First and foremost, it could be offensive to decontextualize certain kinds of religious practices and transplant them into secular clinical settings. These practices are usually overseen by elders and traditional healers (Portman and Garrett, 2006) and an abundance of literature urges mental health practitioners to partner with these members of indigenous tribes and nations (Dufrene and Coleman, 1992; King, 2008; Gone, 2010; Trimble, 2010). This could be regarded as a case of cultural appropriation, as there is a power differential and potential to profit from adopting such practices in secular healthcare settings. Thus, there are important moral considerations that would seem to largely or entirely prevent drawing from indigenous practices and requisitioning them for use in contemporary healthcare settings. Additionally, *such practices have not been empirically evaluated in clinical settings, so their safety and effectiveness are mostly unknown*, particularly for individuals who do not share in the worldview associated with such practices. Therefore, applying such practices with the bulk of participants likely to receive treatment in mainstream clinical settings could put participants and patients at increased risk.

Of course, if a participant or patient *already* held these beliefs and chose to interpret their personal experience accordingly (see Graziosi et al., 2021), the therapist should accept this as the patient's worldview and support this participant without disagreeing or suggesting other metaphysical belief systems. As we will reiterate, therapists should not be promoting their own metaphysical belief system to patients (Moreira-Almeida et al., 2016; Johnson, 2020; Koenig et al., 2020; Yaden et al., in press, 2021a). Overall, we believe that treatment should be adapted to the cultural contexts and identities of those seeking treatment but that directly borrowing from indigenous traditions is not an appropriate means to do so for most patients or practitioners.

NEW AGE SPIRITUALITY

Before the current so-called "renaissance" of psychedelic research in the last decade or so, psychedelics were largely associated in the public and even among researchers with the 1960s (e.g., Pollan, 2019). During this period, psychedelics emerged from the laboratory and were adopted by various sub-cultures, including

what has been called "new age spirituality" (e.g., Luhrmann, 2012). New age spirituality is a syncretism of various religions, perhaps especially Hinduism and Vedanta, and involves a set of flexibly defined highly personal beliefs. Such beliefs generally (but not necessarily) involve a divinity of some kind and persistence of consciousness after death (Yaden et al., 2021b). While there was a great deal of research conducted on psychedelics in laboratories all over the US during this period of time, the most high-profile research was conducted at Harvard by professors who were later fired or contract not renewed—Timothy Leary and Richard Alpert (Baumeister and Placidi, 1983). These two researchers explicitly mixed new age spiritual ideals into the therapeutic context in the hopes of enhancing the therapeutic effects of psychedelics (Lattin, 2010).

Some have called for more integration of new age spirituality in contemporary psychotherapeutic settings (e.g., Roberts, 2020). The rationale for this view is that beliefs involving a benevolent all-encompassing divinity that one might encounter and/or connect with appears intuitively likely to reduce the chance for a negative experience and could enhance the beneficial effects of psychedelics. There is in fact good evidence that people report experiences of this kind spontaneously (Yaden et al., 2017b; Griffiths et al., 2019; Davis et al., 2020b). However, the extent to which such experiences are the result of the intrinsic effects of psychedelic substances interacting with innate cognitive/perceptual systems or are culturally constructed from available beliefs and expectations is unknown (see Yaden et al., 2017a). To be clear, we see great potential in studying the interaction of psychedelics with beliefs and practices broadly construed as "spiritual."

However, we see problems with integrating spiritual worldviews into psychedelic psychotherapy in clinical settings. First, there are serious ethical issues with a therapist imposing their own particular worldview (religious, spiritual, atheistic, or otherwise) on a participant or patient (see Johnson, 2020 for a discussion). Psychedelic substances appear to create a suggestable state (Carhart-Harris et al., 2015), which could put participants and patients in a vulnerable position (Johnson, 2020). Additionally, there has been little research on actively encouraging a spiritual framing of psychedelic experiences in therapeutic settings, which means that adopting such a therapeutic frame has unknown risks (see Johnson, 2020). From a secular clinical perspective, we simply have no expertise or knowledge of ground truth regarding metaphysical or religious questions, and the imposition of such content could be considered an epistemological harm (Letheby, 2021). As in the previous section, if a participant or patient holds such beliefs, choosing to engage with them before, during, or after their experience is entirely appropriate and is not the topic under discussion. This does not include the provision of knowledge or expertise but rather taking the patients lead and, for example, using reflective listening to help them process their thoughts and feelings. Here again we emphatically discourage the imposition of a belief-based therapeutic paradigm adopted by researchers and clinicians onto patients or study participants (see Moreira-Almeida et al., 2016; Koenig et al., 2020; Yaden et al., in press).

PSYCHOANALYTIC AND PSYCHODYNAMIC

Psychedelics were generally not commented upon by the founders of the psychoanalytic movement (Sigmund Freud etc.—although Jung has a brief letter on this topic, see Jaffe, 2015), so the typical strategy of referencing and interpreting historical texts that often occurs in psychoanalytic circles is not as possible in this case. In general, psychoanalytic approaches postulate the existence of active unconscious forces or dynamics. Some contemporary researchers and clinicians have promoted the value of the psychoanalytic perspective in understanding psychedelic experience. For example, Carhart-Harris et al. (2014), claim that "scientific research with psychedelics has considerable potential for developing aspects of psychoanalytic theory." Psychedelics are sometimes thought to reveal primary processes (unconscious functioning) in the same way that dreams do, which can then be interpreted by the analyst. Carhart-Harris et al. (2014) also quote Grof in saying: "The phenomenology of the psychodynamic experiences in LSD sessions is to a large extent in agreement with the basic concepts of classical psychoanalysis. . . Observations from LSD psychotherapy could be considered laboratory proof of the basic Freudian premises" (Grof, 1982).

Psychodynamic approaches generally involve less specific unconscious processes than psychoanalysis and refer to a wider range and more eclectic set of approaches than psychoanalysis (Wells, 1963; Eagle, 1984). Many forms of psychodynamic psychotherapy are commonly practiced in contemporary settings, and although their quality is highly variable, there is evidence for the effectiveness of many such approaches (Leichsenring and Steinert, 2017). In terms of psychedelic applications, the most prominent psychodynamic approach is that promoted by Grof (1977, 1980, 1982), which claims that the acute subjective effects of psychedelic substances can best be understood as a figurative and perhaps literal memory of being born (a view with Freudian roots). This "peri-natal theory" of psychedelic experience came to inform his preferred psychotherapeutic framing of psychedelic treatments and was highly influential in underground (i.e., illegal) psychedelic psychotherapy contexts.

At the present time, psychodynamic theory may be the most commonly utilized theory utilized by therapists conducting psychedelic psychotherapy, perhaps because it was ascendant at the time psychedelic therapy was developed and before research essentially stopped in the 1970s.

Furthermore, contemporary psychodynamic approaches conceptualize psychopathology in developmental, cultural, and temporal contexts in which a "persistent personality" navigates conflict and struggles via emotion-laden psychological defenses—understanding these dynamics is ultimately in the service of behavioral change (Fulmer, 2018). These defense mechanisms have been defined as "mental processes that operate unconsciously to reduce some painful emotion" (Paulhus et al., 1997, p. 543). This conceptualization may have been/be useful in approaching psychedelic experience, especially given the flexibility that this conceptualization provides and the intuitive nature of working with an "unconscious."

While sharing a context and goal with psychodynamic approaches, rather than unconscious processes, CBTs target empirically derived processes which are linked (through empirical evidence) to outcomes. As psychedelic therapy emerges from this period of relative quiescence, some have advocated for psychodynamic/psychoanalytic approaches to continue (see Harris, 2021). Psychedelics certainly offer interesting psychological content to try to understand using these perspectives.

However, there are reasons to question this approach. First, psychoanalytic/psychodynamic approaches have fallen largely out of synch with psychological research and cognitive science in general over the past several decades. Psychoanalytic/psychodynamic approaches were criticized decades ago as failing to keep pace with empirical research (e.g., Eysenck and Wilson, 1973; Beck, 1979). Psychoanalytic/psychodynamic approaches are largely separate from scientific research in general, and were used as a paradigm example of an unfalsifiable form of pseudoscience (Popper, 1983). For example, it is generally agreed that there is no way to falsify through a test the proposition of the id/ego/superego structure of the mind. Psychoanalytic/psychodynamic forms of therapy have been generally surpassed by cognitive approaches in terms of empirical support (Beck and Beck, 2011; Beck, 2019), which is discussed in the next section.

COGNITIVE-BEHAVIORAL APPROACHES

The cognitive revolution in psychology built on earlier established empirically based behavioral principles and marked a shift away from the unfalsifiable psychoanalytic understandings of the mind (Miller, 2003). The most prominent pioneer of CBT was psychiatrist Aaron T. Beck, who de-emphasized unfalsifiable theories involving birth memories, early sexual conflicts, and supposed structures of the psyche. Instead, Beck's view took a more empirical approach to psychotherapy development and treatment, focusing more on observable and reportable processes such as beliefs and emotions that could be empirically studied, in theory. In response to critiques that the cognitive approach is too superficial, Beck (2019, p. 17) famously said: "There's more to the surface than meets the eye." By this, Beck appears to mean that there are plenty of reportable beliefs, interpretations, emotions, and behaviors to work with in a psychotherapeutic setting without needing to postulate additional unconscious processes and forces.

Cognitive-behavioral approaches (including traditional CBT, DBT, and ACT, described below) are considered gold-standard forms of evidence-based psychotherapy for many psychological disorders by the American Psychological Association (APA) due to the substantial evidence supporting their efficacy (APA Presidential Task Force on Evidence-Based Practice, 2006; David et al., 2018). Over time, CBT has become more specifically described, articulated, and adapted to various populations and disorders.

Of the cognitive-behavioral approaches, traditional cognitive-behavioral therapy (CBT) involves a systematic assessment of thinking and behavior related to dysfunction and then intentional action is taken to help the client learn more adaptive thoughts and behaviors. Typically, clients are asked to fill out assessment measures specific to their presenting problems, and to self-monitor their own experience; therapists form their case conceptualizations based on these data (Persons, 2008). Sessions are structured to promote efficiency, and clients are guided by therapists to collaboratively evaluate and question their thoughts and beliefs (McGinn and Sanderson, 2001). There are many approaches within CBT to teach adaptive behavior which are both person- and pathology-specific. This traditional CBT approach has empirical support for its utility in treating a wide range of psychological disorders (APA Presidential Task Force on Evidence-Based Practice, 2006; David et al., 2018).

More recent versions of cognitive-behavioral approaches (such as DBT and ACT, described below) are often referred to as "third-wave" cognitive behavioral therapies (Hayes and Hofmann, 2017). Hayes and Hoffman highlight this third wave of cognitive-behavioral approaches as "a set of new behavioral and cognitive approaches. . . Third wave methods emphasized such issues as mindfulness, emotions, acceptance, the relationship, values, goals, and meta-cognition" (p. 245).

One widely practiced third-wave therapy is dialectical behavior therapy (DBT) created by Linehan (2020). It is now used to target a variety of mental health disorders where emotional dysregulation features prominently (Ritschel et al., 2018). DBT elaborates on traditional CBT in a number of ways. First is the central importance of mindfulness skills, which is one of four skills modules (the others are distress tolerance, emotion regulation, and interpersonal effectiveness; Rathus and Miller, 2015). Second, DBT has both an individual therapy and group component which work together to promote symptom reduction and skills use (Linehan, 2015). Third, DBT asks clients to call their individual therapists in crisis situations in order to be coached through effective skills use (*phone coaching*; Oliveira and Rizvi, 2018). These strategies are intended to teach adaptive behavior and ensure that it generalizes to situations in which it is most needed.

Another third-wave therapy is Acceptance and Commitment Therapy (ACT; pronounced "act") the development of which was led by Steven Hayes. Like traditional CBT and DBT, in ACT there is an emphasis on developing awareness of thoughts, feelings, and sensations (Harris, 2006). Like DBT, ACT incorporates mindfulness techniques and promotes acceptance, however, unlike these approaches, ACT doesn't directly target the reduction of dysfunctional thinking or difficult emotions, postulating instead that efforts to control or avoid these experiences contribute to suffering. The ACT approach targets six processes that promote *psychological flexibility,* defined as "contacting the present moment as a conscious human being, fully. . .and persisting with or changing a behavior in the service of chosen values" (Hayes et al., 2012, p. 96–97).

Finally, there are several notable ways cognitive-behavioral approaches may benefit from the partnering with psychedelic administration. First, psychedelics have an impact on processes, notably psychological flexibility (Close et al., 2020; Davis et al., 2020a) and outcomes (e.g., depression and anxiety, Davis et al., 2021; suicidal ideation; Zeifman et al., 2020)

explicitly targeted by cognitive-behavioral approaches. Therefore, empirically understanding the psychedelic experience may provide insight into cognitive-behavioral approaches (and vice versa). This is exemplified by recent work exploring the overlap between psychedelic experience and the sense of self in ACT (Hayes et al., 2020). The authors make explicit that this overlap is an opportunity both for ACT to guide future research in psychedelic science *and* "learn more about flexibility processes" (p. 36). Second, nesting psychedelic administration in cognitive-behavioral-based preparation and integration sessions may amplify the therapeutic effects (and generalization) of these processes and outcomes. Ultimately, consistent with the scientific values of cognitive-behavioral approaches, these sorts of potential synergies must be explicitly tested.

Taken together, traditional CBT, DBT, and ACT (we refer to these three together as cognitive-behavioral approaches) have the merits of more empirically testable claims, theoretical assumptions more linked to contemporary psychological science, and a large base of empirical support for their safety and efficacy. We therefore believe these cognitive approaches ought to be the default psychotherapeutic paradigm paired with psychedelic treatments.

ADDRESSING OBJECTIONS TO THE COGNITIVE-BEHAVIORAL APPROACH

We have encountered some resistance to the view that cognitive-behavioral approaches (CBT, DBT, and ACT) should be the default approach to psychedelic psychotherapy in contemporary healthcare and research settings. Some common objections to this view include issues related to (1) the high prevalence of participants' reports of religious/spiritual/unconscious material, which do not feature prominently in cognitive-behavioral approaches (2) lack of studies pairing CBT with psychedelics, (3) concerns that cognitive-behavioral approaches are often rigidly manualized treatments that unduly restrict patient and clinician choice; and (4) unfamiliarity with concepts from cognitive-behavioral approaches that are relevant to psychedelic treatments.

Regarding objection one, the prevalence of participant reports of content related to religious, spiritual, and unconscious processes, we admit that such reports are prevalent and important to acknowledge. We reiterate our view that participants and patients are free to bring *their own* beliefs and ideologies into psychedelic treatments–as should be the case in all medical and psychotherapeutic treatments (see Peteet et al., 2011). In other words, we are *not* commenting on the frame that participants and patients ought to bring, but rather that used by researchers/clinicians (see Johnson, 2020). In addition, there is much writing to guide how spiritual/religious content can be incorporated into CBT treatments (e.g., Nieuwsma et al., 2016) and ACT, specifically, has a robust theory that addresses typical spiritual experiences that occur in psychedelic-assisted therapy (Luoma et al., 2019) such as mystical experiences that involve self-transcendence (Yaden et al., 2017a) or feelings of interconnection with others or the universe (Watts and Luoma, 2020).

Regarding objection two, the lack of studies pairing CBT with psychedelics: The objection is sometimes made that because psychedelic treatments are so novel, there is a paucity of research on all psychotherapeutic pairings—and, therefore, they should *all* be tried and no particular approach should be assumed the default. While we agree that research is on-going and relevant approaches should be tested, we do not agree that all approaches are equally reasonable candidates. We argue that we have good reasons to choose approaches that fit best with contemporary scientific research, are suited to secular treatment contexts, carry less risk of being culturally offensive, and have more evidence of safety and effectiveness. We believe that CBT represents the strongest family of approaches in each of these regards. Lastly, and crucially, *there have already been successful pairings of cognitive-behavioral approaches with psychedelic treatments*. Specifically, Johnson et al. (2014) combined traditional CBT with psilocybin in a tobacco use disorder trial. Also, ACT has been combined with psilocybin in the treatment of depression (Carhart-Harris et al., 2016; Sloshower et al., 2020).

Regarding objection three, that cognitive-behavioral approaches leads to overly restrictive manualized treatment, we wish to emphasize that we are *not* advocating for the strict application of a particular manualized process in each psychedelic study/treatment, nor for particular interventions to be used in specific sessions. The idea that CBT is an approach that is inherently restrictive of clinician flexibility, creativity, and responsiveness is a straw man. Of course, cognitive-behavioral approaches will need to be adapted to the context of use, for example alongside psychedelic substances (there are numerous examples of doing this for particular diagnoses, patient populations, and other contextual factors; e.g., see Wenzel et al., 2012). Furthermore, any approach can be rigidly applied, including non-cognitive-behavioral approaches. In summary, we believe that cognitive-behavioral approaches should not be used without adaptation to this unique therapeutic context and to the individual patient/participant, but this concern applies to other theoretical approaches as well.

Regarding objection four, unfamiliarity with concepts from cognitive-behavioral approaches that are relevant to psychedelic treatments, we acknowledge that not all researchers and clinicians have had exposure to cognitive-behavioral approaches (e.g., CBT, DBT, ACT) and particularly how cognitive-behavioral approaches are capable of addressing the unique characteristics involved in psychedelic assisted psychotherapy, such as spiritual experiences (see Luoma et al., 2020). Furthermore, we recognize that there are a great number of popular books and articles advocating for the pairing of psychedelic treatments with indigenous practices, new age spirituality, and psychodynamic approaches—-and that there is a relative paucity of such resources for cognitive-behavioral approaches in the domain of psychedelic treatments. This simply speaks to the need for more work to disseminate cognitive-behavioral approaches that address issues which commonly occur during psychedelic states. One advantage of utilizing cognitive-behavioral approaches with psychedelic administration is that there is a long tradition and much expertise in learning how to rigorously adapt and test cognitive-behavioral principles in a wide variety of clinical contexts.

To be clear, our view that cognitive-behavioral approaches should be considered default for psychedelic treatments rests upon the context in which psychedelic administration is being delivered. We do not posit that all psychedelic use everywhere should be grounded in cognitive-behavioral approaches. However, in the current clinical research context, psychedelic-psychotherapy research programs are targeting outcomes for which cognitive-behavioral approaches have been shown to be effective for in experimental studies (e.g., depression and anxiety, Davis et al., 2021; suicidal ideation, Zeifman et al., 2020). Not only are cognitive-behavioral approaches effective for these outcomes, but they are also currently the gold standard of evidence-based care (APA Presidential Task Force on Evidence-Based Practice, 2006; David et al., 2018). Reiterating the synergy mentioned above regarding the overlap between the effects of psychedelic experience and processes and outcomes targeted in cognitive-behavioral approaches, these approaches are the best fit empirically and ethically.

The next section represents an overview of several concepts and techniques from cognitive-behavioral approaches that appear highly relevant to psychedelic psychotherapy (see **Table 1**).

CONCEPTS FROM COGNITIVE BEHAVIORAL THERAPY RELEVANT TO PSYCHEDELIC TREATMENTS

There are a number of concepts from cognitive-behavioral approaches that appear to be highly relevant to psychedelic treatments. In this section, we provide concepts from cognitive-behavioral approaches to inform each step of psychedelic treatments, which can usefully be divided into (1) preparation, (2) dosing sessions, and (3) integration. In the following, we describe these three broad stages of this process (as described in, for example, Johnson et al., 2008, 2019) and then list concepts from CBT, DBT, and ACT that are relevant with a brief explanation of each. Again, this is not meant to be a comprehensive list—and there is overlap in concepts across CBT/DBT/ACT (i.e., each concept is not necessarily unique to each framework), so this should be considered a starting place to show the rich set of concepts to draw from in these psychotherapeutic paradigms. Note that we use the terms patients (but the terms clients and participants can also be used interchangeably) and therapist (but the terms guides, monitors, facilitators, and clinicians can also be used interchangeably).

Preparation

Preparation consists of the sessions that occur in the days and weeks prior to administration of the psychedelic, during which time participants become familiar with the facilitators who will be present during their dosing sessions. This stage often includes extensive psychoeducation about the framework of the dosing sessions, the effects of the substance in question, and experiences likely to occur during the dosing session. Elements related to various theories of intervention may be brought into this stage as well to help orient patients toward the dosing session and to prepare for any difficulties that may arise. (Various expectancies may also be introduced—inadvertently or intentionally—a topic of on-going empirical research). Below we describe how cognitive-behavioral approaches might be used during preparation sessions.

It is commonly accepted across nearly all psychedelic-assisted therapy approaches, including cognitive-behavioral approaches, that a collaborative therapeutic alliance is essential. This alliance involves having shared goals, an understanding of each other's roles, and a degree of comfort working together (Egan et al., 2014). This alliance helps establish a sense of safety and trust in the therapeutic context that is thought to be important in facilitating an effective psychedelic experience. Cognitive-behavioral approaches generally view a solid therapeutic alliance as *necessary-but-not-sufficient* (Beck et al., 1979), and thereby includes other strategies often used in preparing and orienting clients to therapy.

Cognitive Behavioral Therapy

Structured Session Format

A hallmark of traditional CBT sessions is the predictable structure of the session, which is itself a therapeutic tool. Sessions typically have four components: (1) initial check-in, (2) setting an agenda for the session, (3) completing the agenda, and (4) summarization and setting action plans (McGinn and Sanderson, 2001). Examples of agenda items include: treatment targets occurring both in and out of session, high priority-problems or goals, and targets the client wants to put on the agenda (Persons, 2008). Setting the agenda, like the rest of CBT, is a *collaborative* process—the client and therapist are working as a team (Persons, 2008).

The structure of a session provides both patients and therapists with a sense of what to expect. Psychedelic psychotherapy sessions that are predictable in form can help session monitors to make efficient use of time as there is limited time in any therapy session. Organizing and structuring time provides scaffolding for participants and communicates to them that the therapist respects their time and wishes to make the session maximally useful for them. This, along with the predictability and familiarity, can encourage rapport between session therapists and patients.

Psychoeducation

Psychoeducation is a key aspect of traditional CBT, DBT, and ACT. CBT psychoeducation includes a summary of initial assessment results, orienting patients toward the treatment modality and providing a rationale for interventions or treatment strategies (McGinn and Sanderson, 2001). For instance, in psychoeducation for obsessive-compulsive disorder, a patient receives didactic instruction on the cycle of avoidance that maintains unwanted intrusive thoughts and how therapy, using this understanding, is expected to target these symptoms (Abramowitz and Jacoby, 2015). This normalizes symptoms and provides a rationale for why the proposed treatment is expected to be clinically useful.

Psychoeducation for psychedelic therapy, for instance, might involve education about the patient's symptoms and what the treatment itself will entail. It is important that psychedelic

TABLE 1 | Concepts from cognitive-behavioral approaches relevant to psychedelic treatments, by therapy phase (preparation, dosing session, integration).

Concept	Citations	Description	Relevance to psychedelic treatments
Preparation			
CBT			
Structured session format	McGinn and Sanderson, 2001	Predictable session structure (check-in, setting agenda, completing agenda, summary and assigning homework/action plan).	Make efficient use of time, provide structure and predictability for participants, encourage collaboration and rapport.
Psychoeducation	McGinn and Sanderson, 2001	Summary of initial assessment results (discussion of presenting problem/diagnosis), orienting clients toward the treatment modality and providing a rationale for treatment.	Psychoeducation for psychedelic therapy should communicate how psychedelic therapy works or that the mechanism is hypothetical if still under investigation.
Self-monitoring	Egan et al., 2014	Encourage clients to pay attention to thoughts, emotions, and behaviors.	Empowers participants to develop a sense of empiricism about their own experience, develop a sense of baseline experience.
Preparation: DBT			
Pre-treatment and Commitment strategies	Swenson, 2016	Sessions are aimed at increasing commitment to the treatment plan and motivating engagement in therapy.	For the practitioner/monitor: reinforces that treatment is ultimately the participant's decision and facilitates space for that decision to be explored even once "treatment" has begun.
Therapy-Interfering Behavior (TIB) as a key target	Linehan, 1993, p. 129	Focus on behaviors or patterns of interaction that could interfere with effective therapy.	Allows for an open conversation about which parameters might be therapy interfering for given client, session monitors/practitioners become mindful of their own potentially therapy-interfering behaviors
Skills training	Linehan, 1993, p. 329	Teach patients skills to address difficult thoughts and emotions.	Provide participants with tools to aid in tolerating difficulties or making changes in their lives even before any drug is administered. Skills can be called upon during the session and integration phases.
Preparation: ACT			
Psychological flexibility	Luoma et al., 2017	Exercises aimed at supporting the three pillars of psychological flexibility–openness, awareness, and engagement to help clients respond effectively to the challenges of life.	Exercises based on openness, awareness, and engagement could conceivably potentiate psychedelic sessions.
Developing alternatives to struggle and avoidance	Bennett and Oliver, 2019	Help the client be more open to new patterns of behavior which are not organized around avoidance and escape; cultivate openness and acceptance	Acceptance has been proposed by previous authors as one process through which psychedelics may have their effects (Watts et al., 2017). Practice with this orientation may be useful during session as well.
Connecting with values	Luoma et al., 2017, p. 29	Clarification of values and consideration of the extent to which current life aligns with values.	Psychedelic therapy has been reported to result in shifts in people's life priorities (Belser et al., 2017; Swift et al., 2017) and increase connection with core values (Noorani et al., 2018). Clarification and discussion of values in prep may later facilitate integration.
Dosing session			
CBT			
Core beliefs and cognitive distortions	Beck and Haigh, 2014	Beliefs and thoughts that address the self, one's future, and the world.	During dosing sessions, a participant may encounter core beliefs and cognitive distortions.
Cognitive restructuring	Beck and Haigh, 2014	Targeting dysfunctional or biased reasoning (including core beliefs and cognitive distortions) and to help clients evaluate them.	There is initial evidence to suggest that psychedelic therapy can change various beliefs. Training with this skill may facilitate this desired outcomes.
Relaxation techniques	Clark and Beck, 2010	These techniques include *progressive muscle relaxation (PMR*, *applied relaxation*, and *breathing retraining.*	If these are practiced in advance, session monitors could prompt clients to use techniques (functionally similar to therapeutic touch) to restore a sense of safety and empower participants to continue with the session, should anxiety or panic occur.
Dosing session: DBT			
Mindfulness skills	Linehan, 2015	The core mindfulness skills are the *what* (e.g., observe, describe, and participate) and *how* skills (e.g., non-judgmentally, one-mindfully, and do what works)	Training in mindfulness skills taught during preparation may help client to experience the session in a more engaged manner.
Emotion regulation skills	Linehan, 2015	Emotion regulation skills are often taught in DBT with the caveat that we cannot have total control over our emotions, but useful for modulating emotion.	In session, participants may be better to able to articulate and manage what emotions are coming up and thereby give session monitors a better sense of when to intervene and minimize unnecessary disruption

(Continued)

TABLE 1 | (Continued)

Concept	Citations	Description	Relevance to psychedelic treatments
Distress tolerance skills	Linehan, 2015	*Crisis survival skills* (such as the relaxation techniques described in traditional CBT) and *reality acceptance skills*, which promote a conscious commitment to accept situations beyond one's control.	When challenging experiences arise in the session phase, participants can be encouraged to use the *Turning the Mind* skill, which is a stance cultivated through practice involving choosing to accept one's present experience.
Dosing session: ACT			
Defusion	Luoma et al., 2017, p. 99	Exercises and discussion to help participants to get a better sense of the nature of their unique process of thinking rather than getting caught up (or fused) with a particular thought, sensation, image, or memory.	May help clients be able to let go of the struggle with attempting to understand or more make sense of the psychedelic experience in the moment, to help them engage more fully therapy.
Acceptance	Hayes et al., 2012	Allow thoughts and feelings to come and go without trying to change them.	Helpful for navigating challenging experiences. Participants could be cued to engage in acceptance during difficult moments.
Present moment awareness	Harris, 2009, p. 156	Involves paying attention to one's moment by moment experience (internally and externally)	Helpful for clients who get caught up in repetitive thinking, catastrophic worry, or otherwise unable to return to the psychedelic experience.
Integration CBT			
Teaching adaptive behavior and goal setting	McGinn and Sanderson, 2001	Traditional CBT includes strategies to set specific goals around desired ends and tracking progress.	Integrate the discovery and motivation from the dosing session phase into more lasting behavioral change through setting specific and attainable goals.
Setting homework or action plans (e.g., behavioral experiments)	Bennett-Levy et al., 2004	Client and session monitor activities client can do during the week to practice new behaviors and/or test thoughts and beliefs.	May help to carry over insights from the "non-ordinary" experience in the dosing session to one's return to "ordinary" life and help to form new habits, ways of interacting with the world
Monitoring Progress	Lambert et al., 2003	Systematic assessment, through validated measures, throughout course of treatment.	Ongoing psychometric assessment to supplement clients' reports can help to assess progress see what strategies and behaviors are most helpful in facilitating desired change.
Integration: DBT			
Diary cards	Linehan, 1999	Track behavioral targets, emotions, and skill use over the previous week.	Monitor ongoing challenges, successes, and progress toward goals.
Chain analysis	Rizvi and Ritschel, 2014	Visually depicting the sequence of events (both internal and external) that led up to a target behavior, as well as consequences.	May be used to understand important or profound moments that participants experience in their daily lives and identify opportunities for intervention or new ways of responding.
Cultivating a dialectical stance	Rathus and Miller, 2015	(1) Working on acceptance through validation, (2) working on change through behavior change, and (3) synthesizing these approaches in an adaptive manner.	The dialectic between acceptance and change may have come up in the psychedelic experiences, which can be discussed.
Integration: ACT			
Metaphor and experiential exercises	Bennett and Oliver, 2019	Two clinical tools that are frequently used and allow clients to learn from direct experience or experiential language.	The use of metaphor and experiential exercises is a way of helping to integrate an experience that is difficult to describe in words using therapeutic approaches that are also meant to go beyond words.
Self-as-context	Luoma et al., 2017, p. 28	Practice with the concept of "A continuous and secure 'I' from which events are experienced, a self that contains but is also distinct from those events."	An observing sense of self can provide a stable place from which to observe and process the alterations in sense of self and other that can occur during psychedelic sessions.
Committed action	Hayes et al., 2012, p. 328	Clients commit to specific actions in their lives that will help clients align their daily activities with their values.	This concept (and change process) is of great value in psychedelic therapy, to facilitate lasting behavior change as a result of the sometimes-profound experiences had during psychedelic sessions.

For each of the three phases of psychedelic-assisted psychotherapy, Preparation, Dosing Session ("Session"), and Integration, three concepts from each of the three cognitive behavioral therapies, CBT, DBT, and ACT, were identified as relevant. Together, these 27 distinct concepts are not meant to be an exhaustive list, but rather depict the suitability of the cognitive behavioral therapy framework as the default for psychedelic-assisted psychotherapy.

psychotherapy psychoeducation also address how psychedelic psychotherapy is expected to target a participant's symptoms. If these mechanisms are unknown, hypothetical or under empirical investigation, then *that* should be communicated transparently to the patient during psychoeducation sessions as well as during the informed consent process (Smith and Sisti, 2021).

Self-Monitoring

Self-monitoring is a skill taught to clients early in CBT, that aims "to train clients to pay attention to or monitor particular cognitions, emotions, and or behavior" (Egan et al., 2014, p. 137). Each week during the initial check in and homework review, the therapist can point out patterns and highlight the ways in which these emotions, thoughts, and behavior are affecting functioning.

Self-monitoring could be relevant to psychedelic psychotherapy because it empowers participants to develop a sense of empiricism about their own experience. By encouraging the patient to self-monitor prior to drug administration, it can help to meaningfully develop a sense of baseline experience. Over time, patients can compare their current responses to earlier sessions to see for themselves how treatment is going using online surveys or smart-phone based experience sampling methods (Insel, 2017).

Dialectical Behavior Therapy

Pre-treatment and Commitment Strategies

DBT progresses through various of stages and begins with a series of sessions referred to as *pre-treatment* which are aimed at increasing commitment to the treatment plan and motivation to engage in therapy (Swenson, 2016). Linehan (1993) remarks that "people are more likely to do what they agree to do" (p. 284). An example of a commitment strategy is *door-in-the-face* technique, which asks for a large commitment to change a behavior with the aim of getting any smaller commitment from the patient (Swenson, 2016).

Building commitment in psychedelic psychotherapy preparation sessions may be useful for both the participant and session monitors. Commitment strategies involve conversations around motivations for seeking therapy. It is useful for the session monitor because it reiterates the stance that treatment is ultimately the participant's decision and facilitates space for that decision to be explored even though "treatment" has begun (this can be similar to motivational interviewing techniques, discussed later). If commitment is built, this commitment can also be referred to and re-established throughout the course of psychedelic psychotherapy and perhaps enhance study retention.

Therapy-Interfering Behavior as a Key Target

In DBT, treatment targets are prioritized. In initial sessions following pre-treatment (i.e., Stage 1), the first target is suicidal or life-threatening behavior and the second is therapy-interfering behavior (TIB; Swenson, 2016). TIBs are behaviors by "both the client and therapist that interfere with effective therapy" (Linehan, 1993, p. 129). Examples include a client's non-attendance or burnout on the part of the therapist (Chapman and Rosenthal, 2016). By prioritizing TIB in this way it promotes case conceptualizations that uphold a client's meaningful contact with treatment as crucial.

TIBs is an element of DBT that doesn't fit neatly into one phase of psychedelic psychotherapy (as is the case with many of these concepts). Preparation provides an opportunity to discuss expectations and parameters for what might occur during dosing sessions. For example, in dosing sessions, there is an emphasis on session monitors remaining less involved, redirecting participants toward their own experience, and lending a hand to hold if asked. By incorporating TIB into preparation for psychedelic therapy, it allows for an open conversation about whether these parameters might be therapy-interfering for a given client. Additionally, session monitors become mindful of their own potentially therapy-interfering behaviors, say, if a monitor is more inclined to reach out with a hand to hold for a given client before being asked.

Skills Training

Skills training is a very broad category and can be thought of as an element of all cognitive behavioral approaches. There are several possible DBT skills to draw from, which are covered under the dosing session section, but here we offer discussion of what could be covered in preparation. The DBT skills for adults consist of four modules: mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness (Rathus and Miller, 2015). There is empirical support for DBT skills training as a standalone treatment for various psychopathologies (Valentine et al., 2014).

Psychedelic psychotherapy could benefit from incorporating select DBT skills training into preparation sessions for two broad reasons. First, these skills provide participants with tools to aid in tolerating difficulties or making changes in their lives even before any drug is administered. Second, these skills can be called upon during the dosing session and integration phases and strengthened so that participants develop a proficiency in these skills that gets them closer to the life they want to be living—in DBT referred to as *a life worth living* (Swenson, 2016).

Acceptance and Commitment Therapy

Psychological Flexibility

The overarching goal of ACT is the development of psychological flexibility, a capacity to respond effectively to the challenges of life in an ongoing way. Rigidity and inflexibility are believed to be at the heart of psychopathology (e.g., Luoma et al., 2017; Wolff et al., 2020). In this approach, clients are invited to reflect on and be guided by values-based treatment goals, which do not involve targeting the cessation or reduction of difficult thoughts or feelings (Hayes et al., 2012).

Psychological flexibility may be helpful in framing how dosing sessions are approached and may also be consistent with emerging evidence. A psychological flexibility model de-emphasizes attempts to try rid oneself of unpleasant experiences (*experiential avoidance)*, something that is unlikely to be successful during dosing sessions, and instead emphasizes the utility of openly embracing all the experiences of life in attempt to learn what they have to say about how to live well. Some studies have shown that psychological flexibility

improves during and after therapeutic psychedelic experiences (Davis et al., 2020a; Zeifman et al., 2020) and is associated with therapeutic outcomes. Below we outline how work aimed at supporting the three pillars of psychological flexibility—openness, awareness, and engagement—could conceivably potentiate psychedelic sessions.

Developing Alternatives to Struggle and Avoidance

Most clients come to therapy with the hope that therapy will rid them of painful emotions and thoughts, but unfortunately rigid attachment to such avoidance can promote suffering, as avoidance is central to many forms of pathology. ACT begins to address this avoidance by helping clients to examine the workability of their attempts to avoid or control challenging emotions and thoughts, with the goal of helping the client be more open to new patterns of behavior not organized around avoidance and escape (Bennett and Oliver, 2019). ACT directly encourages acceptance as an alternative and offers various metaphors and exercises as ways to build this ability to let go of struggling with difficult experiences. For example, the experiential *Tug of War* exercise involves the client and therapist engaging in an actual tug of war with the therapist representing the clients' challenging thoughts, emotions and sensations (Bennett and Oliver, 2019, p. 131–133). The exercise ends with the acknowledgment that instead of struggling, clients can always "drop the rope" (Bennett and Oliver, 2019, p. 133).

In preparation sessions, it may be advantageous to cultivate this *openness to acceptance* and the idea that attempting to control thoughts and feelings often creates suffering. This seems especially relevant to psychedelic psychotherapy as acceptance has been proposed by previous authors as one process through which psychedelics may have their effects (Watts et al., 2017) and thus an explicit focus on fostering and supporting this process may fit particularly well with the psychedelic experience.

Connecting With Values

In ACT, *values* refer to "chosen qualities of actions that can never be obtained as an object but can be instantiated moment by moment in actions of being and doing" (Luoma et al., 2017, p. 29). Values are more like the "compass heading" (Bennett and Oliver, 2019, p. 209) or the direction for life, rather than the destination. Questions that are sometimes used to help clients identify their values include, "What kind of mother/son/neighbor/citizen/worker do I want to be?" Getting clients to connect with values offers them an opportunity to create meaning in their lives, right away, in each action they take (Harris, 2009).

Psychedelic therapy has been reported to result in shifts in people's life priorities (Belser et al., 2017; Swift et al., 2017) and increase connection with core values (Noorani et al., 2018). ACT provides a way to frame these shifts in values, a means to resolve any values conflicts that might arise as priorities shift, and support in bridging these experiences toward meaningful life changes. In addition, work on values during preparation could help clients identify an intention for dosing sessions that is self-chosen and hence less likely to avoid patterns of avoidance that maintain suffering.

Psychedelic Administration Session

The psychedelic administration session (or dosing session) is the period of time during which the psychedelic is administered and the acute subjective effects are experienced. Typically, participants will lie down on a couch with eyeshades and headphones in order to be as comfortable as possible during their experience (these are parameters that are being researched in ongoing studies; see Johnson et al., 2008, for a thorough description and safety considerations). There are generally two monitors in the room at all times and the sessions are unobtrusively recorded all measures for the safety of participants and patients. Participants may talk with the monitors, but in such cases, monitors might encourage participants to instead attend to their own inner experience. Participants can, at some research centers such as at Johns Hopkins, ask for the facilitator to hold their hand otherwise offer some sort of minimal supportive touch if frightened or anxious. The following are concepts or skills from cognitive-behavioral approaches that may be relevant during the psychedelic administration session.

Cognitive Behavioral Therapy

Core Beliefs and Unhelpful Thoughts

Through psychoeducation and self-monitoring, CBT clients become familiar with their core beliefs and unhelpful thoughts. These core beliefs often manifest as automatic thoughts (McGinn and Sanderson, 2001). An example of a core belief is: "I am unlovable." *Unhelpful thoughts* are predictable and systematic forms of maladaptive thinking (Yurica and DiTomasso, 2005). Becoming aware of one's unhelpful thoughts comprises an important part of CBT.

During dosing sessions, a participant is likely to encounter core beliefs and unhelpful thoughts because this content, in many cases, is so automatic and engrained. The psychedelic experience offers a new mode by which one may be more likely to identify and engage with them due to the new perspectives introduced during the acute subjective effects. By encouraging participants to discover and label their own automatic thoughts, they may be primed to encounter and discover insights about them in session. Also, by encouraging participants to discover and label their unhelpful thoughts in prep, participants may develop a conceptual scaffolding to use when encountering these unhelpful through in session.

Cognitive Restructuring

Cognitive restructuring in CBT refers to targeting dysfunctional thoughts and helping clients evaluate them (Beck and Haigh, 2014). McGinn and Sanderson (2001) describe cognitive restructuring as a process where "clients are trained to increase awareness of ongoing 'stream of consciousness' during episodes of increased affect, exposing these rigid 'automatic thoughts' which accompany emotional responses" (p. 29).

The concept of cognitive restructuring may be relevant to psychedelic psychotherapy because there is initial evidence to suggest that psychedelic therapy can change beliefs (Nayak et al., in preparation[1]; Timmermann et al., 2021). Cognitive

[1]Nayak, S. M., Singh, M. Yaden, D. B., and Griffiths, R. R. (in preparation). *Belief Changes Associated With Psychedelic Use.*

restructuring (with its necessary component of self-monitoring) offers participants an empirically rooted system to use to monitor, discover, label, evaluate, and test thoughts and beliefs. Therefore, during the dosing session phase, session monitors could gently empower participants to use this system as they see fit to navigate their experience. While more active or structured interventions such as this have generally not been included in dosing sessions in current clinical trials, it provides an interesting potential intervention to explore in future research, if able to be adapted to the context of a dosing session. There exists a tradition, often termed psycholytic therapy (e.g., see Garcia-Romeu and Richards, 2018 for a brief description), of using more active psychoanalytic techniques such as interpretation during psychedelic states. Our suggestion is to consider broadening this strategy of utilizing more active interventions during psychedelic states by testing more recent and empirically based strategies.

Relaxation Techniques

Relaxation Techniques (*distress tolerance skills* in DBT) are sometimes used in traditional CBT. These techniques include *progressive muscle relaxation (PMR),* which involves tensing and relaxing specific muscle groups, *applied relaxation,* similar to PMR but paired with cues (e.g., "relax") and applied outside of the session, and *breathing retraining,* which entails teaching diaphragmatic breathing (Clark and Beck, 2010).

Relaxation techniques are likely to be useful in psychedelic psychotherapy for similar reasons that they are useful in CBT. Anytime emotional or physiological arousal becomes therapy-interfering during the dosing session or otherwise, these relaxation techniques may help decrease arousal so that the participant can continue to engage in treatment. In psychedelic psychotherapy, should pre-session or in-session anxiety or panic occur, session monitors can use techniques (functionally equivalent to therapeutic touch) to restore a sense of safety and empower participants to continue with the session.

Dialectical Behavior Therapy

Mindfulness Skills

In DBT, the mindfulness module aims to cultivate an awareness of internal and external present moment experience. The core mindfulness skills are the *what* (observe, describe, and participate) and *how* skills (non-judgmentally, one-mindfully, and do what works; Linehan, 2015). Rathus and Miller (2015) highlight that "these skills form the core of the entire skills set, as individuals need these skills to be able to make use of the other DBT skills" (p. 97).

During the dosing session phase, session monitors could encourage participants to call upon mindfulness skills taught during preparation. For instance, the words "mindfulness skills" could become a cue for clients to observe their experience, describe what they notice and participate in the present moment. This is the reason why skills training as a whole was suggested in the "preparation" section above, so that session monitors could cue these skills in session.

Emotion Regulation Skills

Emotion regulation skills are often taught in DBT with the caveat that we cannot have total control over our emotions (Linehan, 2015). Instead, these skills are useful in modulating emotion. Some targets of emotion regulation skills include understanding and naming emotions, changing emotional responses, reducing vulnerability to extreme emotions, and managing difficult emotion (Linehan, 2015).

In psychedelic psychotherapy, teaching participants to understand and name their emotions could create a sense of emotional literacy. In session, participants may be better to able to express what emotions are coming up and thereby give session monitors a better sense of when to intervene and minimize unnecessary disruption.

Distress Tolerance Skills

Distress tolerance skills involve more than just managing difficult emotion, rather, this module is for situations that are considered *crises* (Linehan, 1993). The distress tolerance module comprises two parts: *crisis survival skills* (such as the relaxation techniques described in traditional CBT) and *reality acceptance skills*, which promote a conscious commitment to accept situations beyond one's control to minimize suffering though it may not "fix" the situation itself (Linehan, 2015).

During the dosing session, the reality acceptance skills in this module seem especially useful. When challenging experiences arise in the session, participants can be encouraged to use the stance cultivated through practice that acceptance is a choice one must make "over and over again" (Rathus and Miller, 2015. p. 151).

Acceptance and Commitment Therapy

Defusion

Defusion refers to the idea that one's identity does not consist of one's passing thoughts. That is, one can look "*at* thoughts rather than *from* thoughts" (Luoma et al., 2017, p. 99). The aim of defusion is to reduce the influence of narrow and rigid cognitive forms of responding. Through metaphor and experiential exercises, clients come to learn that thoughts need not control behavior (Hayes et al., 2012). Having this distance from thoughts can liberate clients to move in valued directions.

Defusion could be of great utility in psychedelic psychotherapy by allowing patients to notice and disengage from repetitive or unproductive lines of thinking such as obsessive rumination or worry that might occur in session. It may also help clients be able to let go of the struggle with attempting to understand the sometimes confusing components of psychedelic experience that may interfere with full engagement in the therapy.

Acceptance

Experiential acceptance is the ability to allow thoughts and feelings to come and go without struggling against them or trying to change them. In ACT, acceptance is an action one can engage in as an alternative to escape, avoidance, or thought suppression (Hayes et al., 2012). Like DBT, in ACT acceptance is viewed as a process, and defined as "the voluntary adoption of an intentionally open, receptive, flexible, and non-judgmental posture with respect to moment-to-moment experience" (Hayes et al., 2012, p. 272).

Acceptance as it is construed in ACT could be useful to the dosing session phase in two ways. If, for example, the tug-of-war

exercise were introduced during the preparation phase, then the cue "drop the rope" by a therapist might encourage participants to stop resisting challenging experiences that arise. Second, framing acceptance as a values-based choice empowers participants to choose to stay with the struggle rather than feeling coerced by the therapist or their own self-injunctions.

Present Moment Awareness

Defusion and acceptance promote an "open" response style, and present moment awareness promotes a "centered" one (Hayes et al., 2012). It is through contacting the present moment that clients contact a "firm foundation for awareness and action" (Hayes et al., 2012, p. 219).

Defusion and acceptance can promote an open stance toward challenging experiences that arise during psychedelic administration sessions and present moment awareness involves engaging with that experience (rather than being carried away by it or struggling against it). ACT techniques that foster *present moment awareness* might be helpful for clients who caught up in repetitive thinking, catastrophic worry, or otherwise unable to return to what there might be to learn from the psychedelic experience.

Integration

Integration refers to the therapeutic support offered after the acute subjective effects subside, which can be scheduled in the hours, days, weeks, and months following the session. Integration typically involves participants and patients describing their experiences to a clinician, working to make sense of any confusing experiences. Integration also typically involves identifying whether there are any important implications from the dosing session for how the person might want to live their life going forward and considering how to put those implications into practice. There are a number of concepts from cognitive-behavioral approaches that clinicians could draw from during integration in order to help participants and patients understand and make sense of their experiences while leveraging them for therapeutic benefit.

Cognitive Behavioral Therapy

Teaching Adaptive Behavior and Goal Setting

Traditional CBT includes strategies to teach adaptive behavior, such as problem-solving, pleasant activities scheduling, contingency procedures, skills training, and exposure (McGinn and Sanderson, 2001). CBT can involve setting behavioral goals toward valued ends. Participants and patients can then be reminded and supported in making measurable progress toward those goals using concepts like behavioral activation (e.g., Sturmey, 2009), which involves setting more proximate and attainable goals as steps toward larger goals. Behavioral activation may help individuals re-engage in activities that bring them a sense of mastery and pleasure by having them work toward these goals in a systematic way.

Teaching adaptive behavior in psychedelic psychotherapy is crucial because motivational urges or insights gained in the dosing session phase do not automatically impart ability or reduce barriers to engaging in adaptive behaviors. For example, a participant may discover that they are not satisfied by their career and have an urge to change. Also, scheduling pleasant activities to help them engage in what they find fulfilling can serve to integrate the discovery and motivation from the dosing session phase into more lasting behavioral change. There are any number of therapeutic goals that could be set during integration.

Assigning Homework: Behavioral Experiments

Behavioral experiments are a common form of homework aimed at testing the validity of and updating potentially erroneous or maladaptive beliefs. In these experiments, patients test out predictions such as, "She wouldn't want to go to a movie with me," by performing the behavior in question (inviting the friend to a movie) and seeing what actually results.

Homework, and in particular, behavioral experiments have potential value in psychedelic psychotherapy. This concept may help to carry over insights from the "non-ordinary" experience in the dosing session to one's return to "ordinary" life. For example, if, during the psychedelic administration session, a participant has a profound sense that a particular difficult relationship needs tending to, a clinician could assign the homework of engaging in a behavioral experiment of actually tending to those difficult relationships and seeing what happens. The individual could then test whether their beliefs about a given difficult relationship holds true after the relationship has received additional time and attention paid to it.

Monitoring Progress

Monitoring progress through empirically validated measures is at the heart of CBT. There is evidence that when therapists monitor clients' progress through assessment, clients experience better outcomes (Lambert et al., 2003). Specific measures are tailored to the client's presenting symptoms and goals for treatment. Repeated measurement over time allows the therapist to adapt to the treatment to the clients' response. For example, if a particular strategy aimed at improving sleep does not result in improved sleep, the therapist and client may decide to change course. Rather than being viewed as a nuisance, such measures, when used effectively, can be a helpful adjunct to the therapeutic process.

Ongoing psychometric assessment in psychedelic psychotherapy (e.g., using online survey links or smart-phone based experience sampling methods) could provide the clinician with a means through which to supplement clients' narrative reports during therapy. It also allows clinicians to develop an empirically grounded case conceptualization, measuring specific constructs that may mediate change (e.g., psychological flexibility) along with outcome-based measures (e.g., scores of depression or anxiety). Furthermore, assessment helps to keep clinicians from "seeing" change that is not there.

Dialectical Behavior Therapy

Diary Cards

In individual DBT sessions, participants turn in a *diary card*, which tracks life-threatening behaviors, as well as other behavioral targets, emotions, and skills used over the previous week (Linehan, 1999; for example, see p. 185). The diary card is used to elicit content that will provide therapists with a sense

of how target behaviors manifest in a client's life, as well as to identify patterns of behavior (Linehan, 1999).

Depending on the number and frequency of integration sessions that follow the dosing session phase, an adapted diary card may be of clinical utility to clinicians. If a client identifies new behaviors they want to develop or goals they want to achieve, these could be usefully monitored on a diary card and systematically targeted. Furthermore, ongoing problems that have not resolved during dosing sessions could be monitored and subjected to chain analyses (see below). Whether or not diary cards specifically are employed, the CBT principle of checking in on the previous session's action plans at the start of a session is key to communicating that action plans are important and to determining the focus of the current session.

Chain Analysis

Whereas the diary card provides an overview of behavior, chain analysis is a DBT strategy which allow clinicians to focus in on discrete events (Linehan, 1993). It involves visually depicting the sequence of events (both internal and external) that led up to a target behavior, as well as its consequences (Rizvi and Ritschel, 2014).

Chain Analysis which could be applied to the psychedelic experience itself (although the concept is typically applied to problem behaviors). When it comes to integrating the experiences from the dosing session, it may be worthwhile to use the chain analysis to better understand important or profound moments that participants experience in the weeks and months that follow. Chain analyses may reveal thoughts, behaviors, action urges, and emotions that are associated with these positive changes.

Cultivating a Dialectical Stance

At the heart of DBT is a dialectical stance, as a synthesis of acceptance and change (Rathus and Miller, 2015). This dialectical stance promotes a more expansive and nuanced way to view oneself and the experience of others—-moving from "black or white" thinking to "both-and" thinking (Rathus and Miller, 2015, p. 160).

There are numerous apparent paradoxes that can be involved in psychedelic experience, which may be targets of integration sessions. These might include non-ordinary *and* ordinary experience, the profound *and* the mundane, those who "get it" *and* those who don't, urges to quit jobs or leave relationships that are unfulfilling *and* the need to support oneself and connect with others. A dialectical stance is a useful orientation toward challenges such as these as it allows participants to explore goal states while accepting and validating where they currently are in their lives.

Acceptance and Commitment Therapy

Metaphor

An emphasis on experiential forms of learning in ACT leads to a clinical tool that is frequently used: experiential exercises and metaphor (Bennett and Oliver, 2019). Villatte et al. (2014) propose that "the story-like quality of metaphors has the advantage of providing instructive lessons that are rich in emotional and perceptual detail, mimicking direct contact with the environment and making the experience more memorable" (p. 17).

Clinicians might benefit from incorporating some of the metaphors that have come out of ACT into integration sessions. Psychedelic experience can be difficult to put into words, or *ineffable* (e.g., Yaden et al., 2016). Thus, the use of metaphor and experiential exercises is a way of helping to integrate an experience that is beyond words using therapeutic approaches that are also meant to go beyond words. For example, spontaneously visual images that merge during psychedelic sessions could be utilized in ACT as a guide for future behavior without necessarily having to fully understand what the image "means."

Self-as-Context

Self-as-context refers to "a continuous and secure 'I' from which events are experienced, a self that contains but is also distinct from those events" (Luoma et al., 2017, p. 28). Other terms for self-as-context are self-as-perspective, flexible perspective taking, the observing self, pure awareness, or the transcendent self (Luoma et al., 2017). This more flexible and responsive sense of self contrasts with the *conceptualized self*, which includes all the historically derived and verbally constructed self-concepts that are inherently restricting (Hayes et al., 2012).

Clinicians might call upon this concept in integration sessions. Contact with an observing sense of self that is already inherently integrated can provide a stable place from which to observe and process the alterations in sense of self and other that can occur during psychedelic sessions. This allows participants flexibility in regard to which self-concepts (or self-stories) work for them and which interfere with their value driven life. Theory related to self as context can also guide therapists on how to work with alterations of the sense of self, such as reports of "ego dissolution" (Nour et al., 2016; Yaden et al., 2017a) that occur during psychedelic sessions. Furthermore, this process provides a way to work with reports of encounters with external entities or divinities (e.g., Yaden et al., 2017b; Griffiths et al., 2019; Davis et al., 2020b) or perceptions related to the nature of consciousness (e.g., Yaden et al., 2021c) that does not entail taking a stance on whether such experiences are "real" or not (for an extended discussion, see Yaden and Newberg, in press).

Committed Action

Committed Action is the key change process in ACT and is defined as "values-based action" (Hayes et al., 2012, p. 328). Hayes (2019, p. 328) put it this way, "if a client does not change his or her behavior, then all of our efforts working on defusion-acceptance, present moment-self-as-perspective, and values are for naught."

Committed action in psychedelic therapy could look like sticking with a challenging experience in session, allowing oneself to be vulnerable, returning for all of the integration sessions, or making changes in one's life that make it more fulfilling and aligned with one's values. For example, if a patient with alcohol use disorder seeks to cut back on their drinking in order to be more present with their family, they might take make a schedule of just how much and when they will cut back on their drinking over the coming week and then follow that schedule, in service of their longer-term goal and their value of family. The whole

point of cultivating psychological flexibility, ultimately, is to be able to use it as a tool to live more fully. This concept (and change process) is of great value in psychedelic therapy, where the sometimes-profound experiences had during psychedelic sessions may not automatically result in lasting behavior change.

DISCUSSION

We have provided a review of historical, sociological influences on contemporary psychedelic psychotherapy as it is practiced largely in clinical healthcare research settings and have argued that cognitive-behavioral frameworks (i.e., CBT, DBT, and ACT) should be considered the default. That said, to the degree that some investigators choose to use other approaches, we should evaluate outcomes, and ultimately, research randomizing individuals to different therapeutic approaches (within ethical limits), as this would provide the most importance evidence on this topic, at least regarding safety and efficacy. We provided rationale largely resting on more empirically founded and testable theory, stronger connection to the evidence base of contemporary science, reduced potential to cause offense, and large amount of safety and efficacy data across a number of treatment contexts.

There are other frameworks that we have not discussed in great detail here but deserve mention and some discussion, these include motivational interviewing, emotion-focused therapy, and supportive psychotherapy. Motivational interviewing (MI) emerged from the research on addiction and is defined as "a collaborative conversation style for strengthening a person's own motivation and commitment to change" (Miller and Rollnick, 2012, p. 12). Rather than targeting change processes, MI seeks to prepare clients for change by guiding a conversation that ultimately encourages clients to be engaged, empowered, open, and understood (Miller and Rollnick, 2012). MI has been used in at least one clinical trial with psilocybin (Bogenschutz et al., 2015). We believe motivational interviewing could be used as an adjunct intervention. However, we do not believe motivational interviewing is broad enough to be a comprehensive treatment approach for many disorders or difficulties that present as part of psychedelic assisted therapy.

Emotion-focused therapy is a therapy approach emerging from the humanistic tradition that views emotions as centrally important in the experience of the self, in maintaining both adaptive and maladaptive functioning, and in the therapeutic change process (Greenberg, 2011). It has been empirically studied for depression, social anxiety, complex trauma, generalized anxiety, and eating disorders (Goldman, 2019), but the evidence base for this approach is not nearly as extensive as for CBT, including specifically in the context of psychedelics.

The default paradigm currently used in clinical trials with psychedelics is overtly something like supportive psychotherapy, as it is generally characterized as empathetic in a non-directive manner (e.g., Winston et al., 2004). Arguably, this should not change. However, we believe that supportive psychotherapy consists of a set of clinical practices into which concepts from other frameworks invariably slip in. In other words, we believe that many of the clinicians, guides, and monitors who are overtly providing supportive psychotherapy in psychedelic contexts are drawing from an eclectic blend of the other influences on psychedelic psychotherapy that we have already reviewed. To the extent that this is the case, we argue that drawing more explicitly from concepts from cognitive-behavioral approaches (e.g., CBT/DBT/ACT) is advisable.

CONCLUSION

We have argued that CBT approaches have the strongest rationale to be the default option for a psychotherapeutic paradigm to pair with psychedelic treatments in mainstream American and European clinical research contexts. We examined some common alternatives and found that they each have problems that are absent or substantially reduced in CBT approaches. We have also provided a substantial number of concepts from CBT, DBT, and ACT that appear relevant to psychedelic treatments. While we believe cognitive-behavioral approaches should be the default in psychedelic psychotherapy, we are open to and supportive of additional scholarship and research on the other approaches considered here as well as others. Furthermore, the CBT/DBT/ACT concepts listed are provided for illustrative purposes and are not meant to be comprehensive and should be subjected to further research. Overall, we believe participant and patient safety and efficacy should be paramount considerations in psychedelic treatments and we believe cognitive-behavioral approaches currently best fulfill these criteria.

AUTHOR CONTRIBUTIONS

DY conceived the project and wrote the manuscript. DE and MG conducted literature reviews and provided writing. DF-W provided writing and edits. JL and MJ provided writing and edits. All authors contributed to the article and approved the submitted version.

FUNDING

Support for DY, DF-W, and MJ through the Johns Hopkins Center for Psychedelic and Consciousness Research was provided by Tim Ferriss, Matt Mullenweg, Blake Mycoskie, Craig Nerenberg, and the Steven and Alexandra Cohen Foundation. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

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Conflict of Interest: MJ was an advisor to the following organizations regarding the medical development of psychedelics and related compounds: AJNA Labs LLC, AWAKN Life Sciences Inc., Beckley Psychedelic Ltd., Entheon Biomedical Corp., Field Trip Psychedelics Inc., Mind Medicine Inc., and Otsuka Pharmaceutical Development & Commercialization Inc.

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TYPE General Commentary
PUBLISHED 30 September 2022
DOI 10.3389/fpsyg.2022.1020222

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OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

RECEIVED 16 August 2022
ACCEPTED 16 September 2022
PUBLISHED 30 September 2022

CITATION
Burton J, Ratner A, Cooper T and Guss J (2022) Commentary: Psychedelics and psychotherapy: Cognitive-behavioral approaches as default. *Front. Psychol.* 13:1020222. doi: 10.3389/fpsyg.2022.1020222

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Commentary: Psychedelics and psychotherapy: Cognitive-behavioral approaches as default

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KEYWORDS

psychoanalysis, CBT, psychedelic-assisted psychotherapy, psychodynamic psychotherapies, ACT, DBT, psychedelics, psychodynamic psychiatry

A Commentary on
Psychedelics and psychotherapy: Cognitive-behavioral approaches as default

by Yaden, D., Earp, D., Graziosi, M., Friedman-Wheeler, D., Luoma, J., and Johnson, M. (2022) *Front. Psychol.* 13:873279. doi: 10.3389/fpsyg.2022.873279

Introduction

We are writing to express our concern regarding the recently published article, "Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default." We support the authors' efforts to address the issue of standards of care in the rapidly emerging field of psychedelic-assisted psychotherapy. However, we find fundamental problems with the argument that Cognitive-Behavior Therapy (CBT) is a pre-eminent choice in the practice of psychedelic therapy. Contrary to the authors' assertion, we suggest that any such effort to declare a "default" psychotherapy reveals an unscientific, even polemical, bias.

The unscientific basis for CBT as "Default"

The authors assert CBT's scientific supremacy, but in their eagerness, they neglect scientific methods. CBT should, of course, be considered among the psychotherapeutic platforms used in psychedelic therapies, but no single platform can credibly lay claim to "default" status prior to collecting substantial supportive evidence. To date, no comparative studies of psychotherapy platforms have been conducted in the field

of psychedelics. *Varying,* not restricting, the available treatment regimens is essential to compare effectiveness, but the authors recommend restricting the psychotherapeutic approach to their preferred methodology in advance of persuasive data. They justify their recommendation with the assertion that psychoanalytic psychotherapy is unscientific, while CBT carries an empirical "gold-standard" status. Both assumptions are demonstrably false.

The authors' assertion that psychoanalytic psychology is out of date is itself remarkably out of date. Their claim that psychoanalytic psychology lacks supportive evidence is itself lacking in supportive evidence. To make their case, the authors cite work over 40 years old (Eysenck and Wilson, 1973) and exhume philosophy professor Karl Popper's hoary 1920 argument that all psychoanalytic ideas are "non-falsifiable," an argument rejected by subsequent philosophers of science, including Hempel (1965) and Grunbaum (1984). The authors continue their parochial agenda by attributing false centrality to a theory of "birth trauma," as if that outdated, peripheral theory contaminates all ideas in mainstream psychoanalysis.

The evidence for psychoanalysis

In the nearly half century since Eysenck, Wilson, and Beck decried the paucity of psychoanalytic research, neuroscience has validated core psychoanalytic concepts, including unconscious emotion and defense mechanisms (Solms, 2018). Copious research now exists on psychoanalytic efficacy (Gerber et al., 2011). There is robust evidence that psychoanalytic psychotherapy is as effective as CBT and probably has longer-lasting results (Steinert et al., 2017).

Within the psychedelic research literature itself, functional neuroimaging has begun to show an empirical basis for Freud's structural theory of the mind and a correlation between modern neurophysiological models of the Default Mode Network and the psychoanalytic concept of the Ego (Carhart-Harris et al., 2014). The authors dismiss Carhart-Harris's rigorous and meticulous work as a mere "claim."

With increasing frequency, meanwhile, researchers have in recent years questioned CBT's claim to "gold-standard" status (Leichsenring and Steinert, 2017; Wampold et al., 2017). That claim deserves particular scrutiny in the new context of psychedelic psychotherapy. Psychedelics alter the contents of consciousness. CBT does not address, in theory or in practice, the dynamic relations between conscious and unconscious states. Psychoanalytic psychology, by contrast, was founded on the study of these relations. Psychedelics instigate complex changes in patients' attitudes to self and others that are conceivably best understood and supported with psychoanalytic models. Attempting to short-circuit exploration of a role for psychoanalytic psychotherapy in conjunction with psychedelics is not only unscientific, it is not in the best interest of patients.

Discussion

Why would the emerging field of psychedelic-assisted psychotherapy rigidly limit itself to one "default" therapeutic model, except for ideological and emotional reasons? The authors' rush to claim the new territory of psychedelic-assisted psychotherapy for CBT as "default" demonstrates how such claims to "gold-standard" status sometimes do not serve a scientific agenda, but instead do a disservice to patients and practitioners alike.

We offer the above comments not to disparage CBT as a viable and effective model of treatment, but to flag the problem of activism and bias masquerading as science. Especially in the new and exciting field of psychedelic therapy, it is important not to prematurely reject valuable tools, such as psychoanalytic psychology, in order to support one particular agenda and denigrate others.

Author contributions

JB, AR, and TC made initial contributions to the manuscript. AR wrote the first draft. JG provided subsequent contributions and collaborated with JB and AR to create the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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HYPOTHESIS AND THEORY
published: 02 June 2022
doi: 10.3389/fpsyg.2022.866018

Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model

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OPEN ACCESS

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *30 January 2022*
Accepted: *28 March 2022*
Published: *02 June 2022*

Citation:
Brennan W and Belser AB (2022) Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model. Front. Psychol. 13:866018. doi: 10.3389/fpsyg.2022.866018

The current standard of care in most uses of psychedelic medicines for the treatment of psychiatric indications includes the provision of a supportive therapeutic context before, during, and after drug administration. A diversity of psychedelic-assisted psychotherapy (PAP) models has been created to meet this need. The current article briefly reviews the strengths and limitations of these models, which are divided into basic support models and EBT-inclusive therapy models. It then discusses several shortcomings both types of models share, including a lack of adequate attention to embodied and relational elements of treatment, and insufficient attention to ethical concerns. The article then introduces the EMBARK model, a transdiagnostic, trans-drug framework for the provision of supportive psychotherapy in PAP clinical trials and the training of study therapists. EMBARK was designed to overcome challenges that prior models have had in conceptualizing therapeutic change in psychedelic treatment, incorporating elements of non-psychedelic evidence-based therapies, incorporating therapists' prior skills and clinical orientations, delimiting therapist interventions for research standardization, and determining specific factors that contribute to treatment outcomes. The article explains EMBARK's six clinical domains, which represent parallel conceptualizations of how therapists may support therapeutic benefit in PAP treatment, and its four care cornerstones, which reflect therapists' broad ethical responsibility to participants. The article describes how these elements of the model come together to structure and inform therapeutic interventions during preparation, medicine, and integration sessions. Additionally, the article will discuss how EMBARK therapist training is organized and conducted. Finally, it will demonstrate the broad applicability of EMBARK by describing several current and upcoming PAP clinical trials that have adopted it as the therapeutic frame.

Keywords: psychedelic assisted therapy, psychotherapy models, therapist training, research utilization, psychedelic drugs, psychedelic drug use

INTRODUCTION

Psychedelic medicines are a distinctive class of pharmacotherapeutic interventions. Perhaps their main distinguishing feature is that a significant portion of their purported efficacy in reducing psychiatric symptoms is thought to derive, not from their direct biochemical effects on the brain, but from their capacity to foster acute and subacute shifts in a participant's subjective experience that, if skillfully handled, can result in beneficial outcomes (Oram, 2014). As such, all but one of the registered clinical trials of "classic" (Johnson et al., 2019), serotonergic psychedelic drugs being used to treat a mental health condition have couched drug administration within a context of drug-appropriate psychotherapy (Reiff et al., 2020). Accordingly, MDMA, a quasi-psychedelic drug (Nichols, 1986) whose models of clinical application closely match those of classic psychedelics, is expected to become the first FDA-approved drug for which the administration protocol mandates a psychotherapeutic frame (Emerson and Cooper, 2021; Servick, 2021). Although some actors in the field are seeking to develop drugs that replicate the putatively therapeutic neuropharmacology of classic psychedelics while eliminating their subjective effects (Dong et al., 2021)—and thereby the need for supportive therapy (Yakowicz, 2021)—the potential efficacy of this approach remains speculative (Yaden and Griffiths, 2020; Olson, 2021). In fact, it may be more likely that the widely touted increases in neuroplasticity induced by some psychedelics reflect a pluripotent state that requires therapeutic framing to bring about enduring beneficial outcomes (Vollenweider and Kometer, 2010; Carhart-Harris et al., 2018a; Dölen, 2021; Lepow et al., 2021). As such, the first wave of psychedelic medicines in psychiatry will almost certainly hold as axiomatic that psychedelic medicines are best administered within a well-considered context of psychotherapy.

A diversity of adjunctive psychotherapy models has arisen to provide such a context (Horton et al., 2021). They have been developed by clinical research groups within academic, corporate, and non-profit entities to support their trials of various psychedelic medicines in the treatment of a range of indications. The specific approaches of these models have drawn influence from the work of early PAP pioneers inside and outside of formal research contexts (Eisner, 1967; Grof, 1980; Greer and Tolbert, 1986; Stolaroff, 2004), indigenous approaches to the use of psychedelic substances for healing (Fotiou, 2020), and elements of non-psychedelic therapeutic approaches (Walsh and Thiessen, 2018; Horton et al., 2021). Although these models share some similarities (e.g., attention to set and setting, a structure consisting of preparation, medicine, and integration sessions), they vary greatly in how much non-drug therapy time they offer; the extent to which they incorporate extrinsic, non-psychedelic psychotherapeutic knowledge and best practices; and whether they view the support they provide as therapy *per se* or a distinct form of non-psychotherapeutic support. These differences are to be expected given the dearth of research that examines which, if any, of these factors impact treatment efficacy. This article presents a speculative assessment of the strengths and shortcomings of these models based on a review of the available empirical literature on psychedelic-assisted psychotherapy (PAP). For its purposes, it will focus on clinical trials treating specific indications for which the results and/or therapeutic approach have been presented in peer-reviewed publications and that have examined the efficacy of long-acting classic psychedelics (e.g., psilocybin, ayahuasca, LSD) or MDMA due to strong similarities in the therapeutic framing of these drugs. It will omit ketamine and short-acting psychedelics (e.g., 5-MeO-DMT) due to the different considerations for therapeutic framing that they present.

The current article also introduces the EMBARK model of PAP, which grew out of this process of assessment. The current authors (WB and AB) developed EMBARK to provide an optimized therapeutic frame for training therapists to support therapeutic benefit in PAP clinical trials. EMBARK is a transdiagnostic, trans-drug PAP model whose structure can be tailored to any PAP intervention that applies a specific psychedelic medicine to a specific clinical indication. It was developed to serve as an adaptable therapeutic framework to be used in all Cybin clinical trials, though we offer it freely to any other entities in the field who would like to adapt it for their own purposes. For example, Anthony Back, MD, collaborated with the current authors and Ladybird Morgan, RN, MSW, to develop an EMBARK-based approach for a clinical trial at the University of Washington School of Medicine that uses psilocybin to treat COVID-related burnout and symptoms of depression in frontline healthcare workers, which included coauthoring an indication-specific EMBARK manual and EMBARK training for study facilitators.

To create EMBARK, the authors surveyed a range of therapeutic approaches that have shown efficacy in conjunction with psychedelic treatment (see **Table 1**). For the purpose of review, this article divides these approaches into "basic support" and "EBT-inclusive" models, which are distinguished by the lack or presence, respectively, of elements of extrinsic, non-psychedelic evidence-based therapies [EBTs; e.g., Acceptance and Commitment Therapy (ACT), Cognitive Behavioral Therapy (CBT)] that are included in order to provide therapeutic benefit beyond that which is brought about by the administration of a psychedelic medicine in a safe, clinical context.

The current article discusses the structure and components of the EMBARK approach and describes how EMBARK functions as a model of PAP and PAP therapist training. The article will first review some of the strengths, limitations, and underdeveloped qualities of prior PAP models in the field (see **Table 2**) and discuss how the EMBARK model attempts to address them.

ASSESSMENT OF PRIOR PSYCHEDELIC-ASSISTED PSYCHOTHERAPY MODELS

Common Characteristics of Psychedelic-Assisted Psychotherapy Models

Before contrasting basic support and EBT-inclusive therapy models, it would be helpful to briefly discuss a few notable commonalities between them. As noted earlier, all models of

TABLE 1 | Existing models of psychedelic-assisted psychotherapy.

	Drug	Indication	Extrinsic EBT(s) or EBT-derived therapeutic approach used
Basic support models			
Mithoefer et al. (2017; approach used by Bouso et al., 2008; Mithoefer et al., 2011, 2018; Oehen et al., 2013; Ot'alora et al., 2018; Jardim et al., 2021; Mitchell et al., 2021)	MDMA	Post-traumatic stress disorder	None
Moreno et al. (2006)	Psilocybin	Obsessive compulsive disorder	None
Gasser et al. (2014)	LSD	Anxiety associated with life-threatening illness	None
Carhart-Harris et al. (2016) and Carhart-Harris et al. (2018c)	Psilocybin	Treatment resistant depression	None
Griffiths et al. (2016)	Psilocybin	Cancer anxiety and depression	None
Palhano-Fontes et al. (2019)	Ayahuasca	Treatment resistant depression	None
Davis et al. (2021)	Psilocybin	Major depressive disorder	None
Zeifman et al. (2021)	Ayahuasca	Major depressive disorder	None
EBT-inclusive models			
Grob et al. (2011)	Psilocybin	Cancer anxiety and depression	Existential approaches
Johnson et al. (2014)	Psilocybin	Tobacco use disorder	Cognitive Behavioral Therapy (CBT; Quit 4 Life)
Ross et al. (2016)	Psilocybin	Cancer anxiety and depression	Existential approaches, psychodynamic/psychoanalytic, and narrative therapy
Bogenschutz and Forcehimes (2017)	Psilocybin	Alcohol use disorder	Motivational Enhancement and Taking Action (META; based on Motivational Enhancement Therapy) and CBT
Guss et al. (2020)	Psilocybin	Major depressive disorder	Acceptance and Commitment Therapy (ACT)
Anderson et al. (2020)	Psilocybin	AIDS-related demoralization	Brief Supportive Expressive Group Therapy (SEGT)
Monson et al. (2020)	MDMA	Post-traumatic stress disorder	Cognitive Behavioral Conjoint Therapy (CBCT)
Carhart-Harris et al. (2021)	Psilocybin	Depression	Accept Connect Embody (ACE; based on ACT)
COMPASS (2021) and Tai et al. (2021)	Psilocybin	Treatment-resistant depression	Perceptual Control Theory (PCT)

TABLE 2 | Comparative strengths and limitations of basic support and EBT-inclusive models.

	Strengths	Limitations
Basic support models	• Greater participant freedom in meaning-making • Protective of participant autonomy • Less credentialed labor needed • Potential cost savings due to fewer non-medicine session hours	• Missed opportunity for added efficacy • Interventions less operationalized • Staff may be undertrained for challenging clinical and ethical boundary events • Staff not grounded in explicit theory of change may introduce their own • May rely on untested assumption of an "inner healing intelligence"
EBT-inclusive models	• Potential for greater efficacy • Preexisting evidentiary basis • More developed framework for training therapists • Better operationalization of interventions • May require more credentialed staff who can better respond to clinical and ethical challenges • Borrows legitimacy from more established therapies • Provides a sense of competence to PAP-naïve therapists	• Narrowed conceptualization of benefit • Pressure to conform outcomes to predetermined theory of change • Potential invalidation of participant treatment experiences • Possible harm from therapists unprepared for full range of clinical events • Therapists may need to learn new theoretical orientation • Adoption of new orientation may disrupt therapists' authentic presence • May disregard therapists' prior expertise • Limits potential to evaluate contributions of various mechanisms of change to efficacy • Unclear if established efficacy of EBTs is carried over into PAP treatment

Basic support models are those that do not incorporate elements of extrinsic, non-psychedelic evidence-based therapies. EBT-inclusive models are those that do.

PAP treatment to date have included three phases of treatment. The first phase consists of preparation sessions, which are used to prepare participants to receive the benefits of the medicine. The medicine session(s), referring to the day(s) of drug administration, make up the second phase of treatment. Finally, the third phase, which is often referred to as "integration" (Gorman et al., 2021), consists of a process of reflecting on the medicine session(s) and how it may inspire cognitive and behavioral changes that sustain beyond the end of the treatment.

Another commonality is the universal adoption of an "inner-directed" approach during the medicine session. This refers to a therapeutic stance predicated on "the therapist referencing and encouraging the patient to look into their inner experience for insight and solutions" (Gorman et al., 2021, p. 4). As

such, the stance taken by therapists within such an approach is typically limited to interventions that direct the participant's focus inward. To date, this has been the approach taken by all clinical PAP trials during sessions that involve the administration of a psychedelic medicine (Horton et al., 2021). The differences in therapeutic approach between basic support and EBT-inclusive therapy models, as discussed in this article, are thus found almost exclusively in the preparation and integration phases.

Strengths and Limitations of Basic Support Models

Several PAP approaches can be meaningfully grouped under the label of basic support models based on their provision of basic, non-psychotherapeutic support to a participant undergoing a course of PAP treatment. The intent underlying this support is non-additive, in that it is not intended to introduce additional therapeutic benefits beyond those thought to be induced by the safe administration of a psychedelic medicine. These approaches rest on the idea that sufficient benefit is obtained by undergoing an inner-directed psychedelic medicine session, framed by supportive preparation and integration sessions, with minimal therapist intervention. In many such approaches, particularly MDMA-assisted approaches (Mithoefer et al., 2017), treatment benefit is thought to depend on an "inner healing intelligence" (Clare, 2018; Gorman et al., 2021) residing in the participant that, when facilitated by the ingestion of a psychedelic medicine and the adoption of an inward attentional focus, will guide the participant toward positive therapeutic outcomes. Preparation sessions are typically limited to informing the participant about events that may occur during the medicine session and encouraging them to develop personal intentions for treatment. Integration sessions typically center on the provision of non-directive, empathic listening and encouragement to the participant as they debrief and make personal meaning of their experience of the medicine session. These approaches do not encourage clinicians to adopt an indication-specific set of interventions or predetermined theory of change from a non-psychedelic EBT.

A noteworthy clinical strength of basic support models is that they allow each participant to make meaning of their inherently unique experience of their medicine session with minimal imposition from any preordained sense of how it should benefit them. These models do not provide clinicians with predetermined frameworks for interpreting treatment benefits and thereby reduce the possibility that they will make poor-fitting interpretations that may disrupt positive treatment outcomes. These models' interpretive flexibility may also protect participant autonomy as they undergo treatment with drugs that have been known to increase suggestibility (Sjöberg and Hollister, 1965; Carhart-Harris et al., 2015; Timmermann et al., 2020; Dupuis, 2021).

Additionally, these models are likely to be appealing for cost-saving reasons, as the omission of formalized psychotherapeutic interventions means that the provision of PAP treatment may require less credentialed labor. This offers considerable financial advantage given the time-intensive nature of medicine sessions. The non-additive approach of these models also implies that less needs to be accomplished in the non-drug preparation and integration phases, which may lead to fewer treatment hours and further financial benefit.

However, basic support approaches present various significant clinical limitations, several of which are aptly discussed by Sloshower et al. (2020). First, by remaining non-additive and non-specific, these approaches fail to reap the added efficacy that could be gained through the skillful incorporation of evidence-based interventions and theories of change relevant to the indication being treated. Potential synergies between drug effects in the medicine session and indication-specific interventions used in non-drug sessions are left unexplored. Secondly, basic support approaches also present a problem for research rigor insofar as they do not operationalize much of what occurs between the clinicians and the participant during treatment and thereby introduce a significant source of unaddressed variability. Clinicians in prior PAP trials have often applied their prior skills in a way that has not been adequately characterized, which has made it hard to distinguish intervention-independent drug effects from drug effects that synergize with particular therapist interventions.

Additionally, staff provided with minimalist, low-therapy training may be underprepared for challenging clinical situations that can arise during PAP treatment, such as the appearance of trauma or participant boundary-testing. This may contribute to reduced treatment efficacy, increased adverse treatment events, or a greater likelihood of relational boundary transgressions that do significant harm to participants. Finally, the lack of an explicitly proposed, empirically grounded mechanism of therapeutic change in these models may open the door for the inappropriate introduction of therapists' personal beliefs about how psychedelics heal in a way that may constitute an abuse of their authority (Johnson, 2021) and/or another under-operationalized source of variability in treatment outcomes (Sloshower et al., 2020). These models' assertion that treatment benefit is brought about by the guidance of an inner healing intelligence, though based on the clinical wisdom of experienced practitioners, has yet to be subjected to empirical scrutiny and may represent another avenue for the introduction of therapists' personal beliefs about treatment.

Strengths and Limitations of Evidence-Based Therapies-Inclusive Models

A second cluster of PAP models can be characterized by their treatment of the psychotherapeutic frame in which drug administration occurs as an opportunity to bring additional benefit to participants beyond the medicine session alone by incorporating elements of non-psychedelic EBTs into their clinical approach. Preparation sessions may introduce concepts or tools from an EBT to inform the intentions and quality of inward attention that a participant brings to their medicine session in a way thought to be efficacious for reducing their mental health symptoms. Integration sessions may use a predetermined, EBT-derived framework to sift the elements

of a participant's medicine session experience that best fit a fixed set of desired treatment outcomes. For example, the Yale approach to psilocybin-assisted therapy for depression (Guss et al., 2020; Sloshower et al., 2020) teaches participants the basic elements of psychological flexibility found in ACT as a lens for engaging with their internal experience during their medicine session and for making interpretations and changing their behavior after the medicine session. EBT-inclusive approaches may also include non-drug sessions other than preparation or integration sessions whose format is drawn directly from non-psychedelic manualized treatments, such as Motivational Enhancement Therapy (MET; Bogenschutz and Forcehimes, 2017), to provide additional non-psychedelic psychotherapy to the participant undergoing treatment.

EBT-inclusive models have a variety of strengths in comparison to basic support approaches. For instance, they integrate therapeutic interventions and knowledge from extrinsic, non-psychedelic EBTs that may enhance treatment efficacy beyond what drug administration alone can provide (Thal et al., 2021). Secondly, the incorporation of an extrinsic EBT offers a more developed framework for training therapists and delimiting specified treatment interventions, which enhances the ability to assess treatment fidelity in clinical trials. Thirdly, the employment of credentialed psychotherapists, coupled with the use of more developed therapist training, may also reduce the risk of iatrogenic harm caused by improper clinician responses to challenging clinical events. Fourthly, the adoption of a non-psychedelic EBT incurs the political benefit of borrowing legitimacy from more well-established psychotherapeutic approaches, which is shrewd for a field still in its infancy with an underdeveloped theory of therapeutic action. Finally, the incorporation of language from EBTs and the adoption of an empirically grounded theory of therapeutic change may provide a sense of competence and grounding to therapists, particularly those who are new to PAP, which may enable them to work more effectively with participants. This last point may be an important benefit as the field scales up and recruits large numbers of therapists to meet population-level mental health needs.

Generally, the limitations of EBT-inclusive approaches stem from their introduction of potentially deleterious constraints into how therapeutic benefit is conceptualized in PAP treatment. Therapeutic outcomes in PAP are likely to result from a participant's engagement with many facets of themselves and their illness during treatment (Kelly et al., 2021; Thal et al., 2021; Miceli McMillan and Jordens, 2022). Medicine sessions can foster a broad range of experiences that inspire participants to make beneficial meaning of their treatment in an equally broad range of ways that include spiritual, existential, emotional, relational, cognitive, or embodied dimensions (Masters and Houston, 1966; Belser et al., 2017; Watts et al., 2017; Malone et al., 2018; Nielson et al., 2018; Michael et al., 2021). The inclusion of a non-psychedelic EBT that was not developed with this breadth in mind may burden the treatment with an overly narrow frame for conceptualizing benefit. At best, this could lead to missed opportunities for therapeutic benefit through the devaluation of phenomena that do not fit its interpretive framework. At worst, it may encourage therapists to pressure participants into conforming their experiences to a fixed set of desired treatment outcomes, which could degrade the therapeutic alliance and invalidate the participant's personal understanding of a deeply meaningful experience. For example, if a participant's experience in a medicine session focuses on grieving the loss of a loved one, PAP therapists trained in an ACT-based approach that focuses primarily on increasing psychological flexibility (e.g., Guss et al., 2020; Sloshower et al., 2020) may shift the focus of integration sessions away from the relational or affective dimensions of this experience, which may be most meaningful for the participant, in favor of exploring its metacognitive significance. Harm may then be done to a participant when they lose ownership of the process of making meaning of their experience.

Additionally, training therapists to adopt a constrained understanding of psychedelic phenomena may increase the risk of iatrogenic harm in a way similar to that of basic support models insofar as it underprepares them for the full spectrum of challenging clinical events they may encounter. An EBT-inclusive model firmly rooted in an existing therapeutic approach may also burden study therapists with the challenge of becoming proficient in a potentially novel way of working, while disregarding much of the existing knowledge, skills, and awareness they would otherwise bring to their work. The requirement to work within an unfamiliar therapeutic approach may also be a detriment to therapists' ability to engage with participants with the type of authentic, abiding presence thought to be important in PAP (Phelps, 2017). Additionally, in a research setting, the adoption of a single theory of change could close off possibilities for noticing and evaluating the contributions of unrelated mechanisms of change outside of the employed therapeutic model. Finally, while much of the appeal of EBT-inclusive models is based on their adoption of EBTs with an established evidentiary basis, it remains unclear whether these EBTs' proven efficacy is conveyed on the PAP models that attempt to integrate them.

Lack of Attention to Embodied Phenomena

Most PAP models to date have paid little attention to the role of embodied events in therapeutic outcomes, despite their prevalence in participants' accounts of their medicine experiences (Belser et al., 2017; Watts et al., 2017). This inattention may reflect the ongoing effort to characterize PAP within the institutional bounds of Western psychiatry and psychology, which attend more exclusively to cognitive and neural phenomena. As such, beneficial outcomes of PAP treatment have been conceptualized in neuropsychological terms that omit participants' experiences of embodiment (Kelly et al., 2021; Thal et al., 2021), such as the "reset" of a maladaptive neural status quo (Carhart-Harris et al., 2017; Carhart-Harris and Friston, 2019), increased psychological flexibility (Watts and Luoma, 2020; Agin-Liebes et al., 2022), cognitive reappraisal (Agin-Liebes et al., 2022), altered neural responses to affect (Barrett et al., 2020), or increased neuronal and mental plasticity (Kočárová et al., 2021). This centering of the brain-mind may seem unremarkable, given the prevalence of neuropsychological explanations offered by most psychotherapies. But its appropriateness is less clear

when applied to the more body-inclusive experiences elicited by psychedelic medicines.

Several qualitative studies of PAP participant experiences (Belser et al., 2017; Watts et al., 2017; Bogenschutz et al., 2018) include accounts of unprompted somatic phenomena that arose in PAP medicine sessions and were experienced by participants as important to their treatment. They included interoceptive experiences of locating undesirable psychic content (e.g., grief, shame, resentment, anger) or physical illness (e.g., cancer, sequelae of problem drinking) in their lived experience of their bodies, as well as "purgative," "purifying," (Watts et al., 2017, p. 550) or "washing" (Belser et al., 2017, p. 370) experiences that diminished the perceived personal impact of these maladies, sometimes by way of vomiting or spitting (Bogenschutz et al., 2018). These participants' experiences of discharging unwanted material resonate with some indigenous frameworks for the use of psychedelic medicines that consider various forms of embodied "purging" to be instrumental in healing (Fotiou and Gearin, 2019). They also bear a similarity to phenomena suggested as potentially therapeutic by a range of understudied somatic psychotherapy approaches that have grown outside the walls of academic research, such as Somatic Experiencing (Levine, 1997) and the Trauma Resiliency Model (Grabbe and Miller-Karas, 2017). These approaches suggest that life events that adversely impact psychological functioning, such as traumas, also leave a harmful memory trace in one's body that can be "discharged" through somatic events like sobbing, involuntary shaking, or trembling (Van der Kolk, 1998). The omission of these and other somatic phenomena from most prior PAP models may thus reflect cultural bias and a carrying over of the institutional blind spots of academic Western psychiatry and psychology.

To date, PAP clinical trials have considered the mind to be the locus of therapeutic outcomes while the body is the site of unwanted adverse treatment events, such as nausea, paresthesia, or pain with no organic cause. We suggest that earlier PAP models (with few exceptions; see Mithoefer et al. (2017), Gorman et al. (2021)) may have ignored the therapeutic relevance of these and other embodied phenomena to the detriment of treatment efficacy, and we would argue that a considered incorporation of practices for supporting and responding to somatic events skillfully and ethically may enhance treatment outcomes.

Lack of Attention to Relational Elements of Treatment

PAP models to date have primarily framed treatment benefit from within what Barnes and Briggs (2021) have called a "one-person psychology," in that they view therapeutic change as emanating from an internal, subjective process that occurs during a medicine session. In most PAP clinical trials to date, particularly those with classic psychedelics, participants have been invited to don an eye mask and headphones for the duration of the medicine session and "go inward" to have an inner-directed experience with limited intervention from clinicians (Horton et al., 2021). However, some participants have still opted to engage interpersonally with the clinicians from within the altered relational dynamics of a medicine session. These dynamics are likely to differ significantly from those found in talk therapy and may include heightened participant suggestibility, vulnerability, and sensitivity; alterations in the meanings and expectations that the participant ascribes to the relationship; amplification of the participant's attachment style or other habitual relational behavior; and increased participant-led boundary testing (Sjöberg and Hollister, 1965; Passie, 2012; Carhart-Harris et al., 2015; Taylor, 2017; Dupuis, 2021). Additionally, even if a participant remains inward for the full duration of a medicine session, they may experience increased feelings of social connectedness and emotional empathy (Pokorny et al., 2017; Carhart-Harris et al., 2018b) that will subsequently impact their relationships post-medicine, including those with the clinicians during the subsequent integration phase.

Prior PAP approaches to working with classic psychedelics have provided clinicians with little guidance on how to engage with these altered relational dynamics in a way that contributes to therapeutic benefit. For basic support approaches, this is likely due to the general lack of hands-on guidance they offer therapists. EBT-inclusive models have likely omitted this relational focus due to their reliance on extrinsic EBTs that lack a relational focus, such as third-wave behavioral approaches (Walsh and Thiessen, 2018). However, Mithoefer et al. (2017) have suggested that the altered therapist-participant dynamics found in MDMA-assisted treatment may provide unique opportunities for relational repatterning work between participants and clinicians that could lead to durable improvements in social and psychological functioning. Elsewhere, it has been suggested (Barnes and Briggs, 2021; Barnes, 2022) that similar opportunities might be present in treatment with classic psychedelics as well. In support of this notion, a recent survey study found that individuals who attended group psychedelic ceremonies and felt they had a positive relationship with the ceremony facilitators self-reported greater improvements in wellbeing than those who did not (Kettner et al., 2021). Additionally, Murphy et al. (2022) recently found that the strength of the therapeutic relationship in the preparation phase of a course of psilocybin-assisted treatment for depression predicted greater emotional-breakthrough and mystical-type experience in the medicine session, which in turn led to greater reductions in depressive symptoms. The lack of attention paid by most current PAP models to relational aspects of treatment may represent another under-characterized avenue of therapeutic benefit in PAP and a missed opportunity for therapist training.

Insufficient Focus on Ethics

The altered relational dynamics found in PAP treatment may also present novel relational ethical challenges that fall outside of the scope of clinicians' prior professional training in ethics. These challenges often stem from the effects of the psychedelic medicine on a participant's subjectivity, which include increased suggestibility, disruption of interpersonal boundaries, heightened transference, attempts to reenact of traumatic early life dynamics, and increased tendency to ascribe great wisdom or power to therapists (Harlow, 2013, as cited in Passie (2018), p. 12; Taylor (2017); Northrup, 2019). Failure to navigate these challenges may lead to a variety of transgressions

that could harm participants, such as therapist sexual abuse, other forms of harmful touch, confusion of the therapeutic frame, or the inappropriate imposition of the therapist's ideas. Several high-profile cases of sexual abuse in research (Goldhill, 2020) and underground (Hall, 2021) settings corroborate these concerns of relational harm, as do published warnings from respected PAP researchers about other sources of relational harm risk specific to PAP (Anderson et al., 2020; Johnson, 2021).

There remains an unmet need for a more commensurate response to this added risk of harm in PAP treatment. Responses so far have included the development of psychedelic-specific codes of ethics for practitioners (MAPS, 2019), attentiveness to personal risk factors in trial therapist supervision (Tai et al., 2021), and reminders placed in therapist training manuals to maintain healthy boundaries (Mithoefer et al., 2017; Guss et al., 2020). However, therapist training in PAP clinical trials has yet to devote adequate attention to ethical concerns despite their central importance in the provision of safe, efficacious care to participants. The field has struggled to rise to the full breadth of the ethical responsibility that PAP treatment warrants, which includes not only the prevention of boundary transgressions, but attentiveness to other areas where ethical competence is needed, such as attending to cultural considerations (Fogg et al., 2021), ensuring that structural injustices are not replicated in treatment settings (Michaels et al., 2018; George et al., 2020), and providing care that is mindful of the understudied risks to participant wellbeing posed by psychedelic medicines, particularly in the presence of trauma (Haridy, 2021; Love, 2022). Taken together, these concerns represent areas for ethical growth to which future PAP models should attend.

HOW THE EMBARK APPROACH RESPONDS TO THESE CHALLENGES

The authors developed the EMBARK model of PAP and PAP training as a response to these concerns. The following section describes how the EMBARK model addresses the limitations of the existing basic support and EBT-inclusive models discussed so far.

Conceptualizing Therapeutic Change

The EMBARK approach conceptualizes change in PAP treatment in a way that avoids both the agnosticism of basic support models and the constrictive overdetermination of EBT-inclusive models. Its essential structure is made up of six clinical domains, or parallel conceptual avenues by which benefits may arise, which reflect the model's openness and responsiveness to the plurality of ways in which participants may benefit from PAP. They form an acronym that gives the approach its name: **E**xistential-spiritual, **M**indfulness, **B**ody-aware, **A**ffective-cognitive, **R**elational, and **K**eeping momentum. Each domain represents a conceptual through line in PAP treatment that organizes a cluster of possible in-session events in a way that facilitates working with these events therapeutically. This multimodal organization allows the model to have a structured sense of how to prepare therapists to support participants without losing sight of the diversity of paths that each unique participant's course of treatment could take. Each individual participant's treatment experience will likely only occur within one or a few of these domains, and the selection process is guided by the natural unfolding of the participant's therapeutic process. The inherent unpredictability of this unfolding necessitates that EMBARK therapists be trained to competence in all six domains, and taught the skills to flexibly employ the relevant domains, prior to the start of treatment. These six domains will be discussed in more detail later.

Incorporating Extrinsic Evidence-Based Therapies

EMBARK was designed to be capable of curating helpful elements from several non-psychedelic EBTs and other therapeutic approaches without wedding itself to one. This allows it to reap the benefits of extrinsic EBTs—helpful conceptual frameworks, efficacious treatment goals—without sacrificing the model's conceptual multiplicity by adopting a single, constrictive theory of change. EMBARK's six-domain structure facilitates the infusion of elements from multiple indication-specific EBTs that support therapeutic outcomes in each domain. For example, an EMBARK approach to treating alcohol use disorder may incorporate elements of Mindfulness-Based Relapse Prevention (MBRP; Bowen et al., 2009) in its "Mindfulness" domain, Cognitive-Behavioral Therapies (CBTs) in its "Affective-cognitive" domain, and Motivational Interviewing (MI; Riper et al., 2014) in its "Keeping momentum" domain. An EMBARK approach to another indication would likely incorporate elements of different EBTs shown to be efficacious in treating that indication. In any case, EMBARK's coherent overarching structure enables all incorporated techniques to coexist in a clear, meaningful, and synergistic way. As a participant's unique course of treatment begins to favor one domain over another, EMBARK therapists can draw more heavily from the extrinsic EBTs associated with that domain and guide the treatment toward outcomes that are in line with that domain's proposed mechanism of therapeutic change.

Delimiting Interventions

As noted earlier, basic support approaches give therapists little sense of what interventions they should or should not use, while EBT-inclusive approaches can be prescriptive about this in a way that often asks therapists to work outside of their expertise. To avoid these issues, EMBARK therapists are instead provided with a set of treatment tasks for each phase of treatment (e.g., "help the participant understand the importance of approaching challenging feelings and beliefs in the medicine session") that can be completed by way of a wide range of interventions. In carrying out these tasks, therapists are encouraged to use whichever interventions and modalities they are most comfortable and experienced with, as long as they abide by a set of general guidelines laid out in the treatment manual (e.g., "be respectful of the participant's hesitance about approaching confronting personal material"). This way of providing flexible structure eases the burden on therapists to become proficient in novel clinical approaches and

allows them to draw on their existing skill sets. Having clearly defined tasks and guidelines also facilitates the operationalization of what needs to be accomplished in sessions for the purposes of standardization.

Determining Contributing Factors in Treatment Outcomes

A clinical trial that uses an EBT-inclusive model runs the risk of improperly characterizing the factors that contribute to efficacy. For instance, successful treatment outcomes in an MET-based PAP trial treating substance abuse may be conceptualized in the language of reduced ambivalence and increased motivation for behavioral change, when participants' success in abstaining may be due more to the alleviation of mental pain by way of somatic trauma processing or enhanced resilience conferred by spiritual factors. EMBARK's pluralistic approach to mechanisms of change, reflected in its six domains, gives clinicians and researchers a framework that could support less biased, more exploratory inquiries into what treatment events support benefit, while still providing sufficient structure for proposing specific, empirically informed hypotheses. As researchers begin to address the question of how PAP has its therapeutic effects, the EMBARK model presents a compelling way to operationalize, examine, and disentangle the impact of a broad spectrum of treatment events.

EMBARK'S STRUCTURE

The following section provides an explanation of EMBARK's foundational structure: its six clinical domains, four care cornerstones, and three phases of treatment. Several of the domains reflect EMBARK's incorporation of the neglected elements of PAP treatment discussed above, and the care cornerstones demonstrate the model's centering of ethical concerns in its approach to therapist training. The final subsection on the three phases of treatment provides an explanation of how the other elements of EMBARK's structure come together into a unified treatment approach.

EMBARK's Six Clinical Domains

Each EMBARK domain refers to a set of related treatment events that can bring about therapeutic benefit if worked with in a way that is responsive to their unique requirements. For each domain, an EMBARK approach to a specific indication includes (1) one or more proposed mechanisms of therapeutic change, (2) specific therapist tasks and guidelines for interventions that support these mechanisms, and (3) indication-specific treatment goals that follow meaningfully from phenomena in the domain. Therapists are tasked with determining when one or more of these domains become salient in a participant's treatment and providing them with the support required to obtain benefit within this domain. In this section, each domain will be described generally, and an example of how therapeutic interventions in this domain might look will be drawn from the EMBARK manual for the study of psilocybin in the treatment of major depressive disorder (MDD).

Existential-Spiritual

Psychedelic medicines are well known to catalyze profound encounters with mystical or spiritual content (Griffiths et al., 2006; Breeksema et al., 2020; Podrebarac et al., 2021) and existential concerns, such as mortality (Swift et al., 2017), alienation (Watts et al., 2017), or questions of life meaning (Ross et al., 2016, 2021; Belser et al., 2017). This is perhaps not surprising, given the historical and current use of psychedelic plants and fungi in the religious practices of many cultures worldwide (Schultes et al., 2001). Several PAP clinical trials have found that participants often report profound experiences of an existential or spiritual nature (Johnson et al., 2014; Bogenschutz et al., 2015; Belser et al., 2017; Podrebarac et al., 2021) that may hold enduring significance for them (Griffiths et al., 2006). The potency of participants' mystical experiences has been found to correlate with a range of treatment benefits, including reductions in symptoms of depression (Davis et al., 2021) and treatment-resistant depression (Roseman et al., 2018), increased motivation to stop problematic cocaine use (Dakwar et al., 2014), decreases in cancer-related depression and anxiety (Griffiths et al., 2016; Ross et al., 2016), greater success in nicotine cessation (Johnson et al., 2014), and other positive changes in psychological functioning (Griffiths et al., 2018). Despite calls for further elucidation of specific therapeutic mechanisms in this domain (Roseman et al., 2018; Breeksema and van Elk, 2021; Jylkkä, 2021; Sanders and Zijlmans, 2021), existential and spiritual elements of PAP warrant recognition as potential sources of treatment benefit (Johnson et al., 2019).

The current state of our knowledge suggests that anti-depressive outcomes may be facilitated simply by having a mystical experience during a medicine session (Roseman et al., 2018; Davis et al., 2021). However, providing support for a participant's post-medicine spiritual self-development may contribute additional benefit, as suggested by prior PAP research (Griffiths et al., 2018; Lafrance et al., 2021) and non-psychedelic findings of negative correlations between spirituality and depressive symptoms (Koenig, 2009; Bonelli et al., 2012). The role of EMBARK therapists treating MDD by way of this domain is thus to create the conditions for mystical or spiritual phenomena to potentially arise and to support participants in using them as an impetus for spiritual growth. In the preparation phase, therapists assess for any intrinsic motivation a participant may have to bring existential-spiritual elements into their treatment and work with them in developing this motivation into their intentions for the medicine session. For the medicine session, therapists prepare the physical treatment space in a way that demonstrates respect for the subjective sense of sacredness that may arise for the participant and open the session with a brief, collaboratively designed ritual. If phenomena in this domain arise during the medicine session, therapists are invited to use supportive psychotherapy or evidence-based interventions of their preference during the integration phase to explore the participant's experience, support them in developing a sense of what actions it could motivate, and co-create plans for life changes and/or further spiritual self-development. Examples of approaches with evidentiary bases to use in this process include meaning-oriented psychotherapies (Vos et al., 2015),

Logotherapy (Thir and Batthyány, 2016), or Spiritual Guidance (Miller et al., 2008), which is derived from the evidence-based approach of MI (Riper et al., 2014), despite not being an EBT itself. Throughout all phases, therapists are taught to attend to their own biases and beliefs in order to avoid imposing their own understanding or interpretation on a participant's experience in this domain.

Mindfulness

This domain refers to treatment events that result in the participant becoming more capable of recognizing symptomatic internal states and responding to them with a greater capacity for self-compassion and self-regulation. Mindfulness in EMBARK has significant conceptual overlap with the notion of "psychological flexibility" that the ACE Model (Watts and Luoma, 2020) derives from ACT. In previous PAP trials, participants have often experienced various forms of disruption of their habitual self (Belser et al., 2017; Roseman et al., 2018), a sense of "mental freedom" (Watts and Luoma, 2020, p. 95), or an increased feeling of sovereignty in how one relates to the workings of their own mind (Bogenschutz et al., 2018). Overall, the "M" domain represents a place in EMBARK for preparing the participant to attend to their thoughts and feelings with compassion during a medicine session and for working with increases in psychological flexibility and other metacognitive shifts during integration.

In the treatment of MDD, mindfulness has been found helpful in disrupting ruminative thought patterns (Watkins, 2016), enabling more cognitive flexibility (Kohtala et al., 2018; Shapero et al., 2018), and fostering a more compassionate stance toward oneself (Segal et al., 2012). To support these outcomes, EMBARK therapists begin a course of PAP treatment for MDD by teaching basic mindfulness skills to the participant. This teaching is only meant to ensure that the participant knows how to attend to their internal experience during the medicine session, which is when a more enduringly increased capacity for mindfulness may arise. During the integration phase, therapists help to anchor whatever aspect of mindfulness arose for the participant through the use of indication-specific mindfulness practices. Therapists may also help the participant integrate a new feeling of self-compassion or support them in using the momentary abatement of ruminative thoughts as an opportunity to develop mindfulness-based skills that may prevent a recurrence. Therapists can use their own mindfulness-based interventions within the bounds of the guidelines provided, or they can use suggested interventions drawn from Rumination-Focused CBT (RF-CBT; Watkins, 2016) and Mindfulness-Based Cognitive Therapy (MBCT; Segal et al., 2012) included in the treatment manual. At all times, therapists are taught to work with the participant in this domain within a trauma-informed approach to mindfulness and to avoid imposing one's own beliefs or biases onto the participant's experience.

Body Aware

As discussed earlier, PAP participants have reported that embodied phenomena are a notable part of their experience of a medicine session. There are few EBTs that provide support in conceptualizing or responding to these phenomena, though innovative somatic psychotherapy approaches have offered suggestions (Levine, 1997; Grabbe and Miller-Karas, 2017). EMBARK therapists are prepared to respond to embodied treatment events using the most widely accepted elements of these novel somatic approaches, such as "pendulation," or the process of helping a participant alternate between active, embodied engagement with trauma material and self-soothing (Grabbe and Miller-Karas, 2017). EMBARK also encourages integration of somatic elements from more established EBTs, such as somatic awareness training exercises and self-regulation skills from MBRP or Dialectical Behavioral Therapy (DBT; Linehan, 2014) to support therapeutic outcomes in this domain.

Importantly, the techniques used by EMBARK therapists in this domain do not require them to work with the body in an intensive, hands-on way and are thus not prohibitively far beyond their standard psychotherapeutic training. In preparation, therapists train the participant in basic somatic awareness so that they can attend to and thereby facilitate pro-therapeutic bodily phenomena during the medicine session. Once the medicine is administered, the therapists' role is to guide the participant back toward an awareness of their body when clinically indicated and help them remain within their zone of optimal arousal through the use of the self-soothing interventions discussed earlier or therapist-participant touch-based interventions.

While some have asserted the importance of therapist-participant touch in PAP (Mithoefer et al., 2017; McLane et al., 2021) based on historical assertions by authorities in the field (e.g., Martin, 1957; Eisner, 1967), others have noted that there remains a lack of knowledge or consensus around the efficacy, safety, or necessity of therapist-participant touch in PAP (Devenot et al., 2022). EMBARK therapists are thus instructed to prioritize non-touch interventions and limit their touch-based interventions to basic supportive touch that minimizes points of contact between parties, like handholding or placing a hand on a participant's shoulder to convey support or offer grounding. More intensive forms of touch (e.g., full-body embraces) are omitted until further research establishes them as safe, effective interventions. Therapists also rigorously assess for the participant's consent to touch-based interventions during preparation and proactively give participants a chance to reject any form of touch during preparation, immediately before the provision of touch in the medicine session, and at any time during the touch, so as not to move beyond the participant's espoused level of comfort.

Since most interventions in this domain involve supporting the participant in mindfully attending to their body, the "B" domain shares some practical overlap with the "M" domain. The primary distinction between the Body aware and Mindfulness domains is found less in their associated interventions than in participants' subjective experiences of how benefits arise and the integration goals that best support these benefits. Body aware treatment goals follow from medicine session events that a participant locates in their body (e.g., "I saw the [pain in my chest] [. . .] then I felt so much lighter, like something had been released," Watts and Luoma, 2020, p. 95) and involve integration practices that work with shifts in somatic awareness. Treatment

goals in the Mindfulness domain involve benefits that adhere more closely to the core concepts of psychological flexibility and other metacognitive shifts ("I got a wider perspective [. . .] that there's a lot more going on than just the minor things that were going on in my head," Watts and Luoma, 2020, p. 96) and are sustained with practices that build upon a participant's revised relationship with the contents of their mind.

In the treatment of MDD, somatic phenomena are hypothesized to contribute to therapeutic outcomes in two ways. Depressive symptoms are notable for their disturbance of embodiment (e.g., fatigue or energy loss, disruptions of sleep and appetite, weight gain or loss). It has been suggested (Ratcliffe, 2015; Doerr-Zegers et al., 2017; Rønberg, 2019) that disruptions of one's lived experience of their body are the most fundamental and cross-culturally consistent MDD phenomena. As such, the experiences of enlivenment and sensory embodiment that some PAP participants describe (Watts et al., 2017) may form the basis for a relationship with one's body that opposes the recurrence of depressive symptoms. If such an experience arises for a participant, therapists may work with them to build and strengthen this new relationship.

Additionally, it is likely that treating MDD will often involve working with trauma. The comorbidity and symptomology of MDD and trauma has been posited as evidence that many cases of MDD can be meaningfully thought of as a subtype of PTSD characterized by an internalizing response to trauma (Flory and Yehuda, 2015). Although classic psychedelics have not yet been used to address trauma in a completed clinical trial, it has been suggested (Bird et al., 2021) that the disinhibiting effect of psilocybin on frontal-limbic neural circuits of emotional regulation are similar to those of MDMA, which has more established efficacy in treating trauma (Bahji et al., 2020; Illingworth et al., 2021; Smith et al., 2022). Classic psychedelics may thus have facility in trauma treatment by way of similar disinhibitory mechanisms. It is likely that PAP treatment of MDD with a classic psychedelic will sometimes facilitate the appearance of trauma symptoms, possibly in the form of the somatic phenomena described earlier (nausea, shaking, etc.). When this occurs, a skillful therapeutic response may facilitate lasting resolution.

Affective-Cognitive

During a medicine session, some PAP participants experience dramatic shifts in their emotions and cognition. Participants have often reported that they experience a degree of emotionality that is ordinarily unavailable to them, including feelings of bliss, love, despair, fear, and grief, often in the context of a healing catharsis (Belser et al., 2017; Watts et al., 2017; Breeksema et al., 2020). They may also find themselves confronting maladaptive self-beliefs with a directness they would normally avoid (Bogenschutz et al., 2018). Engaging non-defensively with these emotions and beliefs during a medicine session has become a widely accepted practice among PAP models. This practice mirrors that found in several non-psychedelic EBTs, such as ACT's emphasis on acceptance (Hayes et al., 2012) and Emotion-Focused Therapy's (EFT; Greenberg and Watson, 2006) emphasis on entering into maladaptive states in service of transformation. This domain serves as a space within EMBARK for incorporating approach-oriented practices for working with emotions and self-beliefs in way that best addresses the indication being studied.

For example, the EMBARK approach to MDD in this domain begins with the notion that many depressed individuals have developed a habitual response to challenging feelings that entails dimming their awareness of them through a kind of automatic, unconscious avoidance and characteristic depressive experience of feeling numb and withdrawn (Tull et al., 2004). Participants in PAP medicine sessions have often experienced a greater facility in reconnecting with this avoided material and have implicated these experiences in their positive treatment outcomes (Gasser et al., 2015; Watts et al., 2017; Bogenschutz et al., 2018; Watts and Luoma, 2020). In the preparation phase of MDD treatment, EMBARK therapists are tasked with helping participants understand the importance of adopting an approach orientation during the medicine session. They also help the participants develop one or more self-soothing techniques. During the medicine session, the therapists' role is to remind the participant to welcome challenging content if needed and to help them utilize the previously learned self-soothing techniques when necessary. To integrate these experiences, EMBARK therapists help participants use experiences of approaching challenging material as the basis for updating maladaptive core beliefs about oneself or the world and cultivating an enduring attitude of greater acceptance in their emotional life. All of these interventions are taught and employed in a way that is respectful of participant autonomy, the principles of trauma-informed care, and cultural differences in relating to and expressing one's emotions.

Relational

As noted earlier, practitioner-participant interactions are often significant events in medicine sessions that have yet to be adequately characterized by other PAP models. These interactions may be home to amplified versions of dynamics that are typically found in any relational form of psychotherapy, including transferences, projection, or reenactments of traumatizing dynamics or events. As in talk therapy, the appearance of these phenomena represents an opportunity for clinical gain if handled skillfully or rupture and harm if handled poorly. EMBARK therapists are thus trained to work ethically and efficaciously in this domain through the didactic and experiential processes discussed later under the Ethically rigorous care cornerstone.

In the treatment of MDD, these relational events are framed as potential moments of relational repatterning that may reduce depressive symptoms. A core element of depression is social isolation, both actual and felt (Meltzer et al., 2013; Morrison and Smith, 2018). This isolation may derive from patterns or beliefs learned in early life relationships, such as a sense that one is unacceptable, deserves to be alone, or may lose love if they express themselves freely in the presence of another person. The altered relational dynamics of a PAP medicine session may provide opportunities for relational repatterning that supplants these maladaptive beliefs. EMBARK therapists are also prepared to support relational benefits that may arise for the

participant outside of their interactions with the therapists, such as an internally felt sense of social connectedness or emotional empathy (Pokorny et al., 2017; Carhart-Harris et al., 2018b) or an autobiographical review process that examines past and present relationships in the participant's life (Belser et al., 2017; Watts et al., 2017). If these shifts in social cognition occur and are skillfully worked with in the integration phase, a depressed participant can be helped to use them as the grounds for a less isolative social life.

Keeping Momentum

A course of PAP treatment is brief, and its most enduring benefits have been conceptualized as those that continue to unfold well beyond the final session (Mithoefer et al., 2017; Dölen and Briggs, 2021). PAP participants often emerge from a medicine session with a sharp uptick in the sense of motivation, self-efficacy, and commitment to making pro-therapeutic changes to their behavior or life context (Bogenschutz et al., 2018; Griffiths et al., 2018; Nielson et al., 2018). Some may also develop a clarified sense of their deeply held values, which may form the basis for beneficial post-treatment actions (Watts and Luoma, 2020). At the neural level, it has been suggested that the plasticity brought about by many psychedelic medicines may signal the reopening of a social reward critical learning period for weeks after administration, suggesting that pro-therapeutic changes may take root during a time period that extends beyond the end of what is typically considered integration (Nardou et al., 2019; Dölen, 2021; Dölen and Briggs, 2021; Lepow et al., 2021). The EMBARK approach recognizes this unique opportunity. Therapists are trained to support a participant's movement from the setting of intentions to the planning of concrete actions by attending to importance of post-treatment changes throughout all stages of PAP treatment.

For MDD or any other indication under study, these changes are expected to look very different for each participant. EMBARK therapists are trained to apply a broad lens to what helpful post-treatment change might look like. For some participants, the most supportive change may be at the level of personal behaviors, such as problem drinking or procrastination. For others, change may be warranted in their personal contexts, such as relationships or work environments. Some participants may find additional benefit in taking aim at collective concerns that have a bearing on their life, such as structural racism or exploitative work conditions, through participation in collective organizing. The EMBARK approach recognizes the potential of both individual and collective forms of change in the service of enhancing a participant's psychological, spiritual, and social wellbeing.

EMBARK's Four Care Cornerstones

The EMBARK approach rests upon four pillars of ethical care. They represent the model's commitment to the notion that efficacious treatment is inextricably linked with ethical treatment. These pillars are woven into all levels of any EMBARK approach to a specific indication, from conceptualization to treatment. Subject matter experts were invited to teach an EMBARK training module on each cornerstone (see below), and key elements from their teachings have been written into EMBARK manuals.

Trauma-Informed Care

This cornerstone reflects a recognition of the prevalence of trauma likely to be found in PAP clinical trial participants. Moreover, it marks the need for greater attentiveness to the unique and sensitive ways that trauma may manifest in PAP medicine sessions and the potential for retraumatization that may occur in the absence of adequate training. Therapists trained in the EMBARK approach are provided with psychedelic-specific training in how to identify and respond to trauma when it arises, ways to avoid re-traumatization, and strategies for maintaining their own wellbeing in service of sustainably supporting participants.

Marcela Ot'alora G., MA, LPC, contributed her approach to trauma-informed care to the EMBARK training program. Her training materials applied the Substance Abuse and Mental Health Services Administration's (2014) SAMHSA six key principles of trauma-informed care (safety; trustworthiness and transparency; peer support; collaboration and mutuality; empowerment, voice, and choice; cultural, historical, and gender issues) to PAP treatment, along with the additional principles of choice and autonomy. These principles were discussed in conjunction with important practical considerations and attention to ways in which therapists may unwittingly cause harm to participants who carry trauma. EMBARK manuals emphasize these principles and considerations throughout treatment, with particular attention paid to ensuring that any exercises that invite the participant to focus inwards (e.g., mindfulness, somatic awareness) are conducted in a way that is sensitive to the needs of those with trauma.

Culturally Competent Care

The field of mental health has reached a consensus that the ability to provide care to those who differ from their therapist in terms of race, culture, gender, sexual orientation, or class is an essential part of delivering effective treatment (American Psychological Association, 2017). However, training therapists to consider these factors when treating those who are culturally different has often lagged behind this realization. This has been particularly true in clinical PAP trials, which have received much scrutiny for not recognizing the importance of cultural considerations (Herzberg and Butler, 2019; George et al., 2020; Williams et al., 2020; Fogg et al., 2021). While an appropriate response to these concerns would entail structural and cultural changes in the field of PAP research that go beyond therapist training, EMBARK training was designed to minimize iatrogenic harm by helping therapists to engage in culturally humble and attuned ways that avoid replicating oppressive dynamics in the therapist-participant relationship.

NiCole T. Buchanan, Ph.D., has led the training module on this cornerstone. She has provided materials for therapists on a variety of areas pertaining to cultural competence in clinical work: privilege, power, implicit bias, awareness of one's social position, concerns around language and non-verbal communication, cultural influences on the expression of emotions and disclosure of struggles, norms around touch and relationships, use of the DSM-V Cultural Formulation Interview (American Psychiatric Association, 2013), the adoption

of an anti-oppressive advocacy approach to the role of therapist (Ali and Lees, 2013), and more. Psychedelic-specific topics that she addressed in this module include the influence of the War on Drugs on People of Color seeking psychedelic treatment, responding competently to intergenerational and collective content that arises in medicine sessions (e.g., cultural grief), and considering cultural appropriation in music selection. Attentiveness to these topics have been incorporated into EMBARK manuals' approaches to PAP treatment.

Ethically Rigorous Care

As noted earlier, PAP treatment presents unique ethical challenges that, if mishandled, could lead to boundary transgressions that do considerable harm to participants. EMBARK responds to this heightened potential for relational harm by interweaving ethical considerations and training into many aspects of its approach, including the guidelines it offers for therapist interventions. EMBARK therapists are also supported in their own ethical self-reflection and growth through ongoing supervision, participation in peer consultation groups, and other practices that aim to enhance their ethicality, as therapists' own self-reflection and growth is central to their capacity to engage with participants in ethically grounded ways. The model also recognizes the importance of organization-wide commitments to preventing and responding to boundary transgressions with integrity and encourages those who employ EMBARK to adopt such commitments.

Kylea Taylor, MS, LMFT, has taught this module in the EMBARK training. She presented therapists with techniques for attending to how their personal material may be activated by the unique demands of PAP work. Her didactics touched on considerations around touch, multiple relationship, power differentials, suggestibility, and other psychedelic-relevant topics not adequately covered by therapists' standard ethical training. Attentiveness to these elements is also written into EMBARK manuals' instructions on setting relational boundaries, being mindful of and proactively discussing relational dynamics with participants, assessing consent for touch, and other ethical practices. Suggested practices for continued ethical development are discussed in an appendix found in all manuals as well.

Collective Care

The underlying causes of the struggles and symptoms that bring PAP participants into treatment are not always entirely locatable in the personal and biological conditions of their lives. The fields of medicine and psychology have become increasingly attentive to the fact that the micro-level conditions they treat are heavily influenced by the macro-level or structural conditions of the society in which participants live (Ali and Sichel, 2014). These societal factors include discrimination built into governing institutions (e.g., legal systems, policing), inequities in access to resources (e.g., housing, medical care, work, social services), structural deficits in community cohesion and mutual support, and systemic inattentiveness to those with increased needs (e.g., those with disabilities, the elderly). EMBARK therapists are trained to attend to structural factors in their work and are offered recommendations on how they can broaden their sense of their role and become more holistic advocates for the participants they have committed to serve. Additionally, the model recognizes that much of the onus for collective care falls upon the organizations that employ it and thus encourages any groups who use EMBARK to commit resources to addressing structural concerns relevant to the populations they serve.

Florie St. Aime, LCSW, led the EMBARK training in this cornerstone. She facilitated an exploration of psychotherapy and PAP's situatedness within deeply engrained systems of domination, anthropocentrism, and historical inequities, with a focus on the implications this has for how suffering is treated in PAP clinical trials. Her presentation also focused on historical and ancestral dimensions that may arise in PAP and what it would mean to respond to them with more collective notions of care. In the EMBARK manuals, this cornerstone shows up most notably in the integration phase, which holds that pro-therapeutic, post-treatment change at the personal level can be most supportive to participants when it occurs in conjunction with changes to the broader structural context of their lives.

EMBARK's Three Phases of Treatment

The EMBARK model adheres to the three-phase PAP treatment design that has been used in all clinical trials published to date (Horton et al., 2021). It consists of non-drug preparation sessions prior to administration, medicine sessions in which the psychedelic medicine is administered, and non-drug integration sessions after the date of administration.

For the sessions within each phase, therapists are given a set of general tasks, as well as domain-specific tasks for each of the six domains (see **Figure 1** for examples of domain-specific tasks in all three phases). For the preparation and medicine phases, these two sets of tasks are woven together into suggested agendas for each session, which therapists can apply with flexibility and responsiveness to the needs of a specific participant (see **Figure 2** for an example agenda). In the integration phase, therapists and participants collaboratively choose which integration goals they will pursue based on their pertinence to what arose in the participant's medicine session (see **Figure 1** for examples of integration goals). Each indication-specific EMBARK treatment manual provides guidance on which integration goals to consider with the participant based on the specific treatment events that arose during the medicine session (see **Figure 3** for an example). This section further details how EMBARK's eclectic, six-domain approach comes together into a unified approach across the three phases of treatment.

Preparation Sessions

All EMBARK protocols developed so far have included three preparation sessions leading up to each medicine session, though this may change if called for by the indication under study. The therapists' general aims for this phase have included building rapport and trust, learning about the participant's experience of their mental health challenges, explaining basic elements of PAP treatment and what to expect from the medicine session, providing preparatory instructions about diet and aftercare, and responding to participant questions about PAP treatment.

	Preparation	Medicine	Integration (*as relevant*)
Existential-spiritual	• Provide a framing for the medicine session that facilitates existential and spiritual content • Assess for existential or spiritual themes and work them into intentions	• Create a physical and relational container facilitative of existential or spiritual content • Open session with a collaborative ritual	1. Nurture any interest in spiritual self-development that arose for the participant 2. Connect any existential or spiritual insights that arose to the participant's MDD
Mindful-ness	• Provide basic psychoeducation on the use of mindfulness in the medicine session • Teach and practice basic mindfulness skills	• Encourage mindfulness with brief pre-dosing practice • Provide a therapist presence that exemplifies mindfulness	3. Support sustained capacity for recognizing and interrupting ruminative thought processes 4. Build upon any newfound capacity for self-compassion
Body-aware	• Teach and practice basic somatic awareness exercise for use in medicine session • Discuss and assess consent for touch interventions	• Guide participant back to their body when needed • Provide supportive touch (with consent and within scope of competence) • Elicit self-soothing, if necessary	5. Support enhanced somatic awareness and/or embodiment as a basis for improved self-care practices 6. Attend to any trauma processing that occurred during the medicine session
Affective-cognitive	• Assess for relevant content and encourage an intention to explore it in medicine session • Help participant understand importance of approaching challenging feelings and beliefs during medicine session • Teach and practice a self-soothing technique	• Encourage the participant to approach challenging thoughts and feelings • Elicit cognitive self-soothing, if necessary (overlap with "B" domain)	7. Build on any moments of "moving toward" challenging emotions to establish a new approach orientation in the participant's life
Relational	• Build rapport of trust and acceptance • Relational check-in • Discuss participant's comfort with receiving care • Set relational boundaries	• Provide abundant care and CUSHION presence • If invited by participant, provide relational contact that is mindful of non-ordinary dynamics	8. Explore and draw takeaways from any relational moments that arose in the medicine session 9. Apply feelings of connectedness or empathy toward reducing isolation
Keeping momentum	• Explain that post-treatment behavioral changes will be required to sustain benefits • Listen for existing motivation to make changes and develop into intentions	• Listen for and record statements of motivation or intention to make life changes	10. Support the clarification and enactment of values 11. Help to actualize any newfound desire to make post-medicine life changes

FIGURE 1 | Domain-specific therapist tasks across three treatment phases of EMBARK approach to MDD. Integration aims are numbered to correspond to the integration aim guidance checklist (**Figure 3**).

Preparation session #3 (90 minutes)

Suggested agenda:

- General check-in
- Present agenda for the day's session
- Check in about intentions (K)
- Check in about at-home mindfulness practice (M)
- Teach and practice somatic awareness exercise (B)
- Explore existing self-soothing resources and/or develop new ones (A / B)
- Check in about therapeutic relationship & touch-based interventions (R / B)
- Discuss logistics:
  - Arrival details
- Suggest at-home preparation
  - Continue somatic awareness practice

FIGURE 2 | Example agenda for preparatory session #3, final preparation session before medicine session in EMBARK approach to MDD. Letters in parentheses indicate the domain supported by each task.

Therapists are also given domain-specific tasks in the preparation phase (see **Figure 1**), which may vary across protocols in response to the specific proposed mechanisms of change for the clinical indication under study. These tasks lay the groundwork for the participant to receive benefit within whichever of the six domains become important for them during the medicine and integration phases. It is considered important to prepare every participant for potential benefit across all six domains because EMBARK therapists make no determination before the medicine session about which domains may or may not become relevant later in treatment, despite any prediction or wish held by them or the participant during this phase. Even if a participant frames their MDD in, for example, primarily spiritual terms and expresses a desire to address their symptoms within a spiritual framing, it is still very possible that treatment benefits will occur for them in other domains, in addition to or instead of the "E" domain, if they are properly prepared. During preparation, the participant's lived experience of their symptoms and their functional significance are assessed, but no attempt is made by therapists to use this information to focus the participant's treatment on a specific subset of psychedelic-induced phenomena during the medicine session. However, this information is taken into consideration later during the integration phase when deciding what integration goals would be most supportive.

Since it is unknown during the preparation phase which domains and domain-associated mechanisms of change will be most relevant to the specific participant, therapists' role in this phase tends to be more standardized than it is in later phases. However, while preparation tasks are fixed in their intent, therapists are invited to bring in interventions from their preferred clinical orientation(s), as long as they conform to the guidelines that ensure that the intended utility of each task is conferred to the participant. For example, therapists tasked with teaching basic mindfulness skills to a participant may do so using mindfulness-based tools from ACT, DBT, other mindfulness-based EBTs, or a meditative spiritual tradition, provided that the tool meets the following criteria set forth in the EMBARK manual: (1) it invites the participant to cultivate a receptive, attentive state, (2) does not contain elements that could potentially clash with a participant's religious beliefs, (3) and abides by trauma-informed practices detailed in the manual. The manual also provides example interventions for therapists who do not have relevant expertise to bring in for any given task.

Ethical considerations based on the four care cornerstones are woven throughout the guidelines set forth for therapist interventions. For example, the guidelines for the discussion of therapist-participant dynamics requires that it include an exploration of cultural dynamics, in line with the cornerstone of culturally competent care.

Medicine Sessions

At the outset of a medicine session, the therapists maintain an agnosticism about which benefits and which domains will ultimately become most salient for a participant, much as they did in the preparation phase. The pre-dosing therapist tasks (see **Figure 1**) thus serve a similar purpose to the tasks in the preparation phase in that they set the stage for phenomena in any domain to arise and bring the potential for benefit. These stage-setting tasks are woven together into a suggested pre-dosing agenda for the medicine phase that includes a collaborative ritual (E), a check-in about intentions (K), and a brief somatic awareness practice (B). The six EMBARK domains thus continue to serve therapists as a conceptual frame for laying the groundwork for a broad variety of pro-therapeutic outcomes.

However, once a psychedelic medicine is administered, the therapists' role becomes more responsive to the specific situation and less about a domain-agnostic approach to preparation. At this point, the course of a participant's treatment starts to come into focus, and specific EMBARK domains present themselves as more pertinent to the participant's experience of the medicine. EMBARK's six-domain framework comes to serve therapists in a new way as a practical rubric for helping them to characterize in-session events and determine what domain-specific interventions

these events might call for. For example, if they observe the participant experiencing what they identify as a somatic trauma process, they can recall the training they received in the Body aware domain, and apply the interventions associated with it. Support in identifying and responding to these events is provided in the EMBARK training program (see later section) and in each indication-specific EMBARK manual.

The value of organizing the preparation work by domains becomes clear during this phase, as many of the responsive interventions applied in a particular domain will draw upon work that was conducted with the participant during the preparation phase in that same domain. For example, a reminder to "move toward" challenging emotional material will draw from preparatory psychoeducation provided in the Affective-cognitive domain, or a reminder to use a somatic self-soothing technique in response to intense somatic events will rely on what was taught during preparation in the Body aware domain. Therapists' incorporation of their own favored interventions during the preparation phase also ensures that they will be working squarely within their competence during this more unpredictable phase as well.

Integration Sessions

At this point, the therapists and participant are likely to have a strong sense of the most beneficial direction for a participant's continued therapeutic progress. During the first debrief session, all parties collaboratively determine what treatment goals might be best to work toward in integration. This process entails (1) debriefing and supporting the participant's sense of what transpired in the medicine session, (2) relating material that arose in the medicine session to their symptoms and treatment goals, (3) collaboratively identifying new attitudes, beliefs, behaviors, values, or other subjective shifts that may contribute to symptom reduction, and (4) planning post-treatment changes that may support and sustain this outcome.

A set of suggested integration goals are provided in each indication-specific manual, along with guidelines and suggestions for working toward each of these goals. These goals are organized by domain to provide continuity with events that arose in the medicine session. Together, therapists and participants choose a subset of these goals, or develop their own, as long as they are based on a clear clinical rationale. This selection process is guided primarily by what transpired in the medicine session using a tool provided in each EMBARK manual (see **Figure 3**). For instance, a participant who had an experience that they identify as spiritual may benefit from support in advancing their spiritual self-development or spiritual practices (E), or a participant who had a strong emotional opening might be best served by continued processing and reflection that may lead to revised core beliefs or a sustained movement away from emotional avoidance (A). However, the selection process is also informed by the participant's previously stated intentions for treatment and the functional meanings of their symptoms. For instance, if a depressed participant initially framed their suffering in terms of loneliness and set an intention of understanding their isolation, it might benefit them to consider goals in the Relational domain, even if nothing observable transpired in that domain during the medicine session.

All integration goals are framed in terms of three possible spheres of change: individual behavior, personal context, and broader context. Individual behavior changes may include stopping a maladaptive behavior, changing an old behavior, or adopting a new practice. Personal context changes may include updates to social, vocational, or physical contexts that support treatment benefit, such as moving away from a social circle that encourages problem drinking or moving into a vocational field more congruent with one's revised personal values. The broader context refers to structural, cultural, or economic conditions that have real, mental health consequences for the individual. Participants who decide that change at this level would be supportive for them may benefit from taking collective action (e.g., community activism, labor organizing) that addresses broader conditions in a way that feels congruent with their revised values or sense of self and/or serve as a form of socialization or behavioral activation. This may have acute benefit for them (Fang et al., 2018; Hayhurst et al., 2019; Hui et al., 2020) while also contributing to the amelioration the conditions that had engendered or exacerbated their distress in the first place (e.g., exploitative work conditions). Participants and therapists determine together which of the three spheres might be appropriate foci for post-treatment changes that support participant wellbeing.

The number of integration sessions is left to the discretion of the group employing EMBARK, though all EMBARK manuals written to date have included a standard of three integration sessions per medicine session. It is suggested that, whatever the intended number may be, therapists and participants both use their judgment to determine if additional sessions would be supportive of the participant's wellbeing and to undergo these sessions whenever possible. Otherwise, therapists working within the EMBARK approach are required to be prepared to make appropriate outside referrals if a participant requires ongoing therapeutic support. While EMBARK was designed to support short-term PAP interventions in clinical trial settings, its authors recognize the crucial importance of aftercare (Watts, 2022) and urge any organization adopting the EMBARK model to recognize the intensive nature of PAP treatment and ensure that participants' wellbeing is properly supported after their participation in the trial.

CUSHION PRESENCE

The quality of presence provided by clinicians during medicine sessions is considered to be a central element of PAP, due in large part to the heightened sensitivity of a participant in that setting (Johnson et al., 2008; Phelps, 2017; Thal et al., 2021, 2022). In EMBARK, therapists are encouraged to adopt a presence that reflects attributes represented by the acronym "CUSHION." These attributes include Calm, Unhurried, Supportive, Human, Impeccably boundaried, Openhearted, and Non-judgmental. Training in the EMBARK approach encourages therapists to engage in self-directed practices of their choice (e.g., mindfulness,

	Did the participant...	Integration aim(s) to consider
□	...experience any spiritual or mystical phenomena?	1, 2
□	...have any "big picture" insights about meaning or purpose?	1, 2
□	...describe any aspect of their experience as sacred or holy?	1
□	...feel they learned something from God, their higher self, or other spiritual entities?	1, 2
□	...feel they came into their "truer" or "higher" self?	1, 2, 10
□	...adopt a position that may indicate prayer or meditation?	1, 3, 4
□	...come away with a strong sense of personal purpose, even if hard to put into words?	2, 10, 11
□	...feel a wordless sense of wisdom or knowing?	2
□	...experience a kind of mental quiet, calm, or stillness?	3, 4
□	...experience a sense of mental "freedom" or "liberation?"	3
□	...gain more insight into their internal mental processes?	3, 4, 6, 7
□	...gain more control over their thoughts and feelings?	3, 4
□	...come away with a new view of themselves or know themselves better?	3, 7, 10
□	...feel forgiveness or compassion toward themselves or someone else?	4, 7, 9
□	...give themselves love or care, perhaps through self-touch?	4, 7
□	...have an emotional opening?	4, 6, 7

FIGURE 3 | Portion of integration aim guidance checklist provided in EMBARK manual for MDD treatment. Numbers in the "Integration aim(s) to consider" column refer to suggested integration aims detailed in the rightmost column of **Figure 1**.

grounding exercises) in order to cultivate these attributes in themselves prior to engaging with a participant and ongoingly throughout their work as PAP therapists. EMBARK holds that one's own internal work as a therapist is central to delivering the therapy in a manner that aligns with the four care cornerstones of the program and is inextricably linked with good outcomes.

GROWTH AREAS FOR EMBARK

The authors of EMBARK have intended its development to be an ongoing, iterative process. Some areas in which further development would be helpful have been identified. For example, while EMBARK's delineation of six domains serves as a helpful rubric to add structure to the protean nature of treatment with psychedelic medicines, it also introduces a broad set of required competencies that may seem daunting to therapists. In essence, EMBARK asks PAP therapists to simultaneously consider six possible avenues of healing during treatment and to be able to respond competently to events that pertain to all of them. In response to this concern, aspects of EMBARK, such as its integrative agendas (**Figure 2**) and therapist checklists (**Figure 3**), were designed to help therapists develop a sense of where to direct their attention at all points during treatment. However, the process of streamlining EMBARK is still underway, and further supports for therapists will continue to be incorporated.

EMBARK's inherently eclectic design may also leave it prone to some of the same shortcomings attributed earlier to basic support models (see **Table 2**), particularly in the operationalization of interventions used in a clinical trial. The breadth of possible interventions, coupled with the allowance that therapists can draw from their favored clinical orientation(s), may complicate the creation of adherence criteria. The authors feel that the intervention guidelines presented in the manual for therapist interventions can serve as a strong foundation for drafting clear, meaningful criteria, even if the specific interventions they allow for are diverse. In future iterations of EMBARK, these interventions guidelines will continue to be refined with an eye toward their enhanced contribution to the process of developing adherence criteria.

EMBARK also shares a limitation with EBT-inclusive approaches in that it is unclear if the efficacy of the EBTs it incorporates is preserved by the way in which they are brought in. Ultimately, this is a clinical question to be answered by further research, perhaps in a head-to-head trial that compares EMBARK to an EBT-inclusive approach that relies on a single EBT applied in a way that hews closer to its original, empirically validated form.

Finally, EMBARK's situatedness within a Western medical framework and its prioritization of EBTs limits its ability to draw from other rich sources of knowledge on the use of psychedelic medicines, including indigenous approaches. EMBARK's authors made this scope decision so that the model could be maximally useful in clinical trials that assess whether psychedelic medicines can be efficacious within the institutions of Western psychiatry and psychotherapy and their associated conceptualizations of healing. In making such a choice, EMBARK lost the ability to directly incorporate a great deal of wisdom from other legitimate models of how psychedelics can be of benefit to humanity. It is the authors' hope that others with greater expertise in non-medical approaches will find value in putting them in dialogue with EMBARK.

EMBARK TRAINING

The EMBARK training approach described in this article is intended to train PAP clinical trial facilitators to basic

competency in supporting participant benefit in a clinical trial as described previously. It consists of training in four areas: specific training modules in the EMBARK clinical domains and care cornerstones, training in specific skills required for working in a clinical trial, indication-specific training, and experiential training in an expanded state of consciousness. Taken together, the total length of training is 60 h and can include a several-day experiential retreat, if desired. Other aspects of training, such as the specifics of supervision and peer consultation or whether trainees are required to be licensed or license-eligible psychotherapists prior to EMBARK training, are left to the discretion of the group adapting EMBARK in consideration of the specific needs of their participants and trainees. In its trial-specific form, as presented here, EMBARK training is not intended to provide facilitators with the competencies required to become a state license-eligible psychotherapist. However, we suggest that EMBARK's six domains and four cornerstones could be used as the basis for developing a more in-depth PAP facilitator training program in another setting that also provides elements of general competency in psychotherapy.

Training in Domains and Cornerstones

EMBARK therapists receive specific training in the knowledge, skills, and awareness required to support benefit in the six clinical domains. Trainees also receive specific training in each care cornerstone to ensure that they can provide care in line with the full breadth of their ethical commitment to the participants under their care. These 10 modules use a flip class design that asks trainees to complete readings and watch a 1-h prerecorded video before engaging in a live 2-h training session. An additional introductory module that precedes these presents an overview of the EMBARK approach to orient therapists to the model. Once the one introductory and 10 core modules are complete, trainees undergo a final integrative module that draws all that they learned into the integrated treatment approach found in the manual for that trial. Throughout each clinical trial, EMBARK therapists are also required to engage in ongoing clinical supervision and regular peer-led consultation groups.

Organizing PAP training around the six domains and four care cornerstones allows for the recruitment of 10 different faculty members who are experts in each of these areas. This presents an additional advantage over a single-teacher approach in that trainees will receive a variety of perspectives on how to conduct PAP treatment. This model also ensures that each teacher presents material from within a domain that speaks to their particular area of expertise, rather than asking one teacher to speak to all domains. For example, Jeffrey Guss, MD, an expert in relational psychoanalysis, taught in the Relational domain for the inaugural EMBARK training, while Adele Lafrance, Ph.D., an expert in EFT, taught in the Affective-cognitive domain.

Indication-Specific Training

As a transdiagnostic model of PAP, EMBARK is being adapted for different indications, including MDD, alcohol use disorder, anxiety disorders, etc. For each clinical trial that applies EMBARK to the PAP treatment of a specific indication, therapists undergo an additional training module on the particularities of working with that indication. This module is led by a faculty member who is a recognized expert in the treatment of the indication under study. Additionally, it is recommended that each clinical trial that employs EMBARK invite clinical supervisors with expertise pertinent to the indication under study.

Clinical Trial Training

When the EMBARK approach is used in a research setting, study therapists are also required to undergo training in skills relevant to conducting PAP in the context of a clinical trial. Currently, this includes four 2-h modules that cover the basics of clinical research, ethics and consent in clinical trials, roles and responsibilities in clinical trial documentation, and responding to adverse events. It also includes self-paced training in the International Conference on Harmonization Good Clinical Practice (ICH-GCP), Basic Life Support (BLS), the use of the Columbia Suicide Severity Rating Scale (C-SSRS), and certification in the Collaborative Institutional Training Initiative (CITI) Program.

Experiential Training

It has been suggested that personal experiences with altered states of consciousness may improve PAP therapists' ability to support participants by giving them an enhanced understanding of the subjective experiences their participants may undergo in a psychedelic medicine session (Nielson, 2021). It may also give therapists a firsthand sense of the vulnerability and suggestibility engendered by psychedelic medicines in a way that could help them minimize relational harm to participants. As such, one organization funding and administering clinical trials assessing the efficacy of MDMA in the treatment of PTSD has obtained permission to conduct a healthy volunteer trial that allows trained study therapists to undergo a medicine session as a participant (MAPS, 2020). However, providing an experiential training opportunity has proven challenging for other research groups due to legal factors, stigma around drug use, and this practice's affront to the institutional logic of psychiatry, which does not value or require personal experience with medications administered to patients (Nielson and Guss, 2018). This practice has also come under scrutiny for potentially introducing a source of bias into research in that therapists who take a psychedelic medicine for the first time in preparation for working on a clinical trial may develop an inflated sense of the drug's capacity to heal, which could have implications for research blinding and objectivity in the presentation of results (Anderson et al., 2020). Furthermore, investigator self-disclosures about personal experience with psychedelic drugs has been found to degrade perceptions of their integrity as a researcher held by psychedelic-naïve observers (Forstmann and Sagioglou, 2021). Given this set of important considerations, clinical research groups who employ the EMBARK approach are free to decide whether they will include an experiential

training component and whether this component will include an opportunity to take a psychedelic drug or an alternative practice (e.g., breathwork).

EMBARK IN ACTION

Although EMBARK has been trademarked by Cybin Inc., it has been made freely available to any group interested in adopting it for their own purposes, research-related or otherwise. As noted earlier, the EMBARK approach is adaptable to almost any PAP clinical trial that uses a psychedelic medicine to treat a clinical indication. The approach is also flexible enough to serve as the basis for a more in-depth PAP therapist training that supports trainees in becoming more skilled PAP providers. For instance, EMBARK will be used to train the therapists who staff a low-cost/no-cost psychedelic treatment clinic under development at Lenox Hill Hospital with the support of a grant from Cybin.

At Cybin, upcoming clinical trials using the proprietary CYB003 and CYB004 formulations will use the EMBARK approach to target MDD, alcohol use disorder (AUD), and anxiety disorders. Treatment manuals have already been written for MDD and AUD, which have tailored the EMBARK approach to these indications. For example, the AUD manual incorporates a strong focus on relapse prevention in its treatment goals and sets intervention guidelines based on the practices of several AUD-specific EBTs, such as MBRP (Bowen et al., 2009) and MI (Riper et al., 2014). Despite the considerable differences between AUD, MDD, and anxiety-related disorders—as well as the differences between CYB003 and CYB004—the EMBARK model's flexible, open architecture has been found to be meaningfully applicable to developing therapeutic approaches for all studies described here.

EMBARK is intended to continually evolve by way of collaborative input from research groups outside of Cybin that adapt the model for their own purposes. For instance, the collaboration between the current authors and Dr. Back on adapting EMBARK for his clinical trial, discussed in the introduction, led to enduring changes in the way EMBARK is taught and presented to therapists. Some of Dr. Back's innovations have become standard in other EMBARK manuals, such as the inclusion of an integration guidance checklist (see **Figure 3**) and "cheat sheets" that provide a concise summary of therapist tasks, clarified presentation of therapist tasks throughout the manual, and a reorganized section on managing challenging medicine session events. Dr. Back also co-developed the EMBARK training program his study facilitators underwent, which will serve as the template for future trainings. Additionally, Ladybird Morgan, RN, MSW, a lead facilitator for this study, authored a section on diversity and inclusivity that is now found in all EMBARK manuals. As more outside groups shape EMBARK to their own needs, we hope that its open-source model will be further developed and strengthened through a continual process of collaborative peer review.

CONCLUSION

The field of PAP research may be seen as entering its own critical period of social learning. It has begun to engage with questions of how to ensconce itself within the lineup of more established psychotherapeutic approaches. To do so, it has wisely looked outside itself to the clinical frameworks offered by leading EBTs. This cross-pollination will be helpful if and when PAP scales up, as it makes PAP more accessible to the thousands of therapists seeking to participate in the process. However, the field must not lose sight of the irreducible differences between PAP and the EBTs it borrows from. It should carefully consider the pros and cons of how it interfaces with existing psychological knowledge, lest it lose something essential.

We offer the malleable, plug-and-play structure of the EMBARK model as a useful staging ground for any attempt at the judicious creation of a syncretic treatment approach. It is presented here as an adaptable frame for PAP that synthesizes current knowledge in the field in the service of supporting our evolving collective understanding of the spectrum of ways in which psychedelic medicines may bring novel, beneficent possibilities to participants and societies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

WB and AB were main contributors to the development of the EMBARK model presented in the manuscript, collaborated on the organization of the manuscript and the ideas set forth therein. WB wrote the initial draft of the manuscript. AB provided edits and input toward the final draft. Both authors contributed to the article and approved the submitted version.

FUNDING

Both authors have received financial compensation from Cybin, Inc., during the time in which the EMBARK model was developed and when this article was written. WB was a paid consultant at Cybin, and AB was Cybin's Chief Clinical Officer. Cybin, Inc., also paid for the open access publication fees by way of reimbursing WB, who outlaid the initial payment.

ACKNOWLEDGMENTS

We are grateful to Sarah Scheld, MA, and Alex Kelman, Ph.D., for their suggestions on earlier drafts of this manuscript. We also express gratitude to Anthony Back, MD, Jeffrey Guss, MD, and Robin Brody, PsyD for their collaboration and feedback during the development of EMBARK.

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Conflict of Interest: Both authors have received financial compensation from Cybin, Inc., during the time in which EMBARK was developed and when this article was written. WB was a paid consultant at Cybin, and AB was Cybin's Chief Clinical Officer. In the last 3 years, AB has also received financial compensation for psychedelic research-related activities from Yale University, NYU School of Medicine, MAPS Public Benefit Corporation, Heffter Research Institute, Synthesis Institute, Chacruna Institute, and Adelia Therapeutics and has filed patents on the use of psychedelic compounds for the treatment of psychiatric indications.

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SYSTEMATIC REVIEW
published: 10 June 2022
doi: 10.3389/fpsyg.2022.887255

Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions

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Modern clinical research on psychedelics is generating interesting outcomes in a wide array of clinical conditions when psychedelic-assisted psychotherapy is delivered to appropriately screened participants and in controlled settings. Still, a number of patients relapse or are less responsive to such treatments. Individual and contextual factors (i.e., set and setting) seem to play a role in shaping the psychedelic experience and in determining clinical outcomes. These findings, coupled with data from literature on the effectiveness of psychotherapy, frame the therapeutic context as a potential moderator of clinical efficacy, highlighting the need to investigate how to functionally employ environmental and relational factors. In this review, we performed a structured search through two databases (i.e., PubMed/Medline and Scopus) to identify records of clinical studies on psychedelics which used and described a structured associated psychotherapeutic intervention. The aim is to construct a picture of what models of psychedelic-assisted psychotherapy are currently adopted in clinical research and to report on their clinical outcomes. *Ad-hoc* and adapted therapeutic methods were identified. Common principles, points of divergence and future directions are highlighted and discussed with special attention toward therapeutic stance, degree of directiveness and the potential suggestive effects of information provided to patients.

Keywords: psychedelic-assisted psychotherapy, set and setting, theoretical models, psychedelics, review

OPEN ACCESS

Edited by:
Stig Poulsen,
University of Copenhagen, Denmark

Reviewed by:
Brian Barnett,
Cleveland Clinic, United States
Samuli Kangaslampi,
Tampere University, Finland

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Specialty section:
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

Received: *01 March 2022*
Accepted: *11 May 2022*
Published: *10 June 2022*

Citation:
Cavarra M, Falzone A, Ramaekers JG, Kuypers KPC and Mento C (2022) Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. Front. Psychol. 13:887255. doi: 10.3389/fpsyg.2022.887255

INTRODUCTION

We are currently witnessing a growth in interest in psychedelic substances and their potential use for the promotion of mental health (Nutt et al., 2020). After an early phase set between the '50s and the '70s of the previous century when applications were being tested in psychotherapy (Abramson, 1960; Grof et al., 1973) and, more specifically, for the treatment of neuroses (Crocket et al., 1963), alcoholism (Smith, 1958; Leuner, 1967), end-of-life anxiety (Kast, 1967; Grof et al., 1973; Grof and Halifax, 1978), and chronic pain (Fanciullacci et al., 1977), psychedelic research almost got to a standstill. While modern clinical studies are obtaining promising results in some of the most difficult to treat psychiatric populations (for recent reviews see Wheeler and Dyer, 2020; Andersen et al., 2021), a portion of patients do not seem to benefit from psychedelic-assisted therapies (PAT)

or end up relapsing (Nutt et al., 2020). While this issue may arise in part due to the limited number of sessions that are admissible in a clinical trial (Grof, 2016), such variability urges researchers to find ways to ways to increase response rates and the stability of clinical improvement.

Several authors hypothesized that the therapeutic effects of psychedelics cannot be explained by their pharmacological properties only (a model referred to as *psychedelic chemotherapy*; Pahnke et al., 1970) but rather that individual ("set") and contextual ("setting") factors play a pivotal role in some of the observed clinical gains with psychedelics (Leary, 1961; Pahnke et al., 1970; Hartogsohn, 2017). Classic psychedelics seem to increase neuroplasticity (Ly et al., 2018; de Vos et al., 2021; Hutten et al., 2021) and environmental sensitivity or suggestibility (Carhart-Harris et al., 2015; Carhart-Harris and Nutt, 2017; Carhart-Harris and Friston, 2019) both during the dosing session itself and in the following days (Majić et al., 2015). In a way, psychedelics seem to open a window of flexibility (Kuypers et al., 2016) that may relax higher level priors and increase sensitivity to bottom-up information (Carhart-Harris et al., 2018b; Carhart-Harris and Friston, 2019). In the context of psychotherapy, this could imply that patients are offered a window of opportunity to become more effective in modifying rigid behaviors, thought patterns, and emotional reactions and that psychotherapy itself must be carefully honed to take advantage of this fertile state.

Despite evidence and theoretical reasons supporting the importance of set and setting (Carhart-Harris et al., 2018b), we still lack a model identifying the specific factors on which to focus to maximize the effectiveness of PAT. Modern research still has to tackle the delicate matter of clearly describing the role of the therapist during dosing sessions and in the wider context of PAT. Current suggestions emphasize the importance of building rapport, "letting go" of resistance, promoting openness and reliance on unconscious processes in the context of a non-directive relationship (Johnson et al., 2008; Richards, 2015; Roseman et al., 2018). In the light of such considerations, the current review aims at collecting and describing the psychotherapeutic models that have been already used in clinical studies to provide a picture of current practices adopted by clinicians and researchers in the context of clinical research. Outcomes of such studies will be reported and common principles, points of divergence and future directions will be highlighted and discussed. All models will be presented using the name that the respective authors used to refer to them.

METHODS

We performed the following searches in Pubmed/Medline and Scopus databases: "psychedelic AND assisted AND psychotherapy," "*substance name* AND assisted AND psychotherapy," "psychedelic AND enhanced AND psychotherapy," "*substance name* AND enhanced AND psychotherapy." We restricted our search to clinical studies (i.e., which involved patients suffering from a psychiatric condition or psychological distress), written in English, which made use of a psychedelic or empathogen substance (i.e., LSD, psilocybin, MDMA, ayahuasca, ketamine, DMT, 5-MeO-DMT, mescaline), which contained a description of a structured associated psychological intervention and were published before September 2021. A total of 15.959 articles resulted from the search and 15.470 unique articles were identified. Two of the authors (M.C., C.M.) independently screened the articles to determine eligibility and when judgment differed discussions were held until consensus was reached. After screening titles and abstracts according to the above-mentioned criteria, 15.079 were excluded and 391 retained. Forty-five articles were retained after full-text screening, 7 were added after an iterative reference list search and 3 were added thanks to comments received during the paper review process. The resulting number of included papers is therefore 55 (**Figure 1**). We decided to organize the psychotherapeutic models in two main categories: *ad-hoc* therapeutic models (i.e., models were originally devised for use with psychedelics compounds) and adapted models (i.e., models that were devised in a more "traditional" psychotherapeutic setting and were later adopted for PAT).

RESULTS

We identified a total of 55 papers (**Table 1**) that reporting the results of a total of 26 studies in which the following therapeutic models were used: Cognitive Behavioral Conjoint Therapy (CBCT; $n = 3$; 1 open-label study), Cognitive Behavioral Therapy (CBT; $n = 7$; 1 case study, 2 open-label, 1 RCT), Human Relations Training Laboratory Group (HRTL; $n = 1$; 1 open-label), Ketamine Enhanced Therapy/Ketamine Psychedelic Therapy (KET/KPT; $n = 5$; 1 case study, 1 case series, 1 observational study, 2 RCTs), Medication-Assisted Psychotherapy (MAP; $n = 7$, 1 RCT, 1 pre-post, 1 case series), MDMA-Assisted Therapy plus Mindfulness Skills Training (MDMA-ATM; $n = 1$; 1 open-label), MDMA-Assisted Psychotherapy (MDMA-AP; $n = 14$; 1 case series; 1 small sample within-subjects, 3 RCTs, 1 pooled analysis of 6 RCTs), Motivational Enhancement Therapy (MET; $n = 5$; 1 open-label, 1 pilot RCT), Preparation Support Integration (PSI); ($n = 7$; 1 open-label), Supportive-Expressive Group Therapy (SEGT; $n = 3$; 1 open-label), Trauma Interventions using Mindfulness Extinction and Reconsolidation (TIMBER; $n = 2$; 1 RCT). In this pool, PAT's efficacy was tested in TRD, depression, opioid addiction, tobacco addiction, PTSD, AUD, issues related to life-threatening conditions, social anxiety in autistic adults and demoralization in HIV-infected patients. Notably, 45 papers were excluded because they did not provide a description of a structured psychological intervention. This was the case for studies which did not employ psychotherapy (e.g., Palhano-Fontes et al., 2019), used generic labels (e.g., Müller et al., 2020) or referenced guidelines for safety (e.g., Griffiths et al., 2016).

Ad-hoc Therapeutic Models

Ketamine Enhanced Psychotherapy

Our search identified 5 studies investigating the efficacy of different versions of KET: 1 case series on AUD (Kolp et al., 2006), 1 case study on end-of-life distress (Kolp et al., 2007), 2 RCTs on

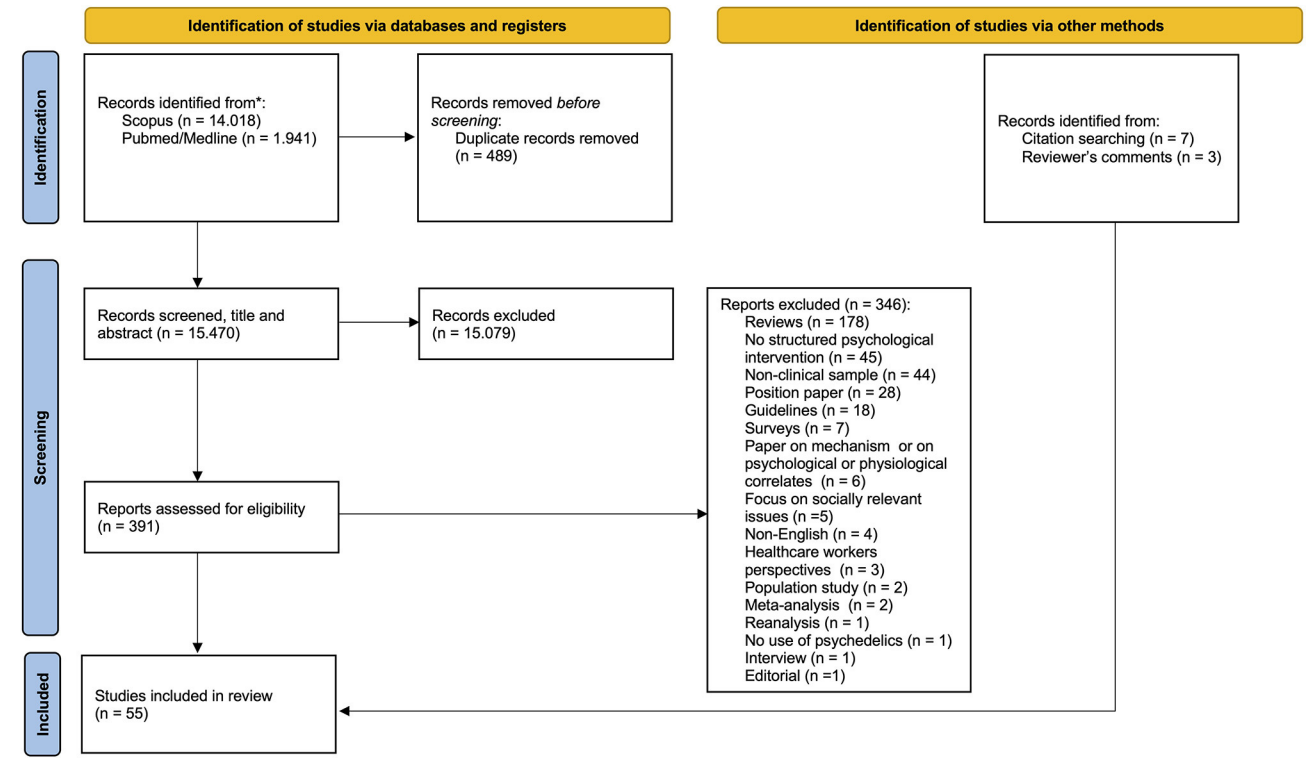

FIGURE 1 | PRISMA flowchart.

heroin dependence (Krupitsky et al., 2002; Kolp et al., 2007), and 1 observational study on AUD (Krupitsky and Grinenko, 1997).

KEP, also sometimes referred as KPT or Ketamine Assisted Psychotherapy, was first introduced (albeit with a different name: affective contra attribution) in a 1992 clinical study on the treatment of alcoholism. It made use of other drugs in addition to ketamine (i.e., aethimizol and bemegride) during a single drug session to enhance emotional experiences and promote the consolidation of memories (Krupitsky et al., 1992; Krupitsky and Grinenko, 1997). Despite ketamine being a dissociative agent that does not act on 5-HT2A receptors as classical psychedelics do (Green et al., 2011), the authors often refer to it and to the experiences it produces as psychedelic. The model was developed in an attempt to integrate the establishment of aversive associations with a previously appetitive stimulus (i.e., aversive conditioning) with the shift in attitudes toward alcohol that psychedelic therapy seemed to promote in earlier studies (Krupitsky et al., 1992). In a later review article (Krupitsky and Grinenko, 1997), the authors describe this three-step approach in greater detail.

In the first stage, preparation is carried out over a 3-month period and aims at preparing patients by informing them about the different states of consciousness they will experience. An exploration of personal motives and goals for treatment along with beliefs concerning the cause of the disease is also carried out. Establishing positive expectations toward the outcome of the experience is considered another important part of preparation together with the co-construction of the therapeutic myth; the latter refers to a therapeutic narrative constructed by the therapist and the patient that could describe and explain the patients' suffering and hint at ways to resolve it (Frank and Frank, 1993). The session should integrate elements from the patients' personal life in an atmosphere of confidence and understanding. More specifically, patients are told that they may experience insights (e.g., on their personal problems, values, beliefs about themselves or the world) leading to adaptive changes in personality and that the psychedelic experience is instrumental in acknowledging the negative effects of alcohol abuse and the positive aspects of sobriety. Furthermore, they are instructed to fully surrender to the experience and are informed that the causes for their alcoholism are unconscious in nature, related to more central personality issues and that such causes will manifest themselves during the experience in symbolic form.

The second stage is the drug session, which is conducted by a psychiatrist and an anaesthesiologist. It includes the use of aethimizol (1.5% 3 ml, i.m.) to promote the consolidation of memory, bemegride (0.5% 1 0 mL, i. v.) to intensify emotional experience, and ketamine (2.5 mg/kg, i.m.) to achieve a psychedelic experience lasting between 45 and 60 min. During the session, new age/soothing instrumental music (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002) is used with the intention to promote symbolic resolution of inner conflicts and facilitating cathartic experiences. Additionally, patients are exposed to so-called "psychotherapeutic influences," i.e., therapist

interventions that are "based on the concrete data of the patient's case history and [are] directed toward the resolution of the patient's personality problems and toward the formation of a stable orientation toward sobriety." At the peak of the experience, while the therapist aims at shifting the focus of the experience toward the dysfunctional aspects of alcohol abuse (e.g., "Your fear is a result of vodka. It is vodka that has led you to the edge of the abyss"), patients are given the chance to smell alcohol to establish aversion toward the substance. Once the dissociative effects subside, the experience is discussed and interpretations are offered. Finally, patients are asked to write down a detailed report of the session (Krupitsky and Grinenko, 1997).

The third and final stage of KPT consists of a variable number of group psychotherapy sessions carried out the day after the drug session. In this context, the psychiatrist promotes integration *via* discussion, interpretation of the experience and consideration of lifestyle changes.

In the original 1992 paper, the authors employed this model to treat 86 male AUD patients and reported a remission rate of 69.8% at 1 year compared to 24% of the control group. KPT (in combination with existential psychotherapy) was also used to treat heroin addiction (Krupitsky et al., 2002) and was subsequently adapted to Ketamine-Enhanced Psychotherapy (KEP) to reportedly "extend it into another cultural context: the US" (Kolp et al., 2007). In this latter form, the treatment was used to treat end-of-life anxiety with the following structure: 3 weekly preparation sessions (75–80 min), one ketamine session (1–3 h) and a final integration session (75–80 min). KEP was also offered to patients suffering from alcoholism in two other formats: outpatient and intensive. The outpatient format consists of 3 preparation sessions, one of which is devoted to the formulation of a "psychospiritual" goal: a therapeutic objective that integrates the patients' personal motives for treatment, their goals for their future sober life and spiritual growth (Wolfson and Hartelius, 2016). By the latter, authors refer to a multitude of feelings, experiences and attitudes that usually concern feeling unity with others and the universe, increased chance of converting to a religion, experiencing a so-called "separation of consciousness from the body," the feeling of being in contact with a higher power, the belief in the existence of "other dimensions or worlds that are parallel to ours" and similar other transpersonal phenomena. The treatment then proceeds with 1 ketamine session and 3 integration sessions (Kolp et al., 2006; Krupitsky et al., 2007). All integration sessions had the same structure and lasted 50 min; the ketamine session lasted for 3 h.

The intensive format had the same general structure of outpatient KPT and added daily all-day activity programs including psychotherapeutic and psychoeducation groups along with training in mind-body techniques. Initial data were collected in a clinical study in Russia in which the percentage of abstinent patients at 1 year post-treatment in a KPT group was compared with that of a control group (Krupitsky et al., 2007). The authors of the Russian study reported that 65% of patients in the KPT group ($n = 111$) remained abstinent compared to 24% ($n = 100$) in the control group. In the U.S., several adaptations of this model were created in an attempt to replicate results and progressively improve its efficacy even more (Kolp et al., 2006). In the first attempt the authors maintained the same structure of KPT as described above but condensed it in a 10-session, 10-week program which comprised 1 screening session, 4 preparation sessions, 1 goal-setting session, 1 ketamine session and 3 integration sessions. Contrary to expectations, this treatment led to an abstinence rate of only 25% in a group of 20 patients. Subsequently, the model was adapted to take place in a residential group setting and as such substituted the individual sessions with 30 weekly hours of psychoeducation, group activities, guided imagery exercises along with breathing, meditation, yoga, and cooking classes. The authors reported the results of 3 iterations of this model with each lasting, respectively, 1 week (35% 1-year abstinence rate, $n = 15$), 2 weeks (60% 1-year abstinence rate, $n = 10$), and 3 weeks (70% 1-year abstinence rate, $n = 15$). In all 3 iterations, patients with a history of psychedelic use were excluded at screening (Kolp et al., 2006). In summary, this treatment format progressively increased the 1-year abstinence rates over 1 (35%), 2 (60%), and 3 (70%) weeks of treatment.

In a double-blind, active-placebo controlled study, 70 detoxified patients suffering from heroin addiction were randomized into two groups employing KPT (Krupitsky et al., 2007). Both groups received 10 h of preparatory existential psychotherapy, 1 ketamine only infusion session (i.e., no other drugs were administered) and 5 more hours of integration psychotherapy. While one group received a high dose (2.0 mg/kg i.m.), the other received a low non-dissociative dose (0.20 mg/kg i.m.). Results showed improved abstinence, relapse rates, craving, and anhedonia in the high dose group while both groups showed improvements in anxiety, depression, internal locus of control, understanding of the meaning and purpose in life and spiritual development. The abstinence rate was about 85% at the 1-month assessment, about 18% at the 24 months follow-up and remained significantly higher for the KPT group over all timepoints. A subsequent study suggested that increasing the number of both ketamine (2.0 mg/kg i.m.) and integration sessions from 1 to 2 may lead to better abstinence rates at the 1-year follow-up (Krupitsky et al., 2007).

KEP was also used in two case studies (a success and a failure) involving a 62-year-old female and a 46-year-old male patients diagnosed with life-threatening illnesses and suffering from death-related anxiety (Kolp et al., 2007). The authors' intention was to highlight how certain patient characteristics may modulate treatment efficacy. While the female patient reported remission from panic attacks, discontinuation of morphine and lorazepam, increased feelings of comfort, the male patient did not resolve his death anxiety. This difference in clinical outcomes was attributed to the fact that while the woman was willing to discontinue benzodiazepine and decrease opiate use before the session, the man did not. They also pointed out that the woman never used psychedelics before while the man had an extensive history of psychotropic drug use. The authors of this paper seem to suggest that the efficacy of KEP is moderated by history of psychedelic use and they further hypothesize that the "novelty factor" associated with these substances may play a role in improving outcomes. Finally, they suggest that the concurrent use of other CNS depressants may diminish the patients' response

TABLE 1 | Summary of included studies.

References	Participants	Study design	Drug sessions	Type of psychotherapy	Control group	Primary timepoints	Primary outcome measures	Results
Wagner et al. (2019), Monson et al. (2020), and Wagner et al. (2021)	6 couples	Pre-post	2, MDMA (75, 100 mg)	CBCT	None	End of treatment and 6-month follow up	CAPS-5, PCL-5, CSI	Improved symptomatology and couple satisfaction
Wilkinson et al. (2021)	40, TRD	RCT	28 responders to previous course of 6 ketamine infusion sessions (0.5 mg/kg) randomized to either CBT ($n = 14$) or ($n = 14$) TAU	CBT	TAU	14 weeks after last infusion	MÅDRS, QIDS	Significantly lower QIDS in CBT group. Significantly lower MÅDRS for the whole sample.
Ocker et al. (2020)	1, opioid addiction	Case study	5-day ketamine infusion (10 mg/h,0.09 mg/kg/h−70 mg/h, 0.6 mg/ kg/h)	CBT	None	30-day follow up	NRS, opioid use	Pain-free and no reported opioid use
Wilkinson et al. (2017)	16, TRD	Open-label	4, ketamine (0.5 mg/kg)	CBT	None	End of treatment and 12 weeks after last ketamine session	MÅDRS, relapse rate	Most relapses occurred after the completion of the CBT course. Ketamine non-responders did not seem to benefit from CBT.
Johnson et al. (2014, 2017), Garcia-Romeu et al. (2014), and Noorani et al. (2018)	12, tobacco addiction	Open-label	2 or 3, psilocybin (20 mg/70 kg, 30 mg/70 kg)	CBT for smoking cessation	None	6-month follow up, 12-month follow up	Biomarkers of smoking status and self-report measures of smoking behavior	80 and 67% abstinence
Bowen et al. (1970)	81, AUD; 59, AUD	Open-label clinical trial	1, LSD (500 or 25 μg)	HRTL	No drug or "low" dose.	1 year after end of treatment	Custom adjustment level measure	No significant differences.
Kolp et al. (2006)	∼70, AUD	Case series	1 or 2	KEP	None	1 year	Abstinence rates	25–70%
Kolp et al. (2007)	2, LTI	Case study	1 (150 mg i.m.)	KET	None	End of life	Qualitative reports	Case 1: remission from panic attacks, relief from pain, discontinuation of painkillers. Case 2: no reported improvements.
Krupitsky et al. (2007)	59, heroin addiction	RCT, single vs. repeated ketamine doses	1 or 3, Ketamine (2.0 mg/kg im)	KPT	Single ketamine dose	1-year follow up	Abstinence rates	Greater abstinence rate in the repeated dose group
Krupitsky et al. (2002)	70, heroin addiction	RCT	1, ketamine (2.0 mg/kg im)	KPT	Ketamine, low dose (0.20 mg/kg im)	2-year follow up	Abstinence rates, Craving VAS	Greater abstinence rate and lower craving scores
Krupitsky and Grinenko (1997)	111, AUD	Non-randomized controlled trial	1, ketamine (2.5 mg/kg, im)	KPT	TAU	1-year follow up	Abstinence rate	Greater abstinence rate
Ross et al. (2016), Belser et al. (2017), Swift et al. (2017), Malone et al. (2018), and Agin-Liebes et al. (2020)	29, life-threatening cancer	RCT	1, psilocybin (0.3 mg/kg, p.o.)	MAP	Niacin	7, 6.5, 4.2 years	HADS, BDI, STAI	Improved depression and anxiety scores
Pahnke et al. (1969)	31, life-threatening cancer	Pre-post	1, LSD (200–500 μg)	MAP	None	End of treatment	Custom rating scale filled by external observers (e.g., relatives, clinical staff)	Improved scores of emotional and physical distress
Kurland (1985)	4, life-threatening cancer	Case series	1–4, LSD (100–400 μg)	MAP	None	End of treatment	Unstructured clinical evaluation	Improvement in mood, optimism and pain management

(Continued)

TABLE 1 | Continued

References	Participants	Study design	Drug sessions	Type of psychotherapy	Control group	Primary timepoints	Primary outcome measures	Results
Danforth et al. (2018)	12, autistic adults	RCT	2, MDMA (75–125 mg)	MDMA-assisted therapy and mindfulness for adult autistic individuals	Inactive placebo	6-month follow up	LSAS	Improvements in social anxiety
Jardim et al. (2021)	3, PTSD	Case series	3, MDMA (75, 75, 125 mg)	MDMAAP	None	2 months after treatment	CAPS-4	Improvements in symptoms, depression Clinically significant CAPS score reductions; improvements in BDI, PTGI and GAF
Mithoefer et al. (2011, 2013, 2018, 2019), Oehen et al. (2013), Ot'alora et al. (2018), Barone et al. (2019), and Jerome et al. (2020)	105 (pooled), PTSD	RCT	2, MDMA (75–125 mg)	MDMAAP	Inactive placebo or active control (40 mg MDMA)	End of treatment, 12-month follow-up (minimum)	CAPS-4	Improvements in CAPS-4 scores between baseline and end of treatment and between end of treatment and follow up
Bouso et al. (2008)	6, PTSD	RCT	1, MDMA (50 or 75 mg)	MDMAAP	Inactive placebo	End of treatment	SSSPTSD, STAI, BDI, HAM-D, MSF, MS, SE/R	Reduced symptomatology
Mitchell et al. (2021)	90, PTSD	RCT	3, MDMA (80–120 mg each)	MDMAAP	Inactive placebo	2 months after treatment	CAPS-5, SDS	Reduced symptomatology and disability
Wolfson et al. (2020)	18, LTI	RCT	3, MDMA (125 mg)	MDMAAP	Inactive placebo	1 month after second MDMA session	STAI	Reduced trait anxiety
Sessa et al. (2019, 2021)	4, AUD	Pre-post	2, MDMA (187.5 mg for each session)	MDMAAP plus elements from MET and third wave CBT	None	9 months	PHQ-9, GAD-7, SADQ, SIP	Improved psychosocial functioning, reduced in alcohol consumption
Dakwar et al. (2020), Rothberg et al. (2021)	40, AUD	RCT, pilot	1, ketamine ($n = 17$; 0.71 mg/kg) or midazolam ($n = 23$; 0.025 mg/kg)	MET	Midazolam	21 days after infusion	Abstinence, time to relapse, heavy drinking days,	Significantly better abstinence rate, time to relapse, heavy drinking days in ketamine group
Bogenschutz et al. (2015), Bogenschutz et al. (2018), and Nielson et al. (2018)	10, AUD	Open label	1 or 2, psilocybin (0.3 mg/kg, 0.4 mg/kg)	MET plus preparation and integration	None	9-month follow up	Abstinence rates and % of drinking and heavy drinking days	Improved abstinence rates after psilocybin session (s) and reduced drinking and heavy drinking days
Carhart-Harris et al. (2016), Carhart-Harris and Nutt (2017), Watts et al. (2017), Erritzoe et al. (2018), Roseman et al. (2018), Stroud et al. (2018), Mertens et al. (2020)	20, TRD	Open-label	2, psilocybin (10 mg, 25 mg)	PSI	None	1 week, 3 and 6 months	QIDS	Improved depression at all timepoints
Anderson et al. (2020), Agin-Liebes et al. (2021), and Stauffer et al. (2021)	18, demoralization	Open-label	1, psilocybin (0.3 mg/kg)	SEGT	None	End of treatment and 3-month follow up	DS-II	Improved demoralization at the 3-month follow up
Pradhan et al. (2017, 2018)	20, PTSD	RCT	1, ketamine (0.5 mg/kg)	TIMBER	Inactive placebo	3 months after drug session	PCL, CAPS	Better and more sustained response

AUD, Alcohol Use Disorder; BDI, Beck Depression Inventory; BDI, Beck Depression Inventory; CAPS, Clinician Administered PTSD Scale; CBCT, Cognitive Behavioral Conjoint Therapy; CBT, Cognitive Behavioral Therapy; CSI, Couples Satisfaction Index; DS-II, Demoralization Scale II; GAD-7, Generalized Health Questionnaire-7; GAF, Global Assessment of Functioning; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale-Depression; HRTL, Human Relations Training Laboratory; KET, Ketamine Enhanced Therapy; LTI, Life Threatening Illness; MDMAAP, MDMA-Assisted Psychotherapy; MÅDRS, Montgomery-Åsberg Depression Rating Scale; MAP, Medication Assisted Psychotherapy; MDF, Modified Fear Scale; MET, Motivation Enhancement Therapy; MS, Maladjustment Scale; NEO-PI-R, Revised NEO Personality Inventory; PCL, PTSD Checklist; PHQ-9, Patient Health Questionnaire-9; PSI, Preparation Support Integration; PTGI, Post-Traumatic Growth Inventory; QIDS, Quick Inventory of Depressive Symptoms; QIDS, Quick Inventory of Depressive Symptoms; RCT, Randomized Controlled Trial; SADQ, Severity of Alcohol Dependence Questionnaire; SDS, Sheenan Disability Scale; SE/R, Rosenberg Self-Esteem Scale; SEGT, Supportive Expressive Group Therapy; SIP, Short Inventory of Problems for Alcohol; SSSPTSD, Sever-ity of Symptoms Scale for Post-traumatic Stress Disorder; STAI, State-Trait Anxiety Inventory; TAU, Treatment As Usual; TIMBER, Trauma Interventions using Mindfulness Based Extinction and Reconsolidation; TRD, Treatment Resistant Depression.

to ketamine and potentially cause amnesia of the experience thus hindering therapeutic response.

In summary, across the literature KET is delivered in different formats. It proposes at least 3 preparation sessions, 1 drug session and at least 1 integration session. When administered in residential settings, it may be complemented by other activities and may include an additional drug session. Existential psychotherapy is the most cited model associated with the treatment and principles of behavioral therapy were incorporated in its original conceptualization. The role of therapists appears more directive compared with other models as clinicians are expected to actively work to establish positive expectations about the treatment, provide personality-related etiologies to explain AUD, and work to establish a structured therapeutic myth.

Medication-Assisted Psychotherapy

We identified 5 papers describing the efficacy of MAP in the context of a RCT (Ross et al., 2016; Belser et al., 2017; Swift et al., 2017; Malone et al., 2018; Agin-Liebes et al., 2020). MAP is a treatment model originally developed by Grof et al. (1973) and Grof and Halifax (1978) to be used in palliative care settings but that has been applied in the treatment of other conditions as well. Lysergic Acid Diethylamide (LSD) or Dipropyltryptamine (DPT) was administered in combination with psychotherapy to treat depression, anxiety and pain, and address existential issues in patients suffering from life-threatening illnesses. More recently, the model was used in conjunction with psilocybin administration (Ross et al., 2016; Belser et al., 2017; Agin-Liebes et al., 2020).

In its original structure (Grof et al., 1973; Grof and Halifax, 1978), MAP proposes 6–12 h of preparatory psychotherapy held over the period of 2–3 weeks focusing on the patients' present goals and issues instead of focusing on personal history and remote unresolved issues. Preparatory sessions are aimed at establishing rapport, working on family issues, addressing potential significant intrapsychic conflicts, confronting and accepting diagnosis, prognosis, and death. The overarching goal of the therapeutic model is to facilitate patients in living their days in the fullest and most meaningful way possible. Special attention is placed on preventing feelings of isolation and, therefore, the involvement of family members is encouraged. Once a good therapeutic relationship is formed and relevant issues are explored, patients are given more in-depth information concerning psychedelic sessions and the altered state of consciousness that they will experience. A session with the substance is then held by two trained facilitators in an appropriately furnished room where music can be played. Early accounts (Grof et al., 1973; Grof and Halifax, 1978) propose the use of family photographs to facilitate the resolution of relational problems and to promote the emergence of positive feelings.

More modern versions of MAP (Ross et al., 2016) encourage patients to bring items of personal and/or spiritual significance, to participate in acts (e.g., holding hands) aimed at conveying comfort and unity between the patient and the therapy team before the beginning of the session and to set their intentions toward finding relief from the psychological and existential suffering brought by cancer. During the course of the psychedelic experience, patients lie down wearing eye-shades and are invited to direct attention toward their internal experience. Therapists will remain present during the whole duration of the session and will offer non-verbal (e.g., holding hands, cradling, rocking) psychological and medical support when needed. During the final phases of the session, when the effects of the substance begin to subside, patients are encouraged to discuss their subjective experience in order to consolidate its memory. This phase was compared to psycholytic therapy (Crocket et al., 1963; Leuner, 1967; Gasser, 1996; Majić et al., 2015; Ross et al., 2016), an approach in use in the '60s in which patients would take smaller doses of psychedelics to facilitate the emergence of material during psychotherapy sessions. This process constitutes the first step of the subsequent integration work. Relatives can be invited during the termination period of the drug session. Integrative sessions, usually three, are held after each drug session and are meant to consolidate the memory of the experience and promote the processing of the emerged material.

MAP was recently used in a crossover RCT involving patients suffering from life-threatening cancer (Ross et al., 2016). The trial design involved a single psilocybin (or niacin) session (0.3 mg/kg, p.o.), three 2-h preparation sessions, three 2-h integration sessions and targeted depression and anxiety levels as primary outcomes. Psychotherapeutic work integrated elements drawn from evidence-based psychotherapies addressed to patients with life-threatening illnesses such as supportive psychotherapy, cognitive-behavioral therapy, existentially oriented psychotherapies, and psychodynamic psychotherapy. Results show that the treatment led to significant improvements in demoralization and hopelessness, spiritual wellbeing and quality of life. These changes occurred rapidly after the psilocybin sessions and were maintained at the 6.5 month follow-up. At that time, patients showed lower existential distress and better attitudes toward death. Response rates for depression were about 80% for the psilocybin group and between 20 and 30% (depending on the outcome measure) for the niacin group at the 1-day post session timepoint. Remission rates at the same timepoint were between 80 and 85% for the psilocybin group and between 20 and 30% for the niacin group. At the 7-week post session timepoint response rates were between 70 and 83% for the psilocybin group and between 14 and 40% in the niacin group. Remission rates at this timepoint were between 70 and 80% for the psilocybin group and between 20 and 40% for the niacin group. Response rates at the 1-day post session timepoint for anxiety were about 75% in the psilocybin group and about 40% in the niacin group. At the 7-week post session timepoint response rates were 58% for the psilocybin group and 14% for the niacin group. At the 6.5 months follow up, after the crossing over, response rates varied between 60 and 80% for depression and between 60 and 75% for anxiety. Long-term follow up (4.5 years) analyses of a subsample of patients from the above-mentioned study revealed that response rates were 57% for anxiety and ranged between 57 and 79% for depression. Remission rates ranged between 50 and 79% (Belser et al., 2017; Agin-Liebes et al., 2020). An earlier single sample, pre-post study (Pahnke et al., 1969) tested the efficacy of this model (using LSD, between 200 and 500 μg p.o. or dipropyltryptamine, between 60 and 105 mg

i.m.) on a group of 31 cancer patients. Results showed "dramatic improvement" in 20% of patients, "moderate improvement" in 41.9% and no improvement in 22.6%. A very similar model, albeit labeled Psychedelic Peak Therapy (PPT), was described in a case series study (Kurland, 1985), which described the effects it had on 2 female patients suffering from breast cancer, 1 female patient suffering from pancreatic cancer and 1 female patient suffering from cancer to the uterine cervix. The authors reported improvements in all four patients in measures of mood, optimism and pain management.

In summary, MAP proposes 6–12 h of preparation, 1 drug session held by two trained facilitators and 3 integration sessions. The therapeutic model is eclectic, unstructured and integrates elements from multiple and diverse theoretical frameworks.

MDMA-Assisted Psychotherapy

Our search identified 12 papers (one of which analyzed the pooled results of 6 separate studies) describing the findings of investigations conducted on 6 separate samples (1 case series, 3 RCTs, 1 pooled analysis of 6 RCTs) that used MDMA-assisted psychotherapy for Post-Traumatic Stress Disorder (MDMA-AP) (Bouso et al., 2008; Mithoefer et al., 2011, 2013, 2018, 2019; Oehen et al., 2013; Ot'alora et al., 2018; Barone et al., 2019; Jerome et al., 2020; Wolfson et al., 2020; Jardim et al., 2021; Mitchell et al., 2021). Furthermore, we identified two papers that were based on the same small-sample within-subject study applying the model in an observational study on Alcohol Use Disorder (AUD; Sessa et al., 2019, 2021).

MDMA-AP (Mithoefer, 2016) is a structured approach to PAT that was developed by the Multidisciplinary Association for Psychedelic Studies (MAPS). MDMA-AP is an attempt to harness the pharmacological effects of MDMA to enhance psychotherapy effectiveness and aims at reducing or eliminating symptoms and achieving better functioning and wellbeing (Mithoefer, 2016). More specifically, the premise is that the substance-induced reduction in fear, increased interpersonal trust and positive emotions toward oneself and others will facilitate a corrective re-experiencing of the traumatic event in the context of a caring and supportive therapeutic relationship.

This treatment is based on earlier contributions by authors who proposed the use of psychedelics in psychotherapeutic settings (Pahnke et al., 1970; Greer and Tolbert, 1998), decisively relies on both preparation and integration sessions and adopts a seemingly non-directive, non-judgmental and empathetic approach to therapy (Mithoefer, 2016). The fundamental idea entails recruiting the patient's "inner healing intelligence"—i.e., "a person's innate capacity to heal the wounds of trauma" (Mithoefer, 2016)—to facilitate the processing of trauma through direct confrontation, mind-body techniques and a mindful and accepting mindset toward the MDMA-elicited internal experiences (Mithoefer, 2016). Therapists are encouraged to adopt a "beginner's mind"—i.e., an attitude that considers "any experience as an opportunity to heal and develop trust in their own inner healing intelligence"—while being receptive to potential hidden meanings and sources of insights emerging from the experience (Mithoefer, 2016).

To conduct MDMA-AP, therapists must undergo a specific training, should be proficient in administering treatments for PTSD, are encouraged to learn Holotropic Breathwork to gain experience with different states of consciousness, Internal Family Systems Therapy to learn how to work with multiple parts of the self, Sensorimotor Psychotherapy and/or mindfulness-based methods along with other breathing and bodywork techniques to help patients remain focused on the present experience and process trauma through their bodies (Mithoefer, 2016). Preliminary phases include the preparation of an appropriate physical setting and the adoption of mindsets and techniques that are thought to facilitate the therapeutic process on the therapists' part (Mithoefer, 2016).

The room in which the MDMA sessions will be held should be private, quiet, comfortable, well-furnished and allow for the presence of two therapists and music during the course of the experience (Mithoefer, 2016). Therapists are required to support patients through somatic manifestation of traumas, accept potential transpersonal experiences that may emerge during drug sessions and be ready to work with multiple parts of a patient's self. Such multiplicity is defined by the authors as a healthy phenomenon that "may be more pronounced in people who have experienced trauma" (Mithoefer, 2016). MDMA-AP places emphasis on preparation sessions as a means to determine patient eligibility, establish a functional therapeutic alliance, gather information about personal and trauma history, enquire about expectations, address concerns and prepare patients for the subsequent phases of the treatment (Mithoefer, 2016). Clinical studies usually include 2–3 preparation sessions each lasting 60–90 min (Bahji et al., 2020) which focus on personal history, therapeutic alliance and preparation of patients for the psychedelic session (Mithoefer, 2016). The general aim is to establish a sense of safety and comfort, an attitude of curiosity toward inner experience and trust toward one's inner healing intelligence (Mithoefer, 2016).

Unless medical or psychological contraindications are present, patients will take part in one or more drug sessions several weeks apart. MDMA sessions, 1–3 in clinical studies (Bahji et al., 2020), last 6–8 h and are facilitated by two co-therapists, preferably one female and one male (Mithoefer, 2016). Therapists are required to maintain an empathic presence and to seek a balanced attitude between keeping in mind the patients' intentions for the session and being open to the emergence of unexpected perceptions or memories, or ideas (Mithoefer, 2016). Therapeutic interventions are non-directive and encourage patients to adopt a similar attitude toward the experience (Mithoefer, 2016). In fact, they are advised to follow the spontaneous evolution of the experience and to trust their inner healing intelligence (Mithoefer, 2016). Painful memories, perceptions and ideas may emerge and, should therapists observe the adoption of avoidant attitudes on the patients' part, they should encourage them to mindfully confront such material and advise them on techniques they can use to work through the emotional distress (Mithoefer, 2016). Regular check-ins with silent patients are recommended in order to learn about their psychological state and experience (Mithoefer, 2016). During the later part of the session, while the effects of the substance begin to subside, therapists are advised

to ask whether the patient is willing to provide more details about their experience (Mithoefer, 2016). These may be further discussed during follow-up (integration) sessions (Mithoefer, 2016). Patients are accompanied until the end of the session and are helped in resolving any potential emotional or physical distress that may persist (Mithoefer, 2016). Once the session is over, patients may be offered to spend the night in the treatment facility where their mental and physical state will be monitored by the clinical staff (Mithoefer, 2016). They can invite a significant other in. The morning after the MDMA session, the first integration session takes place (Mithoefer, 2016).

Integrative sessions-−2–3 in clinical studies (Bahji et al., 2020) aim at integrating the experience in the patients' ongoing therapeutic process and everyday life and usually last 60–90 min (Mithoefer, 2016). MDMA-AP rests on the assumption that the effects of the treatment will continue to unfold between sessions and after the treatment program is complete (Mithoefer, 2016). Patients are therefore informed that new insights, improvements in resilience, emotional wellbeing and relational skills may keep occurring (Mithoefer, 2016). Furthermore, should they experience psychological problems or suffering as a result of the MDMA-induced experience, integration sessions can be used to tackle such issues and define the therapeutic trajectory (Mithoefer, 2016). In this phase, therapists answer patients' questions, adopt a supportive and validating attitude toward the experience and encourage them to process new insights concerning their trauma, history, relationships and personal life (Mithoefer, 2016). The non-directive character of the therapy is maintained through the integration phase and while interpretations by the therapist are allowed, they "should be minimized" (Mithoefer, 2016). Integrative work begins the morning after the first MDMA session (Mithoefer, 2016). Patients are invited to discuss their experience in greater detail. Therapeutic work may be complemented by focused bodywork (e.g., "giving resistance for the participant to push against;" Mithoefer, 2016), breathing techniques and other approaches to facilitate the processing of the emerged material (e.g., trauma-related memories and physical sensations) through arousal regulation (Mithoefer, 2016). Before the closing of the treatment program, patients' potential concerns and questions must be addressed and the techniques and procedures that they found useful can be reviewed and consolidated.

MDMA-AP has been tested in several studies investigating its potential in the treatment of PTSD in various populations. A recent review and meta-analysis reported high rates of clinical response (72%) and more than 2 times the probability of achieving remission in the experimental groups with large effect sizes in symptom reduction at long term follow-up (between 12 and 74 months; Bahji et al., 2020). A study which tested this model plus elements from third wave CBT and MET as a potential treatment for AUD reported that in a sample of 14 previously detoxified patients, an 8-week course of MDMA-AP led to a significant drop in average units consumed per week from baseline (130.6 units/week) to the 9 months follow up (18.7 units/week) in 11 patients (79%) with 9 patients (64%) who were completely abstinent (Sessa et al., 2021). Finally, MDMA-AP was used to treat anxiety associated with life-threatening illnesses in a sample of 18 patients in a randomized pilot study (Wolfson et al., 2020). While the MDMA-AP group reported greater reductions in anxiety, the difference failed to reach the significance threshold.

In summary, MDMA-AP proposes 2–3 preparation sessions, 1–3 drug sessions held by two facilitators (preferably a male and a female) and 2–3 integration sessions per drug session. The therapeutic model places emphasis on non-directiveness, provides suggestions that highlight the role of the inner healing intelligence (the construct considered responsible for clinical change by the authors), aims at establishing positive expectations about the treatment and enquires about those of patients, allows for therapist direction of the session in case avoidant tendencies are observed and encourages interpretation and search for hidden meanings on the therapist side. Furthermore, bodywork techniques, mindfulness and sensorimotor psychotherapy are considered valuable tools to work through the physical manifestations of trauma. Given that the patients' psyche is conceptualized as made of several parts, elements from Internal Family Systems therapy are used throughout all phases of treatment.

Preparation, Support, Integration

Our search identified 7 papers describing the findings of 1 open-label feasibility study employing the PSI model to treat patients suffering from Treatment Resistant Depression (TRD) (Carhart-Harris et al., 2016, 2018a; Watts et al., 2017; Erritzoe et al., 2018; Roseman et al., 2018; Stroud et al., 2018; Mertens et al., 2020).

PSI (Carhart-Harris et al., 2018a) is a psilocybin-assisted model to treat TRD. The model is briefly outlined in two papers (Carhart-Harris et al., 2016; Stroud et al., 2018) describing the outcomes of an open-label feasibility study. It comprises one 4-h preparation session aimed at building a trusting relationship and encouraging patients to talk about their personal history and their hypotheses concerning the origin of their depression. They receive information concerning psilocybin's psychological effects and take part in a drug-free simulation of the psychedelic session. The two dosing sessions (10 and 25 mg, p.o.) take place 1 week apart and are held in a pre-decorated room in which patients can lie supine wearing eye shades and listen to music. Two psychiatrists supervise the session and adopt a non-directive approach. The aim is to facilitate an "uninterrupted journey" for patients while regularly performing check-ins to keep track of their physiological and psychological state. Once the first session is over, patients are taken back home by a close friend or a relative and are contacted *via* telephone the next day to evaluate their wellbeing and monitor for adverse effects. Two, 3, and 5 weeks after the second dosing session, email assessments of clinical progress are performed. One final follow-up is performed remotely 3 months after the last high-dose psilocybin session. In another description, the model also includes an integration session held the day after dosing in which patients are invited to talk about their experiences and are met with compassionate listening and occasional interpretations to promote and consolidate positive change (Carhart-Harris et al., 2018a; Stroud et al., 2018).

Results reported in the open-label TRD papers show improvements in severity of self-reported depressive and anxiety symptoms 1 week, 3 months ($n = 12$), and 6 months ($n = 19$) after dosing (Carhart-Harris et al., 2016, 2018a). Remission rates were 67% at 1 week and 42% at 3 months while response rates were 58% at 3 months and 31% at 6 months. The 6-month follow-up study also reported decreases in suicidality at 1 and 2 weeks post-treatment (Carhart-Harris et al., 2018a). Further evidence shows that psilocybin and PSI improve processing of emotional faces in TRD patients (Stroud et al., 2018) and that clinical improvements seem to be predicted by the quality of the psychedelic experience (Roseman et al., 2018). Finally, the authors reported significant decreases in neuroticism and increases in extraversion and openness to experience (Erritzoe et al., 2018).

In summary, PSI proposes one 4-h preparation session, 1 drug session held by two psychiatrists and 1 integration session. The theoretical model is broadly described as non-directive and the therapists take an active role during preparation in gathering the hypotheses that participants have concerning the origin of their depression. During the integration phase, therapists are required to offer compassionate listening as well as provide interpretations and facilitate the consolidation of positive change.

Trauma Interventions Using Mindfulness-Based Extinction and Reconsolidation

Our search identified 2 papers investigating the efficacy of TIMBER on a single sample in the context of a RCT (Pradhan et al., 2017, 2018). TIMBER is a psychotherapeutic model conceived to treat PTSD (Pradhan et al., 2017) through the application of the principles of extinction, reconsolidation and arousal regulation. It employs mindfulness techniques and was used to improve the stability of clinical gains that were obtained in a previous study employing ketamine as a therapeutic agent (Feder et al., 2014). TIMBER, in its short version, is administered in the course of a 60-min period and begins with a 10-min reactivation of traumatic memories (Pradhan et al., 2017). More specifically, patients are asked to recall a traumatic event through a pre-prepared personalized script with the objective of activating arousal responses for the following 2–3 min. The 40-min infusion period with 0.5 mg/kg (R, S)-ketamine is then initiated and patients are asked to recall calming memories and to practice the STOPP [Stop, Three mindful breaths, Observe, Practice more, Proceed (Pradhan and Pinninti, 2016)] mindfulness procedure for 5 min to de-escalate emotions such as frustration, anger, anxiety and reduce impulsivity. The goal of this phase is to achieve a state referred to as mindfulness-based detached monitoring.

In a small placebo-controlled, cross-over study (Pradhan et al., 2017), 10 patients with chronic and refractory PTSD were randomized in two groups to receive TIMBER with ketamine (dose, i.v.) or placebo (saline solution). The first session of both programs was the infusion session followed by 11 non-infusion sessions of which two were held in the same week of the infusion while the rest took place on a weekly basis. The psychotherapeutic model for the remaining 9 sessions was the same as that detailed above. Findings showed that before cross-over 9 out of 10 participants reported improvements in PTSD symptoms, depression and anxiety measures independent of group allocation. No significant differences in the magnitude or duration of treatment effects were observed between the two groups. A subsequent extension of the study including 10 additional patients demonstrated a statistically significant 108% increase in response duration (18 days on average) after TIMBER with ketamine compared to TIMBER with placebo (Pradhan et al., 2018).

Adapted Therapeutic Models

Brief Supportive Expressive Group Therapy

Our search identified 3 papers on 1 open-label study employing psychedelic-assisted SEGT to treat demoralization in a sample of demoralized older long-term male AIDS survivors (Anderson et al., 2020; Agin-Liebes et al., 2021; Stauffer et al., 2021). SEGT is a model that was created in the context of palliative care (Classen et al., 1993) and was adapted for use with HIV-infected patients (Maldonado et al., 1996). As described in SEGT manual (Maldonado et al., 1996), the treatment aims at creating an environment of mutual support to contrast the feelings of isolation that are often a consequence of receiving this diagnosis (Maldonado et al., 1996). Patients are encouraged and helped in disclosing their condition to their loved ones and in learning how to ask for the support they need (Maldonado et al., 1996). This is especially relevant when it comes to intimate relationships and importance is placed into promoting conscious and safe sexual practices (Maldonado et al., 1996). Cultivating openness and expression of both positive and negative emotions is a primary goal of the treatment in order to relieve and encourage patients in their personal journeys (Maldonado et al., 1996). Emphasis is given in integrating the changes in self and body image (Maldonado et al., 1996). In fact, patients may find themselves in the position of requiring help in everyday activities for the first time in their lives and such experience may be troubling for some (Maldonado et al., 1996). Furthermore, the onset of opportunistic infections and other related pathologies may lead to changes in appearance that may need therapeutic work to facilitate acceptance and adaptation (Maldonado et al., 1996). After the diagnosis, patients find themselves tackling new challenges in life and, to support them, SEGT strives to expand and improve their coping skills through the experience of their fellow group members and therapist contribution (Maldonado et al., 1996). The development of a life project is encouraged and exploration of life values is intended as a tool to help clarify personal goals (Maldonado et al., 1996). Self-hypnosis is taught as a way to manage pain, improve sleep quality and deal with stress (Maldonado et al., 1996). Given the central role that pharmacological therapy has in the management of the infection and the high risk of poor adherence to treatments, patients are encouraged to be actively involved with the medical staff to promote a good doctor-patient relationship (Maldonado et al., 1996). Finally, receiving the HIV diagnosis may be the first time in which patients are confronted with their own mortality and therapists are instructed to address death related issues, avoidance behaviors and patterns of thoughts to allow group members to explicitly talk about death (Maldonado et al.,

1996). Throughout the duration of the treatment, interaction between group members is actively pursued and the focus of the discussion is kept on personal and concrete issues related to HIV/AIDS in a climate of empathy and unconditional positive regard (Maldonado et al., 1996). SEGT sessions are 90 min long and are conducted by two co-therapists who have experience in working with patients with HIV (Maldonado et al., 1996).

SEGT was used as an adapted model in conjunction with psilocybin sessions in studies aimed at testing its effectiveness in treating demoralization in male older long-term AIDS survivors (Anderson et al., 2020). This integration model included a 90-min psychotherapy session held before group initiation in which patients received psychoeducation on group therapy and psilocybin. Patients underwent 12–15 h of group psychotherapy over the course of 7 weeks and took part in 1 8-h individual psilocybin session (0.30–0.36 mg/kg p.o.). Finally, a second 2-h individual psychotherapy session was held the day after the psilocybin session. The self-hypnosis module of SEGT was replaced by breathing and mindfulness exercises with the intention of providing patients with techniques they could use during dosing sessions. Results showed clinically relevant change in demoralization (Anderson et al., 2020) and significant reductions in self-reported attachment anxiety at the 3-month follow-up (Stauffer et al., 2021). Regarding response rates, 88.8 and 66.7% of participants achieved a 2-point improvement in demoralization at treatment end and follow-up, respectively. Fifty percent and 33.3% of them more than halved their baseline demoralization scores at treatment end and follow-up, respectively. An interpretive phenomenological analysis conducted by the same authors (Agin-Liebes et al., 2021) suggested that patients felt freed from their avoidant tendencies, able to access and process painful and self-transcendent feelings. They also reported an increase in prosocial attitudes and positive emotion along improvements in meaning-making and post-traumatic growth.

In summary, psychedelic-assisted SEGT integrated the psychedelic preparation in the preliminary session normally devoted to psychoeducation on group therapy. The treatment includes 1 psilocybin session and a subsequent integrative session. SEGT emphasizes the importance of tackling specific topics common to HIV-infected patients in group through direct confrontation with themes, emotions and practical issues in an atmosphere of openness and acceptance.

Cognitive Behavioral Therapy

Our search identified 7 papers about the efficacy of psychedelic-assisted CBT. These regarded tobacco dependence (4 papers, open-label study: Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017; Noorani et al., 2018), opioid dependence (1 paper, case study: Ocker et al., 2020) and TRD (2 papers, 1 RCT: Wilkinson et al., 2021); 1 open label study: (Wilkinson et al., 2017). CBT in conjunction with psilocybin has been used to support opioid tapering (Ocker et al., 2020) and, in the form of the Quit For Life programme (QFL) (Marks, 1993), to treat tobacco addiction (Garcia-Romeu et al., 2014; Johnson et al., 2017). Furthermore, it has been employed with ketamine to treat TRD (Wilkinson et al., 2017).

QFL is a self-help CBT-model designed to achieve smoking cessation in 7–10 days and provides patients with tools to prevent relapse (Marks, 1993). The program frames smoking as a "psychological addiction," asserts that quitting can be achieved with a moderate amount of willpower, poses emphasis in increasing patients' self-efficacy and offers 30 different CBT-based approaches to reach such a goal. QFL is administered in the form of a handbook, cards, charts and audio recordings containing a summary of the material, relaxation music and suggestions to promote abstinence. Once a date for actual cessation is set, the first phase of the treatment begins: reduction. At this stage, patients are encouraged to reduce smoking by 50% everyday and are expected to reach abstinence 1 week later. Relapse prevention is the second phase of the program and makes use of several techniques such as mental imagery, suggestion, meditation and relaxation while teaching how to deal with other smokers. The program was initially tested in a two-year follow-up study (Sykes and Marks, 2001; Marks and Sykes, 2002) and authors reported that about 28% of individuals achieved abstinence or significant reductions in the QFL group while only about 6% did in the control group. The difference between groups was statistically significant.

In an open-label pilot study recruiting 15 nicotine-dependent smokers, Johnson et al. (2014) tested the effects of a 15-week treatment program which integrated QFL with psilocybin sessions (2014). To this aim, they structured a model in which participants first established a target quit date (TQD) 5 weeks from the beginning of treatment and then received 4 weekly QFL inspired sessions. Each session also conveyed information about psilocybin, contained a 10-min relaxation exercise along with the smelling of a scented oil and a guided imagery exercise, two elements drawn from another manualized smoking cessation intervention (Zernig et al., 2008). The first psilocybin session took place in week 5, employed an oral 20 mg/70 kg dose and coincided with the TQD. Following the first administration, participants went on with the weekly QFL program and took part in a second 30 mg/70 kg psilocybin session at week 7. Participants who still had not quit by that time, were offered a third psilocybin session at week 13 (30 mg/70 kg, unless the participants themselves wished to lower it) while weekly QFL sessions went on until week 15. During all psilocybin sessions participants were asked to state a previously elaborated motivational statement for smoking cessation. They lay on a couch while listening to music through headphones, received support from the research staff and were involved in a guided imagery exercise during the final phases of the session when the effects of psilocybin were subsiding. Finally, they were asked to write down a description of their experience to be used for discussion in an integration session that was held the following day.

In summary, psychedelic-assisted CBT for smoking cessation proposes 4 QFL/preparation sessions which included relaxation, guided imagery and smelling scented oil, 2 or 3 drug sessions held by at least one staff member and 1 integration session per each drug session. At the 6-month follow up, the authors reported significant reductions in daily smoking compared to baseline and that 80% (12 out of 15) of participants

showed 7-day point prevalence abstinence. At 12 and ≥16-months post-treatment, 67% (10 of 15) and 60% (9 of 15) were confirmed abstinent, respectively (Johnson et al., 2017). Subsequent qualitative analysis of participants' accounts revealed that they experienced insights concerning their reasons for smoking, increased feelings of interconnectedness, awe and curiosity and long-term positive changes in pro-social behavior and aesthetic appreciation (Noorani et al., 2018). Abstainers scored higher on measures of psilocybin-occasioned mystical experiences (Garcia-Romeu et al., 2014).

Ketamine plus CBT for opioid tapering was used in a recent case-study in which a 55-year-old male patient suffering from complex regional pain syndrome treated with opioids for 12 years achieved abstinence after a 5-day ketamine infusion program while continuing a psychotherapy initiated 3 years prior (Ocker et al., 2020). Infusion began at 0.09 mg/kg/h and was titrated twice daily in 0.09 mg/kg/h increments. On the last day the patient had the dose halved in the morning and then discontinued in the afternoon.

Another ketamine plus CBT intervention was used in a study aiming at extending the stability of the antidepressant effect of the substance (Wilkinson et al., 2017, 2021). To this aim, the authors recruited 48 TRD patients and treated them with 6 intravenous infusions of ketamine (0.5 mg/kg over 40 min) during the course of 3 weeks. The 28 (58%) participants who showed an improvement >50% in depression scores were classified as responders and randomly assigned to two groups: 14 weeks of CBT or treatment as usual (TAU; regular visits with physician). The Quick Inventory of Depressive Symptoms scores showed more sustained improvement in the CBT group compared to TAU while the Montgomery Åsberg Depression Rating Scale scores did not reveal effects.

The CBT used in this study was based on Beck's model and comprised psychoeducation, cognitive restructuring and behavioral activation. The model included no preparation sessions and no formal integration sessions. Once the infusion cycle was completed, patients were referred to certified CBT therapists.

Cognitive Behavioral Conjoint Therapy

Our search identified 3 papers on an observational study testing the efficacy of psychedelic-assisted CBCT in the treatment of couples in which one member suffered from PTSD (Wagner et al., 2019, 2021; Monson et al., 2020). CBCT (Monson and Fredman, 2012) is a treatment model for PTSD which, instead of focusing on patients alone, recruits their intimate partners in an attempt to improve treatment outcomes. In this context, PTSD is conceptualized as an interpersonal disorder given (a) the evidence showing that symptom severity correlates with intimate relationship adjustment and aggression (Taft et al., 2011); (b) that the construction of meaning after the traumatic experience is an interpersonal process (Monson et al., 2010); and (c) that the functioning of the relationship itself and of the intimate partner influences PTSD severity (Bradley et al., 2005; Lambert et al., 2012; Shnaider et al., 2014). CBCT promotes the development of new skills in the dyad as a whole and considers the relationship itself the actual client of the treatment (Monson and Fredman, 2012).

The efficacy of CBCT was tested in military samples in both controlled and uncontrolled studies (Liebman et al., 2020). This 15-session program comprises three phases synthesized by the acronym R.E.S.U.M.E. Phase 1 (*R*ationale and *E*ducation) provides psychoeducation concerning PTSD and its relational consequences and aims at building a climate of physical and emotional safety through behavioral strategies intended to increase positive affect and behaviors. Phase 2 (*S*atisfaction Enhancement and *U*ndermining Avoidance) focuses on teaching and training communication skills and treating emotional numbing and behavioral avoidance. The goal is to promote the approaching of feared situations and increasingly engage the dyad in enjoyable activities. Finally, in phase 3 (*M*eaning Making and *E*nd of Therapy) the goal shifts to trauma related appraisals and its consequent current cognitions. The aim is to weaken factors that consolidate PTSD symptoms and relational problems. A recent review shows that CBCT leads to significant improvements in PTSD symptoms, comorbid conditions and relational satisfaction in both clinician and patient ratings (Liebman et al., 2020).

CBCT was recently used in an uncontrolled trial aimed at testing its effectiveness in six couples with the inclusion of two 6-h MDMA sessions (Monson et al., 2020) conducted in accordance with the guidelines specified in an earlier work (Wagner et al., 2019). The first two sessions of the treatment covered the R and E sections and were held on day 1. The next day participants would go through two more sessions covering part of the S and U sections. During the same day they would take part in the first dosing session (75 mg MDMA; 90 min after administration, patients could decide whether they wished to take an optional supplemental half-dose). The rationale was that by that time the couple would have already developed the necessary skills to effectively communicate during the session and share their experience. The first MDMA session was followed by an integration session on day 3 and over the subsequent 3 weeks participants would complete the S and U sections. The second MDMA session (100 mg plus an optional 50 mg) would then be held on day 23, to take advantage of the increased focus on trauma processing that the S and U sections entail. The program then proceeded with an integration session and the completion of modules M and E. All MDMA sessions took place in a room where participants could lie on a reclining chair. They listened to music through headphones, wore eyeshades and were encouraged to "spend time inside." Results showed significant and sustained improvements in clinician-assessed PTSD with almost all participants achieving remission at the 6-month follow up. Five patients out of 6 showed remission at post-treatment follow-up (1 and 6 months). Depression, emotion regulation, trauma-related beliefs along with patient and partner satisfaction also improved. Subsequent analyses revealed improvements in post-traumatic growth measures, relational support, social intimacy as well as greater wellbeing within the couple, improved psychosocial functioning and empathic concern (Wagner et al., 2021).

In summary, psychedelic-assisted CBCT relies on a structured treatment model, does not include formal preparation sessions and places 2 drug sessions once certain communication skills are sufficiently developed. The drug sessions involve both partners and are followed by an integration session each.

Human Relations Training Laboratory Group

Our search identified 1 paper testing the efficacy of combining a large dose of LSD with a Human Relations Training Laboratory (HRTL) group intervention in treating individuals suffering from AUD (Bowen et al., 1970). HRTL (Blake and Mouton, 1964) is a group training intervention built from the assumption that AUD patients struggle in dealing with everyday problems because of a lack of relational skills. The program therefore focuses on lectures on how to "increase effectiveness in groups" (Bowen et al., 1970), structured exercises and a rating system designed to assess progress. Patients were not attending any form of psychotherapy. The study (Bowen et al., 1970) described two experiments. In the first one a group of inpatients was assigned to a single LSD (500 μg, $n = 41$) session plus HRTL while a second one went through the HRTL program alone ($n = 40$). In the second experiment an additional group was included which went through a single LSD session (25 μg, $n = \sim 22$) plus HRTL. In this second experiment the 500 μg group comprised 22 patients and the HRTL only group 15. The LSD session took place during the first 3 weeks of the program in a room furnished informally with "potentially symbolic articles such as a flower, pictures and a two-sided mirror" where music chosen by the participant could be played. The session was preceded by "several group lectures to prepare patients" (Bowen et al., 1970) and during this preparation facilitators aimed at establishing positive expectations toward both the psychedelic experience and the clinical outcomes (Bowen et al., 1970). Patients were also encouraged toward relaxing and "going along" with the experience and were discouraged toward trying to control it (Bowen et al., 1970). LSD sessions were held by nursing assistants who were instructed to give close attention to patients, provide "positive suggestions" regarding their "ability to gain from the experience" (Bowen et al., 1970). Results showed no significant differences between any of the groups (Bowen et al., 1970).

MDMA-Assisted Therapy and Mindfulness for Adult Autistic Individuals

Our search identified 1 RCT investigating the potential of MDMA-ATM in the treatment of social anxiety in adult autistic individuals (Danforth et al., 2018). The treatment program followed a protocol published a couple of years earlier (Danforth et al., 2016).

The rationale for the treatment was built on the basis of (a) research mostly from the '60s and '70s indicating potential for clinical improvement (b) a better understanding of the importance of set and setting in ensuring the safety of patients (c) the copious anecdotal reports of MDMA-induced improvements in empathy, ease of communication, comfort in social settings, feelings of ease in one's own body reported in online fora (for a review see Danforth et al., 2016) and (d) evidence showing that practicing mindfulness skills has beneficial effects in social, emotional and cognitive areas of functioning of autistic individuals (Bögels et al., 2008; Spek et al., 2013). Concerning this latter point, the authors adapted the mindfulness skills training module from Dialectical Behavior Therapy (DBT), an already established model of psychotherapy (Linehan, 2018).

The model is structured in three phases as seen in other approaches. More specifically, before the first MDMA session, participants take part in three 60–90-min preparatory sessions (Danforth et al., 2018) aimed at building rapport, clarifying treatment structure, expected effect of the substance, at discussing relevant issues expressed by participants and practicing mindfulness. Furthermore, the training aims at providing patients with an enriched vocabulary useful to describe the psychedelic experience. Once the preparation phase is complete and before taking the MDMA, patients are involved in a guided progressive muscle relaxation exercise (McCallie et al., 2006) in a room furnished to facilitate feelings of comfort. Patients are then accompanied through the experience by two co-therapists (one male and one female) for the whole duration of the session. During its course, a variety of tasks are proposed including artistic activities, listening to music, writing, introspection and therapist interaction. Therapists should create and maintain a supportive and safe setting and discuss social challenges that patients may have. The MDMA session is followed by 4 non-drug sessions (after 1 day, 2 weeks, 1 month, and 6 months, respectively) during which details concerning the experience are gathered and discussed to facilitate the integration of the experience in everyday life (Danforth et al., 2018). A subsequent MDMA session with corresponding integration sessions then follows. Subsequently, patients are be involved in daily telephone check-ins. In a randomized, double-blind, placebo-controlled pilot study, 12 patients were assigned either to a MDMA-ATM ($n = 8$) or to a placebo plus mindfulness skills training group ($n = 4$). Both conditions comprised 3 preparatory sessions, 2 drug sessions (75 mg MDMA for the first session and 100 mg MDMA for the second or 2 inactive placebo) and 3 integration sessions after each drug session. The MDMA-ATM led to significantly greater improvements in social anxiety scores at the 6-month follow up and response rates (MDMA = 75%; control = 50%) (Danforth et al., 2018).

In summary, this model proposes 3 preparation/mindfulness training sessions, 2 MDMA sessions held by 2 therapists (1 female and 1 male) each preceded by a relaxation exercise and followed by 4 integration sessions. The psychotherapeutic method is adapted from the DBT mindfulness module, an already established model (Linehan, 2018).

Motivational Enhancement Therapy

Our search identified 5 papers on 2 separate studies investigating the efficacy of psychedelic-assisted MET in the treatment of AUD: 1 pilot RCT (Dakwar et al., 2020; Rothberg et al., 2021) and 1 open-label study (Bogenschutz et al., 2015, 2018; Nielson et al., 2018).

MET is a brief treatment model devised to achieve change in problem drinkers and individuals suffering from other addictive disorders (Miller, 1994). MET is based on the principles of motivational interviewing (Miller and Rollnick, 1991) and on

the transtheoretical model of change (Prochaska, 1992) which conceptualizes the process of changing maladaptive behavioral patterns as a cycle comprising 6 stages, i.e., precontemplation, contemplation, determination, action, maintenance, and relapse, each requiring specific therapeutic actions (Prochaska and DiClemente, 1985, 1994). It begins with an initial structured assessment, resolves in 4 sessions held in a 90-day window and considers the mobilization of the clients' own resources as the primary mechanism for effective therapy. This model rests on earlier literature indicating that effective treatments for problem drinkers share some common principles (Orford, 1986): they provide feedback of personal risk or impairment, emphasize personal responsibility, give clear advice, provide alternative options for change, value an empathic attitude on the part of the therapist (as opposed to a more confrontational one) and promote clients' self-efficacy (Prochaska and DiClemente, 1985, 1994).

During precontemplation individuals are not considering change and are usually uninterested in initiating treatment. In contemplation, they begin to consider the problematic aspects of their behaviors and the costs/benefits of change. If correctly facilitated by the therapist, patients will reach the determination stage in which a firm stand to take action is established. Once patients begin to modify the problem behavior, they are considered to have reached the action stage. Should the new behavior pattern persist, after 3–6 months patients are considered to have reached the maintenance stage. Relapse is considered another stage of this cycle and, should patients experience such slips, they will be accompanied through the cycle again. During the first treatment session (Miller, 1994), patients receive feedback from the initial assessment phase which addresses addictive behaviors, symptoms, decisional considerations, and future plans. The second session takes place a week after the first one and is dedicated to build or strengthen patient motivation. The subsequent two sessions, held 4 and 10 weeks after the second one, focus on monitoring and encouraging change and its maintenance. Therapists are required to adopt 5 motivational principles in conducting sessions: express empathy, develop discrepancy, avoid argumentation, roll with resistance, support self-efficacy. More specifically, therapists should aim at building an empathic and collaborative relationship. In this frame, patients are considered the only ones who can decide to change and therapists as supportive consultants who listen rather than tell and build up rather than tear down. Since motivation is conceptualized as the result of increasing discrepancy between the current and desired state, therapists should help to develop such discrepancy in order to increase the chances of opening a discussion on change options. Argumentation is firmly discouraged in order to avoid the strengthening of defensive coping strategies. Additionally, the focus is on the consequences of addictive behaviors (as opposed to diagnostic aspects) and on leading clients themselves to be the ones voicing the arguments for change. Since ambivalence is viewed as a normal part of the treatment of addictive behaviors, therapists are encouraged to "roll with" resistance. Finally, the belief that clients can change their addictive behavior is crucial for therapeutic success, therefore therapists should directly adopt strategies to build and consolidate self-efficacy (Bandura, 1982).

MET was used in conjunction with psilocybin to treat AUD in a proof-of-concept study that recruited 10 patients (Bogenschutz et al., 2015). The intervention model spanned over the course of 12 weeks and employed a total of 7 MET sessions, 3 preparation sessions, 2 psilocybin sessions, and 2 debriefing sessions. More specifically, screened patients were involved in 2 preparation and 2 MET sessions followed by the first psilocybin session (0.3 mg/kg, p.o.). Subsequently, patients took part in a debriefing session, 2 more MET sessions and in another preparation session before proceeding to the second dosing session. In this case the proposed dose was 0.4 mg/kg unless the participant was unwilling to increase it, experienced adverse effects during the first one or already achieved a complete mystical experience. In these cases the employed dose would have been equal to that of the first session. The treatment course ended after another debriefing session and 3 more MET sessions. Psilocybin sessions took place in a living room-like space where patients were asked to lie down on a couch while listening to music through headphones and wearing eyeshades. Results showed that drinking and heavy drinking days decreased across weeks 5–12 compared to both baseline and 4-week since treatment initiation. Improvements were maintained at the 36-week follow-up. No data on response/remission rates was provided. Qualitative analysis of patient accounts of psilocybin sessions (Bogenschutz et al., 2018) revealed themes related to mystical experiences, feelings of forgiveness, self-compassion, acceptance and love as well as experiences of catharsis, increased mindfulness and "spaciousness." According to the authors, the emerged material was personally meaningful to the individuals and tended to frame drinking behaviors in a wider psychodynamic perspective.

In another recent randomized, active-placebo controlled trial that compared the efficacy of a single ketamine hydrochloride (2-min 0.11-mg/kg bolus in saline followed by a 50-min slow-drip intravenous infusion of 0.6 mg/kg) or midazolam (a 2-min saline bolus followed by a 50-min slow-drip intravenous infusion of midazolam, 0.025 mg/kg) administration session combined with psychotherapy to treat AUD (Dakwar et al., 2020), MET was adapted as follows. During the course of 5 weeks, patients were involved in a course of weekly sessions. The initial session aimed at defining goals and elaborating a motivational statement related to quitting drinking. During the following week, they took part in an infusion session and in an additional MET session. The other sessions were scheduled for the following 3 weeks. Results showed better outcomes in the ketamine group in terms of drinking days, heavy drinking days, proportion of abstinent participants, at the 21 days post-infusion time point. Telephone interviews with a subset of the complete sample ($n = 19$) suggested greater rates of abstinence in the ketamine group (75%) compared to the control group (27%) at the 6 months follow-up. Additional analyses showed that the occurrence of mystical-type experiences seemed to play a role in mediating treatment efficacy (Rothberg et al., 2021).

In summary, the first adaptation (psilocybin) saw preparation and integration (debriefing) sessions interspersed in the course of a MET program with 1 preparation session and 1 debriefing

session before and after each drug session. One extra preparation session was carried out at the beginning of treatment. The second adaptation (ketamine) used no formal preparation but included an MET motivational and goal-setting session before the infusion. Subsequently, 4 more MET sessions were administered.

DISCUSSION

The aim of the present work was to review the current therapeutic approaches adopted in clinical research on PAT to highlight common practices as well as diverging aspects and identify issues in need of development. While most of the evidence for the efficacy of PAT can be considered preliminary and the need for more placebo-controlled trials is clear, clinical outcomes in the investigated conditions (most of which are considered chronic and refractory to treatments) seem promising (i.e., reported response rates are between 57 and 88%; reported remission rates are between 18 and 85%), especially considering that improvements are clinically relevant, sustained, observed in a short window of time, with fewer drug administrations and talk-therapy sessions compared to more established therapeutic options. For instance, literature on the efficacy of antidepressants in individuals suffering from end-of-life depression shows no clear differences when compared with placebo (e.g., Ostuzzi et al., 2018). Regarding PTSD, the Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder estimated that up to 50% of diagnosed patients can be classified as non-responders to first-line therapies (Institute of Medicine, 2014). Similar considerations on treatment resistance and risk of relapse can be made for TRD, heroin addiction and tobacco addiction (Krupitsky et al., 2002; Cahill et al., 2014; Carhart-Harris et al., 2018a). As apparent from the outcomes of the selection process (**Figure 1**), several studies were excluded because they did not provide descriptions of structured psychotherapeutic interventions. Most of these excluded studies did not report use of psychotherapy (e.g., several ayahuasca studies such as Palhano-Fontes et al., 2019 or the Grob et al., 2011 psilocybin study), provided only generic labels (e.g., *regular psychodynamic psychotherapy;* Müller et al., 2020) to refer to it (see for instance Berlowitz et al., 2019; Giovannetti et al., 2020) or referenced the Johnson et al. (2008) paper which actually provides guidelines for safety in the context of psychedelic clinical research (see for instance Griffiths et al., 2016; Davis et al., 2021). Regarding the final subset of included studies, despite the fact that proposed theoretical frameworks and treatment structures vary considerably, our review identified factors that are almost constant and still unresolved issues.

Preparation

A preparation phase (varying in duration from 2 to 10 h) is almost always included in both adapted and *ad-hoc* models and its sessions are used for a variety of purposes. In summary, all but 9 reviewed studies ($n = 43$) explicitly mentioned a preparation phase. Almost all approaches use it to establish therapeutic alliance (Kolp et al., 2006; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Danforth et al., 2016; Ross et al., 2016; Anderson et al., 2020; Dakwar et al., 2020; Jerome et al., 2020; Monson et al., 2020). In the case of TIMBER (Pradhan et al., 2017) and of a case report on ketamine plus CBT (Ocker et al., 2020), no details on preparation sessions were reported. In psilocybin plus CBT for smoking cessation (Johnson et al., 2014) and in the CBCT plus MDMA (Monson et al., 2020), no explicit mention of interventions to improve therapeutic alliance was made.

Preparation is almost always described as a setting to discuss issues relevant to the aims of the individual and the supposed therapeutic mechanism of the model. For instance, MAP recommends exploring the themes of diagnosis, prognosis and death while promoting connection with family members as a way to prevent isolation and cultivate meaningfulness (Grof and Halifax, 1978); KPT/KET, when applied to end-of-life anxiety, explores beliefs about death and the afterlife (Kolp et al., 2007); MDMA-AP reviews trauma history (Mithoefer, 2016); PSI and KPT/KET for TRD encourage patients to talk about their hypotheses concerning the origin of their depression, anxiety or addiction (Krupitsky and Grinenko, 1997; Carhart-Harris et al., 2016; Stroud et al., 2018); finally, all adapted approaches include a preliminary phase in which treatment rationale is explained and focus is placed on the aspects that need to be worked upon to achieve remission, wellbeing or improvement in social skills. Furthermore, approaches such as KPT/KET, MET and QFL also explore personal motives that led each patient to pursue treatment and may even require them to produce a motivational statement to be used during the psychedelic session(s) (Kolp et al., 2007; Johnson et al., 2014; Bogenschutz et al., 2015; Dakwar et al., 2020).

This phase has a lot in common with the concept of setting clear intentions that is central to the set and setting theory (Hartogsohn, 2017; Carhart-Harris et al., 2018b) and, while most approaches tend to assume a non-directive stance toward the themes to be discussed and the intentions and expectations to be set, there seems to be an exception in which therapist input plays a more central role. More on the directiveness end of the spectrum, in fact, we find KPT/KET whose preparatory sessions explicitly aim at structuring a therapeutic myth with considerable therapist input (Krupitsky and Grinenko, 1997). More specifically, positive expectations toward outcomes are established and patients are told that they will experience insights, that the causes of their addiction are unconscious in nature and related to their personality and that such causes will manifest themselves during the psychedelic session in symbolic form. Similar interventions, albeit described as less directive, can be found in the MDMA-AP treatment manual (Mithoefer, 2016). The authors, in fact, explicitly ask patients to trust their inner healing intelligence during the therapeutic process therefore assuming its "existence," function and relevance. In both cases, whether such interventions are carried out with the aim of informing about an underlying process or to provide therapeutic suggestions to increase expectancy effects and, ultimately, therapeutic outcome is not explicitly addressed. This issue is especially relevant if we consider that psychedelics seem to increase suggestibility and, therefore, make patients more sensitive to the environment's influence, therapist included. Furthermore, we point out that most papers describing *ad-hoc*

and adapted therapeutic approaches with the exception of KPT/KET and MDMA-AP, only provide brief descriptions of the information and suggestions provided during the preparation phase and therefore do not allow for an assessment of its potential suggestive effects. For instance, therapists should decide what aspect(s) should be discussed and therefore made salient in the preparation phases—be it the present symptoms, cognitions, behaviors, aspects related to conditioning processes, supposed causes, intrapsychic dynamics, existential issues or other clinically relevant themes. These considerations should stimulate clinicians and researchers alike to investigate the effects that such therapeutic strategies may have on outcomes and the most effective ways to frame PAT since the early preparation phases, to maximize effectiveness. In the case of CBCT (Monson et al., 2020) and MDMA-ATM (Danforth et al., 2016), preparation sessions are also used to train participants in acquiring skills that may be useful to go through the psychedelic experience and therapy in general.

Drug Sessions

Drug sessions last between 45 min (i.e., ketamine sessions) and 8 h (i.e., psilocybin sessions), are always supervised by 1 or 2 clinicians, are often held in rooms that are decorated to resemble a living room-like environment rather than a medical office, often make use of music and eyeshades and, in some cases, contain objects of personal significance to the participant. Before the onset of the effects, intentions are often reiterated and participants are often encouraged to shift their attention inward. Based on the descriptions provided in the articles, when it comes to therapeutic stances during dosing sessions we noticed a continuum between two polarities. The first is the non-directive one (Grof and Halifax, 1978; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016), in which therapists only aim at keeping the participants' attention inward and provide verbal and non-verbal support during challenging moments. These interventions include touching, rocking and holding hands as well as suggestions to use previously learned self-regulation techniques such as breathing and imagery exercises. It is the case of MAP, PSI, MDMA-ATM, psychedelic-assisted CBT, MDMA-assisted CBCT, and psilocybin-assisted MET (Grof and Halifax, 1978; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Danforth et al., 2016; Monson et al., 2020). Moving toward more directive approaches, therapists in MDMA-AP are encouraged to identify avoidance strategies, direct patients' attention toward the issues that are considered relevant for the treatment and support them through the process (Mithoefer, 2016). Therapists are also required to remain receptive to hidden meanings that the contents of the session may suggest, thus promoting an actively interpretive stance. As was already apparent in the preparation phase, KPT/KET seems to adopt an even more directive stance. According to the original description of the method, during ketamine infusions, patients should be exposed to psychotherapeutic influences aiming at promoting sobriety and adaptive personality change (Krupitsky and Grinenko, 1997). Furthermore, the fact that this model incorporates spiritual, religious and/or transcendental elements to the therapy session may expose patients to the risk of incorporating the therapists' belief systems (Johnson, 2021). This issue is even more sensitive if we consider the increase in suggestibility that psychedelics seem to produce (Carhart-Harris et al., 2015). The same could be said for non-empirically verified notions concerning the action of psychedelics and the nature of constructs such as the mind, personality, the self and the specific conditions that patients may be suffering from Johnson (2021). Among those examined in this review, TIMBER is the most directive and structured one.

Integration

Integration is a part of all approaches except for TIMBER (Pradhan et al., 2017) and is usually described as a phase in which the insights gained during the psychedelic experience are processed and generalized to everyday life. MAP, MDMA-AP, KPT/KET, and the psilocybin-assisted CBT model for smoking cessation consider the final phase of the drug session—in which the substance's effects are subsiding—as the beginning of the integration phase (Grof and Halifax, 1978; Krupitsky and Grinenko, 1997; Johnson et al., 2014; Mithoefer, 2016). Patients are encouraged to discuss their experience or to write down a report in an attempt to consolidate memories and promote integration to everyday life.

Most studies provide little information about the therapeutic stance held during the integration phase and here too we find coherence with some of the aspects we discussed above. For instance, MDMA-AP suggests the treatment as an ongoing process that unravels beyond the drug sessions themselves, into the integration sessions and in the patients' everyday life (Mithoefer, 2016). As is the case with PSI, SEGT and KPT/KEP, MDMA-AP also allows for occasional therapist interpretations of the psychedelic experience that are aimed at consolidating change and generating meaning (Krupitsky and Grinenko, 1997; Carhart-Harris et al., 2016; Mithoefer, 2016; Anderson et al., 2020). The inclusion of existentially oriented psychotherapies also seems to recur in this phase, supposedly because of its focus on meaningfulness (Grof and Halifax, 1978; Krupitsky and Grinenko, 1997).

Directiveness, Information, Expectation and Suggestion

Early PAT models emphasized the importance of non-directiveness and of letting the therapeutic frame and the contents of sessions define themselves during the course of preparation, drug sessions, and integration (Grof and Halifax, 1978). This general direction was adopted by several more modern approaches and is apparent from both direct descriptions of the methods and the suggestion to integrate elements from therapeutic models derived from very different theoretical premises (e.g., supportive psychotherapy, cognitive-behavioral therapy, existentially oriented psychotherapies, psychodynamic psychotherapy, mindfulness-based treatments).

While this framing allows for considerable flexibility on the therapists' part, it also reveals that a clear picture of what may make PAT work is still missing. Since the first moments of preparation, patients are presented with information and suggestions concerning therapy that will establish specific

expectations. This aspect should be thoroughly investigated, especially if we consider that expectations seem to play a relevant role in defining the effectiveness of clinical interventions (Muthukumaraswamy et al., 2021). In a more practical sense, therapists should know if, how and where they should orient the contents of the sessions and how to treat such materials once they surface. The studies mentioned in this review suggest that the focus could be placed on the supposed causes of suffering, present life, intrapsychic dynamics, existential issues, family issues and/or traumatic events.

Moving to the more interventionist contributions, some of them provide a structured model of the condition (e.g., lack self-regulation skills, maladaptive personality profiles), actively intervene to build a tailored therapeutic myth or suggest the presence of inner processes promoting healing that can act once patients surrender to the psychedelic experience. Considering the potential increase in suggestibility caused by psychedelic substances (Carhart-Harris et al., 2015), a better understanding of what works for whom is highly desirable and future research should focus on determining the general interventions that make PAT work and the specific adaptations that may be required for different patient populations. More concisely, therapists should know what aspects to make salient during the continuous process that is the establishment of appropriate therapeutic sets and settings.

Another way to look at the issue may be framing it in terms of potentially enhanced learning (Banks et al., 2021) and cognitive flexibility (Kuypers et al., 2016) that could facilitate acquisition and extinction. In this framework, psychedelics may be used to optimize already established CBT strategies in order to improve response rates and stability of results. Among the common themes emerged from our review we should also mention meaning-making as an aim of PAT. Aspects related to meaning making seem to be associated with psychological wellbeing (Preller et al., 2017) and psychedelic sessions have been found to increase perceived meaningfulness (Kaelen et al., 2018). Future research should focus on investigating how to integrate the search for meaning in PAT, in terms of the economy of both the single sessions and the therapeutic journey as a whole. Furthermore, while most approaches seem to value rapport, research on the potential moderating effects that varying degrees of therapeutic alliance may have on clinical outcomes of PAT is still in need of development (Carhart-Harris et al., 2018b). Finally, except for one study regarding KET/KPT (Krupitsky et al., 2007), we found no studies directly addressing the effects of treatment duration, number of drug and drug-free sessions on both clinical improvement and its stability in time. This is another relevant area to focus upon in future research.

CONCLUSION

The present paper critically reviews the models of PAT framing to provide a comprehensive picture of current practices in clinical psychedelic research. While some structural aspects of PAT seem to recur in clinical studies, the therapeutic stance and theoretical frameworks seem far from being exhaustively defined. Considering that psychedelics seem to enhance sensitivity to the internal and external environment (i.e., suggestibility), future research should provide more details on how such environments are constructed in terms of suggestions, description of the mechanisms underlying conditions and treatments, setting of expectations, therapeutic models employed and quality of the therapeutic relationship. This review fills a gap in the current literature and provides a systematic way to think about psychotherapeutic framing of PAT. The concepts discussed above are relevant to future construction of studies, designing of training programs for aspiring psychedelic psychotherapists and are presented with the intention to contribute to the development and implementation of PAT in several fields of psychiatric, psychological and medical relevance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MC and CM carried out the paper selection process. MC drafted the paper. All authors took part in the revision process and contributed to the article, design, interpretation of data, and approved the submitted version.

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frontiers | Frontiers in Psychology

TYPE Conceptual Analysis
PUBLISHED 04 August 2022
DOI 10.3389/fpsyg.2022.824077

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OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

RECEIVED 28 November 2021
ACCEPTED 04 July 2022
PUBLISHED 04 August 2022

CITATION
Bathje GJ, Majeski E and Kudowor M (2022) Psychedelic integration: An analysis of the concept and its practice.
Front. Psychol. 13:824077.
doi: 10.3389/fpsyg.2022.824077

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Psychedelic integration: An analysis of the concept and its practice

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The concept of integration has garnered increased attention in the past few years, despite a long history of only brief mention. Integration services are offered by therapists, coaches, and other practitioners, or may be self-guided. There are many definitions of psychedelic integration, and the term encompasses a range of practices and techniques. This seems to have led to confusion about what integration is and how it is best practiced. The primary focus of this manuscript is the presentation of the first extensive review and concept analysis of definitions, practices, and models of psychedelic integration. We provide a synthesized definition of integration, synthesized model of integration, and comprehensive summary of integration practices to bring clarity to the subject.

KEYWORDS

psychedelic, integration, integrate, psychedelic assisted therapy, entheogen

Introduction

Psychedelic substances are garnering increased interest in Western societies after decades of suppression under the War on Drugs. Research and wide cultural use of psychedelics peaked in the 1960's. This era produced more than 1,000 clinical papers covering 40,000 patients and six international conferences on psychedelic drug therapy (Grinspoon and Bakalar, 1979). The impact on art and culture is more difficult to quantify, though in the late 1970s about 10% of high school seniors reported they had used LSD (Nuwer, 2020). Research and broad cultural interest appear to be peaking again in the 2010s and 2020s. A number of psychedelic substances, including psilocybin, ketamine, MDMA, ayahuasca, and DMT, have completed or are undergoing clinical trials for the treatment of mental disorders, with meta-analysis revealing "large" to "very large" effect sizes (Luoma et al., 2020). A substantial curtailing of drug war policies is underway as a number of cities have passed "Decriminalize Nature" ordinances to make the enforcement of plant-based psychedelics the lowest law enforcement priority, and as Oregon, California, and several other states pursue state-wide decriminalization and legalization approaches (Aday et al., 2020). With increasing interest in psychedelics, particularly for psychotherapeutic purposes, and the corresponding expansion of clinics offering ketamine administration or take-home prescription that often include little or no preparation, psychological support, or integration (Ryan and Bennett, 2020), the topic of psychedelic integration is becoming ever more important.

The term "integration" has been utilized to describe the period following a psychedelic experience. A wide range of definitions has been put forward, characterized by an even wider variety of integrative practices, historically without models or guidance as to when and why particular practices might be chosen. Integration is often briefly mentioned in books and articles compared to preparing for, navigating, or facilitating psychedelic experiences, despite being widely cited as very important to retaining benefits and working through psychedelic experiences. In a recent survey of clinicians who received training in psychedelic-assisted therapies, the majority stated a desire for a better understanding of the concept of integration (Ali et al., 2021).

Modern research on the psychotherapeutic use of psychedelics attests to the value of an integration focus. Each of the longstanding organizations funding or organizing psychedelic research have developed treatment protocols that provide time for preparation, psychological support/psychotherapy, and integration, including The Multidisciplinary Association for Psychedelic Studies, the Beckley Foundation, and Heffter Research Institute (Coder, 2017). This focus on the therapeutic process, including integration, was influenced by the work of earlier practitioners and researchers who began developing psychotherapeutic approaches to psychedelics in the 1960s, such as Grof (1980), Metzner (2015), and Richards (2015). While therapists appear particularly interested in integration, we will address the limitations of traditional psychotherapy models as an exclusive basis for integration.

Indigenous cultures

Indigenous use of psychedelics is not a phenomenon of the past, with a number of cultures having longstanding use up to the present day. For example, evidence of the earliest use of peyote by Native Americans, which the Native American Church still utilizes, dates back 5,700–10,000 years (Bruhn et al., 2002). Psychedelic substances have been used by Indigenous cultures for a variety of purposes, including sorcery, spiritual purposes, resolving physical ailments, building alliances, or engaging with culture (Labate and Cavnar, 2014). Broadly, Indigenous healing practices are said to typically rely on three core assumptions (holism, interconnectedness, and harmony/balance) and three primary approaches (heavy reliance on communal, group, and family networks, use of spiritual belief and tradition, and the inclusion of shamans; Sue et al., 2019). Furthermore, mind, body, community, spirit, and nature tend to be seen as a unified entity, with daily life, spirituality, and medicine also not seen as separate. Imbalance or separation between these elements is often seen as a source of illness (Sue et al., 2019).

With regard to integration, it is sometimes said that Indigenous peoples do not have the same need for formal integration because psychedelics are utilized within the community and with a more holistic worldview or because psychedelics are already more integrated into Indigenous cultures that utilize them (Aixala, 2017). In contrast to Indigenous cultures that have a tradition with psychedelics, Western participants may not possess adequate cultural references to comprehend complex, abstract, and symbolic content that often emerges with psychedelics, necessitating therapeutic support throughout the process, including during the integration stage (Loizaga-Velder and Pazzi, 2014). Still, we must acknowledge that treating integration as a separate phase of psychedelic experiences probably imposes Western dualistic thinking. In order to address imbalance and support the realignment of self, shamanic cultures may employ symbolism and rituals already entrenched in the culture, such as hypnosis or trance-like states, drumming, chanting, spirit manifestations, among others, all within a communal context, which stimulate engagement with the innate drive toward physiological, spiritual and social experiences (Winkelman, 2021). These practices may take place before, during, or after experience with the actual psychedelic substance. Contrary to occasional suggestions that integration is only relevant to Westerners, this would seem to suggest that Indigenous cultures tend to be rooted in philosophies and worldviews that encourage an ongoing orientation toward balance and integration. Balance, here, refers to the interconnectedness and harmonious interaction between the physical, emotional, relational, spiritual, and mental aspects of the human experience (Settee and Shukla, 2020). This perspective could be of great value to the more dualistic and linear thinking in Western cultures (Limb and Hodge, 2008).

Nevertheless, Western interest in Indigenous ceremonies, such as ayahuasca shamanism in Peru, has raised concerns about the impact of psychedelic tourism. The unequal, disruptive, and extractive nature of capitalist consumerism has led to reports of negative economic, social, cultural, health, and environmental impact on Indigenous communities from the presence of culturally and linguistically uninformed tourists and their disproportionate wealth (Gurvicius, 2015). As a result, there has been a recent focus on justice and reciprocity regarding Indigenous knowledge, as opposed to extractive approaches that either neglect or harm Indigenous peoples (Martinez, 2021).

Western cultures

Recent research on the psychotherapeutic use of psychedelics has garnered much positive press in several Western cultures. It seems likely that this has shaped expectations that psychedelics are primarily useful for psychotherapeutic purposes. It is also possible that the existing understanding of pharmaceutical drugs has impacted

expectations of how psychedelics work (e.g., as working via direct biomedical effects on passive patients). This idea may run contrary to more complex models of substance, set, and setting, where preparatory processes or intentions are thought to significantly influence psychedelic effects (Hartogsohn, 2017), and may not promote adequate expectations for the value of a facilitator or guide, or active engagement in an integration process afterward. Beyond this therapeutic interest, there remains a broader cultural interest in psychedelics beyond psychotherapeutic application. Reference to psychedelics can be found in art, music, film, and popular writing, and the use of psychedelics spans topics such as creativity, personal optimization, spirituality, recreation, wellness, healing, and social change (Aday et al., 2020). Spiritual hunger (Mahr and Sweigart, 2020), and we would add existential distress associated with climate change and socioeconomic inequality, may also contribute to this broad resumption of interest in psychedelics.

With regard to integration, Western culture is still very much influenced by Cartesian dualism, which creates binaries that polarize and compartmentalize our thinking, for example, mind and body, self and other, or person and nature (Barker and Iantaffi, 2019). We have to wonder if the creation of Western psychology as a science distinct from medicine, social context, and spirituality would be necessary or possible without first cleaving mind from body and person from environment. Abraham Maslow (1968) wrote about the innate drive to self-actualize and return to an essential human core that he saw as obstructed by his (Western) culture. He stated that what socially defines a person as normal is, in reality, "psychopathology of the average," a widespread sickness of inauthenticity, illusion, and fear. Relatedly, Marx (1844), in his Theory of Alienation, described the social alienation of people as a consequence of capitalism, under which workers are directed toward goals and actions that are not their own, and therefore lose their autonomy to create their lives. The result is alienation from their work, from other people, and from their human nature (and one might add from the natural world, as capitalism resulted in a mass migration to cities and away from the sources of the raw materials of production). From these perspectives, Westerners may particularly need support for integration due to first needing to disintegrate limiting mental structures, then orient and adjust toward new, more authentic, and integrated ways of being that may be unknown to them, within the context of a culture that may define them as abnormal for doing so.

Indigenous worldviews and culture, which do not have a history with Cartesian dualism, may provide invaluable wisdom for Westerners to look to in their understanding of psychedelics, holistic living, and healing practices. There is historical context for doing so. Recent anthropological analysis has provided compelling evidence that we have long underestimated the impact of Indigenous worldview, philosophy, and culture on Western thought. Graeber and Wengrow (2021) compiled extensive evidence that Indigenous American critiques of European culture (particularly related to lack of freedom, collectivism, and egalitarianism) were read widely in Europe in the 1600's and had substantial influence on the European Enlightenment. Today, interest in Indigenous knowledge and practices is again swelling, likely at least partly driven by the so-called Psychedelic Renaissance.

In this manuscript we seek to review definitions of integration, integration practices, and models of integration. In doing so, we were mindful of the origin of each of these and the degree to which they reflect Western or Indigenous understandings. In the spirit of integration, we seek to synthesize various perspectives and practices.

Methods

Initial references for this article were identified utilizing PubMed and PsychInfo searches for "psychedelic therapy" and "psychedelic integration" through August 10, 2021. Because our manuscript is not strictly a review of peer-reviewed research but rather of understandings of the concept and related practices, we also searched for these topics on several websites that focus on publishing articles and blog-style posts related to psychedelics, which included Chacruna.net, psychedelicstoday.com, psychedelic.support, and psymposia.com. Our goal was to be extensive in our search for relevant writings, so we also reviewed the reference lists of our initial sources to identify additional references. Our primary sources for integration models include peer reviewed articles and books (including handbooks), for which the quality of peer review was not always evident. We excluded references that did not contain a definition of integration or specific integration practices. We considered an integration model to be present if the authors described an organizational structure for integration activities, a theoretical approach to the process of integration, or a model for navigating the integration process. For references that did not include models, we retained them in a table of integration activities to identify the relative frequency of different types of integration activities mentioned in the literature. This table included thirty-four references. However, we only included a citation of these references if they recommended at least one unique integration activity not already captured in the more comprehensive references. We did not have space, nor was it our intent, to repeat the detailed descriptions of specific integration activities covered at length in some of our references (especially Coder, 2017; Bourzat and Hunter, 2019; Buller and Moore, 2019; Westrum and Dufrechou, 2019; Ortigo, 2021).

Because of the recency of much of the in-depth writing on the concept of integration, we utilized Rodgers (1989) evolutionary concept analysis, which is described as imposing less constraint on the concept being examined than alternative approaches to concept analysis (Pignatiello et al., 2020). This

approach involves reviewing the literature for definitions of the concept, characteristics or attributes of the concept, and examples of the concept. This approach corresponded well with our desire to explore and better understand definitions, practices, and models of integration.

Review of integration definitions, models, and practices

In reviewing the literature, it is possible to identify various degrees of attention to the concept of psychedelic integration. At the broadest level, authors reference the importance of integration without providing many detailed examples or guidance, sometimes not even providing a working definition. At the next level of detail, authors provide detailed examples or recommendations for specific practices that they associate with integration, still often without much guidance or explanation of the purpose of integration. A small number of authors have gone further and elaborated models of integration to provide a detailed framework for an extended integration process. We begin by examining and synthesizing definitions of the concept of integration, followed by a comparison of models of integration, and then review additional integration practices and recommendations within the context of these models.

Definitions of integration

Many definitions of integration have been put forth. We reviewed published definitions in research articles, books, and various online forums to identify a range of descriptions of the concept and to identify common elements. We also sought to capture the less universal components of the definition that appear to influence integration models and practices.

We identified and reviewed 24 distinct definitions of psychedelic integration (i.e., references that provided their own definition rather than citing another definition). In the great majority of definitions, we encountered the idea of the participant implementing and incorporating the key insights and awareness gained in the psychedelic experience into their life. "Psychedelic integration is a process in which the patient integrates the insights of their experience into their life" (Gorman et al., 2021, p. 8). Most of the definitions also emphasized the need to revisit, work through, and make sense of the material and content of psychedelic experiences. "The term. . .[refers] to different aspects of a process that includes making sense out of the experience, filtering the content, assimilating and accommodating the experience psychologically, and implementing insights into lasting changes" (Loizaga-Velder and Pazzi, 2014, p. 148). Most authors did not describe the content in their definitions, beyond referring to it as "experience," though the ones who did elaborate used a range of descriptors, such as "unconscious" or "psychospiritual" content. There was an acknowledgment that content that emerged from psychedelic experiences could be directly beneficial, not obviously relevant, or initially challenging, though none of the definitions pathologized the emergence of difficult or confusing content. "[Santo Daime members] are quite proficient in reinterpreting entheogenic experiences so that difficult, excruciating experiences are reframed as healing, revealing and ultimately positive in the grander scheme of things" (Hartogsohn, 2021, p. 13). Some acknowledged that inadequate social/psychological support may lead to an inability to gain insight or work through less obvious or more challenging content. Nearly all the definitions we reviewed described or implied that integration is a process, one that may take significant time and effort, and without which, insights gained are likely to fade without actualizing meaningful change (Richards, 2017). Some of the definitions focused on the near-term dimension and necessity of post-session support, sometimes referred to as aftercare, while others focused on the longer-term process of internalizing change, prolonging and maximizing benefits, and moving toward greater balance and wholeness internally and with the world (Coder, 2017). Finally, many of the definitions implied or stated that one needed to implement, make use of, bring forward, or otherwise engage in practices to integrate their psychedelic experiences into their lives. "Integration is the process of bringing separate elements together into a whole. . .and anchoring them into our lives" (Bourzat and Hunter, 2019, p. 179).

After reviewing and identifying common elements of many definitions, we propose the following synthesized definition of integration as it relates to psychedelic experiences:

> *Integration is a process in which a person revisits and actively engages in making sense of, working through, translating, and processing the content of their psychedelic experience. Through intentional effort and supportive practices, this process allows one to gradually capture and incorporate the emergent lessons and insights into their lives, thus moving toward greater balance and wholeness, both internally (mind, body, and spirit) and externally (lifestyle, social relations, and the natural world).*

Models of integration

We were able to identify ten well-elaborated approaches to integration. Notably, all of these have been published since 2017, which reflects the recent shift in attention to the concept of integration. We considered an integration model to be present when the authors provided a theoretical basis or organizational framework for the various integration practices they described. The identified integration models were primarily

based on Indigenous worldviews and practices, Transpersonal Psychology, Jungian Psychology, Acceptance and Commitment Therapy, Psychodynamic Psychology, Somatic Psychology, Nature Relatedness, Biopsychosocialspiritual Models, and Harm Reduction. It should be noted that some of these underlying theories were developed with consideration to altered states of consciousness and psychedelic experiences, while others were originally developed for general psychotherapy. Additionally, some of the models are more focused on the mind, while others are more holistic. Next, we review each model of integration and then contrast and synthesize them.

The first model, called Visionary Plant Medicine Integration, is directed specifically toward individuals who have partaken in ceremonial approaches to plant-based psychedelics (Coder, 2017). The author draws from Transpersonal Psychology and cites a number of Indigenous shamanic experiences (including those utilizing mushrooms, ayahuasca, San Pedro, and iboga) to create a holistic approach to integration organized around seven domains of integration practices. These include Reflection, Inner Listening and Creative Expression, Psychospiritual Practice, Meaning Making, Spaciousness and Time, Nature and Grounding, Physical Care, and Cultivating Virtues and Turning Outward (after introspection and self-care). Specific integration practices are presented within each domain, with some guidelines and rationale provided for choosing specific practices.

An integration model called the Holistic Model for a Balanced Life includes domains of Body, Mind, Spirit, Community (including personal relationships), and Natural Environment (Bourzat and Hunter, 2019). The creators of this model organize integration around a three-part framework of returning from the psychedelic experience (with a focus on capturing a narrative of the experience), understanding the experience (identifying themes present within the experience and decoding the content), and implementing concrete integration practices. The model draws from interpretations of Indigenous understandings and practices. Congruent with the Holistic Model for a Balanced Life, the focus is on integrating body-centered, mind-centered, spirit-centered, community-centered, and environment-centered experiences, followed by sharing one's transformations with the world, for the purpose of moving oneself and one's life in the direction of holism. Specific examples and integration practices are provided, along with common themes that emerge during and after psychedelic experiences.

Buller and Moore (2019) provide an organizing structure similar to a biopsychosocialspiritual model to organize a large number of potential integration practices, while not explicitly stating an underlying theory. Their Realms of Integration model consists of domains of relationships, mental and intellect, mind-body, environmental, spiritual, and lifestyle (including career). Although the organizational structure is presented, it is not specifically implemented. A comprehensive list of integration practices is presented, though not all are elaborated upon or clearly connected to the integration model.

Westrum and Dufrechou (2019) offer a model that makes reference to many theories of psychotherapy, but which primarily draws from Transpersonal Psychology while incorporating spirituality and ritual. While no overarching organizational model is provided, there is a focus on psychological, spiritual, existential, ritual, social/communal, and somatic aspects of integration. Psychoeducational content, theory, and corresponding structured integration activities are included. There is a framework for one's approach to integration, which goes by the acronym SAFETY. The letters stand for security (to allow one to move outside comfort zones), accessible (to focus on available and incremental change process), fluidity (being in flow, particularly around obstacles), empowering (moving toward your authentic self), transformational (capturing big transformational experiences), and yours (the personal nature of the experiences and change).

Gandy et al. (2020) utilized nature relatedness and contact with nature as a foundation to explore the congruence and overlap with psychedelics with psychological concepts such as neurobiology, connectedness, mystical/transcendent experiences, and mindfulness. The authors propose to utilize nature and nature-based rituals in psychedelic integration, while also ways to incorporate natural elements into mindfulness training and talk therapy. They do not provide a formal model of integration, but do provide proposals for incorporating nature to broaden treatment options and enhance inner and outer connectedness.

Gorman et al. (2021) developed the Psychedelic Harm Reduction and Integration Model, which the authors describe as being transtheoretical, drawing from mindfulness-based, psychodynamic, psychedelic-assisted, and harm reduction approaches to psychotherapy. Reference is also made to incorporating additional approaches when appropriate, such as person-centered, somatic, motivational interviewing, ACT, or internal family systems. This approach is described not as a treatment modality or a technique, but rather as a model for facilitating psychedelic harm reduction and integration via psychotherapy. Accordingly, rather than focusing primarily on integration practices or activities, the article focuses on clinical issues and challenges that may arise following psychedelic experiences. They provide recommendations for working with clients who have had challenging psychedelic experiences, common fears that arise (e.g., fear of ego dissolution), increased sensitivity, or somatic experiences, while also focusing on maintaining benefits and supporting clients' unfolding process.

Ortigo (2021) incorporates existential, spiritual, and unconscious aspects of psychedelic experiences, with descriptions of integration practices that address each of these areas. The author incorporates Jungian views of the psyche and personality, along with elements of transpersonal psychology. The author develops a phenomenological model

called Modes of Experiencing, focused on experiencing the world through thought, emotion, body, and behavior. These are then situated within a broader Psychedelic Inclusive Model of the Psyche, which expands beyond the conscious aspects of experience to address the integration of psychedelic experiences across conscious and unconscious aspects of the psyche, and in relation to hypothesized collective dimensions of the psyche.

Cohen (2017) focuses on the integration of Ayahuasca ceremonies and investigates participants' experiences through the Jungian lens in developing a psycho-spiritual framework for integration. This research employs Jungian psychology, particularly Individuation as it pertains to the psyche, to describe the integration process. It proposes that for the ego to embrace transformation, there needs to be harmony between the conscious and unconscious, either through an establishment or reunification of that relationship, a bid for wholeness. This approach categorizes five emerging themes: pre-ceremony life experiences, the ceremony, post-ceremony integration, process and practices during and after integration, and ayahuasca itself, across dimensions of emotional, psychological, somatic, and spiritual processing, and connects it with the role of the conscious and unconscious. Although focused on ayahuasca, this approach appears applicable to other psychedelics as well.

Sloshower et al. (2020) elaborate a manualized protocol for the application of ACT to psilocybin-assisted therapy for depression, including a focus on preparation, support/guiding, and integration. The ACT Hexaflex model is utilized, which corresponds to the six core principles of ACT: present moment contact, acceptance, diffusion, self as context, values, and committed action (Hayes et al., 2011). The authors report that ACT was chosen due to perceived congruence with psychedelic and mystical experiences, though it was also chosen in part due to its efficacy in treating depression, not being primarily focused on symptom reduction, and ability to make use of psychological flexibility. In this model, the initial stage of integration does not incorporate ACT techniques but instead focuses on eliciting the client's narrative of the experience. The focus then shifts to identifying parallels in the client's experience to ACT principles, reinforcing examples of psychological flexibility, reflecting on changes that have occurred, discussing values and how the person is living or not living them, discussing cognitive and behavioral patterns theorized to impact depression, behavioral activation to put values into practice, and implementing ongoing mindfulness practice. Integration practices described in the article are largely therapist initiated and correspond to the ACT model.

Watts and Luoma (2020) propose the ACE (Accept, Connect, and Embody) model, informed by the six processes of the psychological flexibility model, which are part of Acceptance and Commitment Therapy. The model provides a framework for clinicians to support patients in their experience of challenges (Accept), move toward positive aspects (Connect), and promotion of embodied action (Embody) necessary to internalize change. Integration in the ACE model involves three stages. In the first stage, the therapist is non-directive, validating the patient and guiding them through unresolved experiences. The second stage is more structured and helps the patient with meaning-making, creating awareness, and translating insights. The third stage is more directive, with the therapist helping the patient come up with goals and identifying behavioral change. While similar to the Sloshower et al. (2020) model, this approach does not incorporate all aspects of ACT.

Contrasting models

In comparing and contrasting the above models, it was challenging to compare them all concurrently because they have different organizational structures (i.e., organized according to integration practices, aspects of the person, model of psychotherapy, or a combination of these), different worldviews (Indigenous and/or Western psychological), different scope (e.g., elaborate focus on the mind versus other dimensions of human experience), and different target audiences (i.e., therapists specifically, facilitators broadly, journeyers, or all of the above). However, it became more feasible to make connections and contrasts across models by first comparing the ones primarily based on theories of psychotherapy and targeted toward therapists (i.e., the last four models above) from the ones that are more holistic or biopsychosocialspiritual and directed toward an audience beyond therapists (i.e., the first six models above). All models are represented in **Table 1** for direct comparison, though as noted detail is lost, particularly with the psychological models.

Reflecting first on the holistic models of integration practices, several attempt to incorporate Indigenous knowledge and practices. One limitation here, as with our own overview of Indigenous practices, is that to our knowledge (based on author bios), none of the authors identify as Indigenous themselves. These models could also be broadly described as biopsychosocialspiritual models (Saad et al., 2017). As such, they expand beyond internal experience and the psychological/emotional process. Most of these models share a focus on several of the following aspects of experience: relational and community, lifestyle and action, the natural world, spiritual and existential, mind and contemplation, and bodily and somatic experience. These models view people as multifaceted and tend to identify the causes of suffering as rooted in imbalance or lack of integration of these interconnected aspects of existence (Saad et al., 2017). Particularly for the approaches that invoke Indigenous worldviews, the need for integration could be seen not as resulting from psychedelic experiences but as a condition of Western culture, with its tendency to place disproportionate value on mind, materialism, and behavior (i.e., Coder, 2017; Bourzat and Hunter, 2019). As such, integration is about more than processing the psychedelic experience or overcoming specific difficulties, even if these might catalyze the process, but are about bringing balance and alignment to

TABLE 1 Comparison of integration models with resulting synthesized model of integration.

Model (Author)	Domains					
Synthesized Model of Integration	**Mind/emotional/ contemplative**	**Bodily/somatic**	**Spiritual/existential/ ritual**	**Lifestyle/ action**	**Relational/ communal**	**Natural world**
Visionary Plant Medicine Integration (Coder, 2017)	Inner listening, reflection, creative	Physical care, time/space	Spiritual practice, meaning making	Cultivating virtues	Turning outward	Nature and grounding
Holistic Model for a Balanced Life (Bourzat and Hunter, 2019)	Mind	Body	Spiritual	Sharing	Community	Nature
Realms of Integration (Buller and Moore, 2019)	Mental/Intellect	Mind-body, surroundings	Spiritual	Lifestyle/career	Relationships	
SAFETY (Westrum and Dufrechou, 2019)	Psychological (Transpersonal)	Somatic	Spiritual/existential/ritual		Social/Communal	
Nature Contact (Gandy et al., 2020)	Psychological (Nature-based)	Affective	Mystical/Awe			Nature relatedness
Psychedelic Harm Reduction and Integration (Gorman et al., 2021)	Psychological (Transtheoretical)	Somatic	Spiritual/mystical	Harm reduction		
Psychedelic Inclusive Model of the Psyche (Ortigo, 2021)	Psychological (Jungian, Transpersonal)	Body	Spiritual/mystical	Behavior		
Psycho-Spiritual Integration Process (Cohen, 2017)	Psychological (Jungian)	Somatic	Psychospiritual			
Acceptance and Commitment Therapy (Sloshower et al., 2020)	Psychological (ACT)			Behavior change		
Psychological Flexibility Model (Watts and Luoma, 2020)	Psychological (ACT)			Behavior change		

one's whole existence. It is assumed within each of these models that integration is often a lengthy process or even the core project of our lives.

By contrast, the psychotherapy models tend to delve in-depth into one or two dimensions of the holistic models (particularly the "mind" dimension). However, we do note that one model (Gorman et al., 2021) falls somewhere between by applying a transtheoretical approach that incorporates a range of psychotherapy approaches and a more biopsychosocial model. The fact that these models focus on fewer dimensions is not to say these approaches are not useful, but they clearly have a primary focus on the mind and mental health, whereas the holistic models equally value and seek a balance between all dimensions of human experience and seek to touch on all of them as part of the integration process. The psychotherapy models also tend to view integration as something that is necessitated by psychedelic experiences rather than a more universal need among Westerners. Thus, the therapy models focus more on processing, making use of, and making changes based on the psychedelic experience, whereas the holistic models are more likely to assume that people are drawn to psychedelic experiences in the first place by their imbalances and lack of integration. Still, for psychotherapists not well versed in incorporating somatic, spiritual, natural, and community-focused interventions into their practice, the psychotherapy models are likely to be an accessible entry point to supporting clients who are utilizing psychedelics. A psychotherapeutic framework may "meet them (clients and therapists) where they're at," though it may not prepare the client or therapist for experiences that transcend typical psychotherapeutic process and content.

We concluded our review of integration models by capturing and contrasting the primary components of each model, which resulted in our proposal of a new Synthesized Model of Integration (**Figure 1**). The six areas in the center of the model are facets of the person and their experience (i.e., mind/cognitive/emotional, bodily/somatic, spiritual/existential, natural world, relational/communal, and lifestyle/action). Our model also includes six continuums on which to organize integration practices along the outer ring of the model. These include the degree to which the practice is more conscious or unconscious, more internally or externally focused, more creative or receptive, more passive or active, more outside of one's comfort zones or gentle self-care, or more contemplative

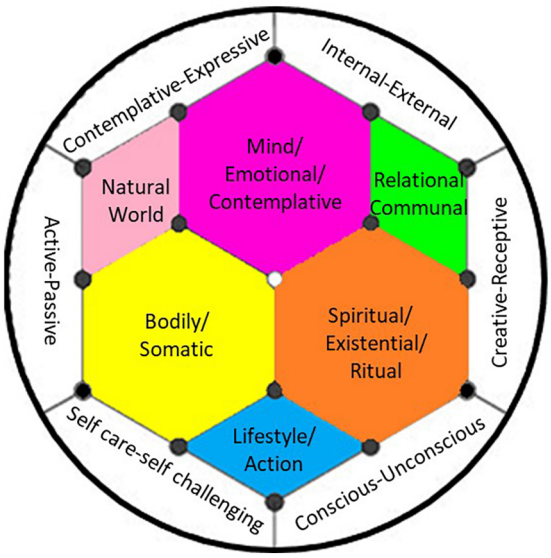

FIGURE 1
Synthesized model of integration: The hexagon reflects six interconnected domains of existence, with the more personal ones toward the center. The outer ring reflects continuums on which integration activities can be placed. The goal is a balance of integration activities addressing all domains of living.

or expressive. We suggest that journeyers reflect on their preferences on each of these continuums and choose a balance of integration practices that addresses each side of each continuum while also drawing from each domain of experience in the Synthesized Model of Integration. Taken together, a balance of integration practices is congruent with the intention to move toward holism.

Integration practices and activities

Integration practices and activities provide the most granular level of analysis of the concept of integration. An expansive range of practices have been suggested in the literature, often without much rationale or context. This likely accounts for some of the confusion about what integration is and how to best practice it. On the one hand, many writings about integration provide only a few examples of integration, while others provide extensive lists. This can lead to a lack of direction at the one extreme or a sense of overwhelm and confusion at the other extreme. The integration models and frameworks already discussed provide guidance for choosing and implementing integration practices. Our synthesized model may provide further framework when attempting to resolve gaps within and contradictions between integration models.

While the great majority of writings we identified on the topic of integration were brief and did not correspond to a theory or model, we reviewed a large number of additional writings to identify a comprehensive list of integration practices not included with the models we have focused on thus far. Notably, the vast majority of integration practices we found in briefer writings had already been referenced in relation to one or more of the integration models. We initially hoped to organize these integration practices according to our Synthesized Model of Integration, though many of the integration practices cut across domains (e.g., mind-body integrative practices). Instead, we coded integration activities by theme (see **Table 2**).

While some themes correspond directly to the facets of our synthesized model (e.g., nature, spiritual/ritual), others were further broken down into subthemes (e.g., bodily/somatic largely corresponds to the diet/health and somatic/movement themes). We note that some integration practices in each theme bridge across multiple facets of our model. For example, outdoor activities like hiking incorporate both nature and physical activity. This may be desirable if the goal is to achieve balance and integration across aspects of living, even if it makes categorization of activities less clear. We are reminded that while categories help us to make sense of the world, they ultimately are mental constructions, and that such categorical thinking reflects a Western worldview (Limb and Hodge, 2008). Lastly, we note that some of our themes involve practices that are supportive of the overall project of integration, though do not correspond to facets of our synthesized model, such as downtime/quiet time or creating space/setting for integration. These are not aspects of individuals but are part of one's set and setting that can support integration.

Expectations and approach to integration

Beyond models and practices, our primary sources emphasize important expectations (part of one's set) that can impact how one approaches integration. First, our primary sources all emphasize that integration requires active effort to revisit and work with psychedelic experiences and content that emerges from them. Without such active effort, valuable lessons tend to fade, and difficult experiences can reinforce traumas or existing patterns and defenses. Contrary to common belief, rather than doing the healing for us, psychedelics may give us an experience of and orientation toward wholeness, along with insight into the barriers and misalignments that will need to be addressed to continue toward or maintain wholeness (e.g., Coder, 2017).

Second, most of our primary references describe integration as not just an event or brief phase but a long-term process. While some changes may occur quickly and permanently, and the initial integration of a fresh experience is particularly important, many aspects of psychedelic experiences may continue to unfold gradually or even over the course of one's lifetime as they become relevant and take on new meaning during different phases of

TABLE 2 Summary of integration practices by theme.

Theme	Integration practices
Artistic/creative	Drawing Mandalas (multiple) Drawing (multiple) Painting (multiple) Art exercises (multiple) Creative expression (multiple)
Music/singing	Listening to music Playing music (Grof, 2008) Chanting/Singing (multiple) Drumming (Kaufman and McCamy, 2019)
Movement/somatic	Drumming (Kaufman and McCamy, 2019) Yoga (multiple) Dance (multiple) Qigong (Buller and Moore, 2019) Tai Chi (Coder, 2017; Bourzat and Hunter, 2019) Progressive Muscle Relaxation (Westrum and Dufrechou, 2019) Walking in nature (multiple) Active movement: Hiking, Bicycling, Sailing, Martial Arts (Coder, 2017; Bourzat and Hunter, 2019) Exercising (multiple) Massage (multiple) Acupuncture (Buller and Moore, 2019) Bath soaks/Shower (Bourzat and Hunter, 2019; Westrum and Dufrechou, 2019) Essential oils/Aromatherapy (Bourzat and Hunter, 2019; Buller and Moore, 2019) Sweat/Sauna (Bourzat and Hunter, 2019) Sensory deprivation/Float Tank (Bourzat and Hunter, 2019) Laugh (Buller and Moore, 2019) Sexual life/needs (Buller and Moore, 2019)
Diet/health practices	Healthy diet (multiple) Fasting (Westrum and Dufrechou, 2019) Naturopathy (Frecska et al., 2016) Colonic irrigation (Frecska et al., 2016)
Quiet time/downtime	Self-reflection/Introspection (multiple) Rest (multiple) Reading (multiple) Time (multiple) Space for emotions (Buller and Moore, 2019) New hobbies (Ortigo, 2021)
Journaling	Journaling (multiple) Dream Journal (Ortigo, 2021)
Therapy/mind focus	Therapy Bibliotherapy (Frecska et al., 2016) Psychotherapy (multiple) Family Constellation therapy (Labate and Cavnar, 2014) Internal Family Systems (Morgan, 2020) Sculpting (Grof, 2008; Labate and Cavnar, 2014) ACT Model (Sloshower et al., 2020; Gorman et al., 2021) Group therapy (Trope et al., 2019) Mindfulness (Gorman et al., 2021) Harm Reduction (Gorman et al., 2017, Gorman et al., 2021) Transpersonal/Psychodynamic (Passie, 2009) Values Clarification/Belief work/Virtues (multiple) Assimilating memories (Richards, 2015; Belser et al., 2017) Emotions work (Kaufman and McCamy, 2019) Reinforcing new habits (Bourzat and Hunter, 2019) Insights/Values into action (multiple)
Meditation/mindfulness	Mindfulness practice (multiple) Meditation (multiple) Walking meditation (Westrum and Dufrechou, 2019) Shinrin-Yoku practice (Gandy et al., 2020) Body scan (Westrum and Dufrechou, 2019) Breathing techniques (multiple) Breathwork (Buller and Moore, 2019; Westrum and Dufrechou, 2019) Mundane activities done with mindfulness (Westrum and Dufrechou, 2019; Bast, 2020)
Nature	Time in nature (multiple) Horticulture (Gandy et al., 2020) Nature walk (multiple) Talk therapy in nature (Gandy et al., 2020) Shinrin-Yoku practice (Gandy et al., 2020) Favorite places in nature (Bourzat and Hunter, 2019
Creating space/ritual	Creating an altar/Sanctuary (multiple) Physical comforts (Bourzat and Hunter, 2019) Arrange comfortable workspace (Buller and Moore, 2019) Organizing/Cleaning (Bourzat and Hunter, 2019) Nourishing environment (Fadiman, 2011)
Spiritual/existential	Spixritual practice (multiple) Intention setting (Frecska et al., 2016; Kettner et al., 2021) Mantra work (Coder, 2017) Gratitude practice (Coder, 2017) Prayer (multiple) Tarot/Medicine (Westrum and Dufrechou, 2019) Sage/Smudging (Buller and Moore, 2019) Self-Awareness/Individuation practice (Ortigo, 2021) Astrology (Buller and Moore, 2019) Inner listening (Coder, 2017) Connect with spiritual mentor/community (Buller and Moore, 2019) Practice openness, presence, awareness (Coder, 2017) Exploring relationship with death (Westrum and Dufrechou, 2019) Reflect on elementals (Coder, 2017)
Dreamwork/Symbolic interpretation	Dream work (multiple) Shadow work (Westrum and Dufrechou, 2019) Dream journaling (Ortigo, 2021) Interpreting symbols (multiple) Exploring metaphors in nature (Coder, 2017)
Community/activism	Community Participation and Support (multiple) Volunteer (Buller and Moore, 2019) Activism (Bourzat and Hunter, 2019) Service (Bast, 2020) Donating (Bourzat and Hunter, 2019) Serving in hospice care (Bourzat and Hunter, 2019) Bring beauty in the world (Coder, 2017) Practice love toward world (Coder, 2017)
Relational/interpersonal	Boundary setting (Bourzat and Hunter, 2019; Buller and Moore, 2019) Building connections (Buller and Moore, 2019) Writing letter to loved one (Bourzat and Hunter, 2019) Reaching out for help (Bourzat and Hunter, 2019) Non-sexual touch/physical closeness (Passie, 2009) Interpersonal closeness (Passie, 2009) Practice love toward others (Coder, 2017) Sharing circles/groups (multiple) Time with loved ones and children (Buller and Moore, 2019)

one's life (e.g., Coder, 2017). Relatedly, there was a theme of integration requiring time and space, or creation of supportive settings (including physical spaces such as altars or meditation sitting areas). Without regular practice and lifestyle changes that allow time to reflect, engage in intentional integration practices, and engage with others, one is unlikely to have an adequate container in which to hold and work with the entirety of their psychedelic experiences.

Some of our references suggested that integration may be more accessible when incremental (e.g., Westrum and Dufrechou, 2019), while also acknowledging that important changes may be more accessible when closer in proximity to one's psychedelic experiences (e.g., Bourzat and Hunter, 2019). Paradoxically, the bigger and more transformational the experience, the more incremental the approach to integration may need to be, as they can take time to digest, and any changes required may take time to implement. For more profound psychedelic experiences, like any other profound experience in life, it would make sense to continue to reflect on the experience and may new interpretations and value from it over the lifetime.

The integration process may also be more congruent with the psychedelic experience if the journeyer can allow it to unfold organically, rather than pushing for an overly task-oriented approach to integration practices (Bourzat and Hunter, 2019). In this sense, integration models can help one to be aware of the many areas of existence and how integration practices can nourish them, but not applied so rigidly as to ignore one's intuition of what is needed but should not be used so rigidly as to ignore what intuitively feels like what is needed. The concept of "inner healing intelligence," is often cited to refer to the innate knowledge and tendency to orient toward healing, growth, and wholeness (Grof, 1996).

Although most of the models encourage starting with contemplation, they do not encourage isolation. Integration is often described as ideally including supportive communities and supportive others (Coder, 2017). It may also include a range of professionals, such as therapists, dieticians, acupuncturists, meditation teachers, massage therapists, spiritual teachers, etc. (Bourzat and Hunter, 2019). The presence of other people as part of the integration process can help us overcome the myth that we are self-contained individuals, with interpreting and capturing insights from psychedelic experiences, and by providing interpersonal grounding or regulation of emotion. However, there generally is a caution given about including those who do not understand or support psychedelic experiences or the sensitive state one is in afterward (Coder, 2017).

Finally, bringing forth one's insights, values, changes, and gifts to the world are treated as a later step in the process of integration (e.g. Coder, 2017; Bourzat and Hunter, 2019; Sloshower et al., 2020). This appears partly practical in that one needs to reflect on what they would want to share with the world and why, but can also be a strategic buffering of potential inflationary experiences where one feels compelled to evangelize or make impulsive changes based on their experiences without first adequately exploring and internalizing them. Not all the models addressed action in the world as part of integration, though we noted that the models addressing action did not take an overly linear view that one must change oneself before changing the world, when in fact these can be mutually reinforcing processes. We are reminded of pioneering action researcher Kurt Lewin, and his circular process of observing, reflecting, planning, acting, and then repeating (Glassman et al., 2013).

Discussion

The concept of psychedelic integration has been criticized as lacking clear definition, having no historical context, and containing a confusing range of activities (e.g., Sloshower et al., 2020). It appears this critique initially stemmed from the historical lack of theories and models to conceptualize the integration process, but more recently from a slew of independently developed definitions and approaches to integration. While psychedelic researchers and practitioners have long highlighted the importance of integration (e.g., Grof, 1980), little structure was provided until recently. Accordingly, we focused our attention on writings that included models of integration, two of which were published in 2017 and the remaining seven in 2019 or later, reflecting the very recent expansion of scholarship on the topic. While it is beyond the scope of this article, we believe that integration does have a historical context and can broadly be seen as a therapeutic common factor, that is a process inherent to, if unnamed by, most theories of psychotherapy (Wampold, 2015). The assumption that insights need support and ongoing processing to result in lasting change is apparent in most theories of psychotherapy, such as through the use of homework or the incorporation of relapse prevention or behavioral activation.

We were particularly aware of the increasing popularity of ACT in relation to psychedelic-assisted therapy, and it may prove to be a very useful framework, though to our knowledge ACT was not developed with psychedelics in mind and therefore may result in fitting client experiences to the theory rather than fitting the theory to the broad range of experiences that come out of psychedelics. While ACT and other psychotherapy-based integration models may provide structure to work on the psychological and behavioral aspects of psychedelic experiences (e.g., meaning making, changing thinking or emotional patterns, or working through traumas), they do not easily incorporate a holistic model of living, possibly with the exception of transtheoretical models that incorporate a range of additional theories to focus on aspects of experience beyond the mind and behavior (i.e., Gorman et al., 2021). Research has shown that Westerners are likely

to focus primarily, but not exclusively, on psychological or mental health-related intentions even when they participate in facilitated shamanic or neoshamanic ayahuasca experiences (Bathje et al., 2021). However, the same study also found that participants experienced a much broader range of impacts from their participation than they intended, more reflective of holistic worldviews. These included transcendent experiences, ego death, feelings of unity or interconnectedness, greater engagement in activism, decreased attachment to materialism, powerful somatic/energetic experiences, mind-body integrative experiences, spiritual/mystical experiences, changes in spiritual beliefs, dietary changes, improvements in physical ailments, and emergent experiences that might be misunderstood as mania or psychosis. While psychotherapeutic models may be particularly helpful for assisting journeyers who have psychotherapeutic intentions or significant mental health needs, these models may not provide a broad enough framework for practitioners or journeyers to respond to this full range of psychedelic experiences. We found that the integration models that were influenced by biopsychosocialspiritual and/or Indigenous perspectives addressed a broader range of themes that may arise in psychedelic experiences, and therefore appear indispensable to psychedelic integration.

We also noted recent critique of the tendency among psychedelic researchers and practitioners to impose spiritual interpretations of psychedelic experiences (e.g., Sanders and Zijlmans, 2021). While we agree that imposing belief and meaning is problematic and we support the use of neutral language or use of the participant's own language, it would be similarly problematic for practitioners not to broach the topic of religion and spirituality or fail to ask participants if they would like to incorporate such focus into their work. We believe integration will be most complete when expanding to address the full range of experiences people have with psychedelic substances. In fact, if we utilize more holistic definitions of integration that value balance, then overly mentalizing the psychedelic experience may create further imbalance by reinforcing our already powerful cultural preference for individualism, behaviorism, and cognition without adequately attending to the spiritual/existential, communal/relational, or the natural world (Limb and Hodge, 2008). In attempting to work holistically, those assisting journeyers with integration will need the humility to recognize the limitations of their training and knowledge, and limitations of their cultural conditioning and worldview. A skilled range of collaborators and referral sources are likely to be valuable in facilitating the integration process.

In examining the existing models of integration, we were able to capture a comprehensive list of integration practices (see **Table 2**), along with a rationale for their breadth. We note that the cultural sources of these integration practices are not always cited, but that many of them come from non-Western religious, cultural, or healing practices (e.g., yoga, use of sage, qi gong, sweat lodges, mindfulness meditation, etc.). In contrasting the models, we were able to contrast existing integration models (see **Table 1**) and incorporate them into a Synthesized Model of Integration that further captures aspects of each (see **Figure 1**). We suggest using this model to develop a balanced approach to integration that addresses each of the six facets of experience and reflect on each side of the six continuums on the outer ring of the model to be sure to choose a balance of integration activities. For those seeking more structure and guidance regarding specific integration practices and how to implement them, journeyers may consult an integration professional and review one of the integration handbooks reviewed in this article for ideas (e.g., creating an altar, getting in touch with the body via somatic practices, reflecting on values, or dreamwork). It seems ideal to have a relationship established with a professional prior to psychedelic experiences so they can aid in preparation and be available in the event of a challenging experience where immediate support is needed. However, we note with humility that our model and its application will benefit from continued refinement, elaboration, and research.

Lastly, it is important to highlight the context, or set and setting, for optimal integration. Because there are so many options for integration, we suggest beginning to address integration during the preparation stage, prior to psychedelic experiences. This can include taking an inventory of one's resources and abilities that will support integration (e.g., artistic skills, wellness practices, favorite places in nature), reviewing integration resources such as the models referenced in this article, reflecting on one's current degree of satisfaction and sense of balance among the six facets of living in the Synthesized Model of Integration, planning to put active effort into integration, planning time and space for integration, and asking an integration professional or supportive people to be available for sharing one's experience. After psychedelic experiences, integration can be supported by reviewing one's original intentions for the psychedelic experience, determining which integration practices are most relevant, committing to regular integration practices, identifying relationships and communities that can support integration, carving out time for integration, and creating or finding physical spaces at home, public spaces, or in nature that support the ongoing unfolding of psychedelic experiences over time. Without time and space, one may end up taking the path of least resistance by attempting to integrate the psychedelic experience into their ordinary state of consciousness and life structure rather than being changed by the experience. This process might also be observed at the societal level, as Western culture attempts to constrain and assimilate psychedelics into existing structures, such as capitalism or the medical model. One's resources, responsibilities, and privileges are likely to come into play with regard to the opportunity to more fully engage the integration process and implement life changes. For individuals

with more constraints and fewer resources, an incremental and gradual approach may be particularly important for integration, while highly resourced and privileged individuals may need to be encouraged to slow down and reflect on change and action.

In conclusion, much work has been done to elaborate on the topic of integration in the past few years. New models and extensive guides for integration practice have been developed. Because of the recency of these efforts, ours is the first article to synthesize definitions, models, and practices related to integration. We hope this will bring more intentional focus to researching and further developing this crucial stage of the psychedelic experience.

Author contributions

GB contributed to all sections and analysis. EM contributed to literature search, introduction, results, analysis, and manuscript formatting. MK contributed to literature search, introduction, results, and analysis. All authors contributed to the article and approved the submitted version.

Funding

This study received funding from Adler University for manuscript submission.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 05 October 2022
DOI 10.3389/fpsyg.2022.948729

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

RECEIVED 20 May 2022
ACCEPTED 16 September 2022
PUBLISHED 05 October 2022

CITATION
Søndergaard A, Madsen MK, Ozenne B, Armand S, Knudsen GM, Fisher PM and Stenbæk DS (2022) Lasting increases in trait mindfulness after psilocybin correlate positively with the mystical-type experience in healthy individuals.
Front. Psychol. 13:948729.
doi: 10.3389/fpsyg.2022.948729

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Lasting increases in trait mindfulness after psilocybin correlate positively with the mystical-type experience in healthy individuals

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Background: Psilocybin-induced mystical-type experiences are associated with lasting positive psychological outcomes. Recent studies indicate that trait mindfulness is increased 3 months after psilocybin intake, preceded by decreases in neocortical serotonin 2A receptor (5-HT_{2A}R) binding. However, the association between psilocybin-induced mystical-type experiences and subsequent changes in trait mindfulness remains unexplored, as does the association between pre-drug trait mindfulness and 5-HT_{2A}R binding in the healthy brain.

Aim: We evaluated whether psilocybin induced lasting increases in trait mindfulness in healthy volunteers, and whether the mystical-type experience was associated with this increase. We further examined the association between pre-drug trait mindfulness and 5-HT_{2A}R binding in neocortex and selected frontolimbic regions.

Materials and methods: Forty-six medium-high dose psilocybin sessions were conducted in 39 healthy individuals. The mystical-type experience was measured with the Mystical Experience Questionnaire (MEQ) at the end of the session. Trait mindfulness was measured using the Mindful Attention and Awareness Scale (MAAS) at baseline and 3 months after the psilocybin session. Thirty-two of the participants completed pre-drug [^{11}C]-Cimbi-36 positron emission tomography (PET) to assess 5-HT_{2A}R binding in neocortex and, *post-hoc*, in the frontolimbic regions amygdala, frontal cortex, and anterior cingulate cortex.

Results: The MAAS score was significantly increased at 3-month follow-up (p = 3.24 × 10^{-6}), a change positively associated with the MEQ score (p = 0.035). Although the association between pre-drug MAAS score and neocortex 5-HT_{2A}R binding was not significant (p = 0.24), *post-hoc* analyses revealed a significant negative association between MAAS and right amygdala 5-HT_{2A}R binding (p_{FWER} = 0.008).

Conclusion: We here show that lasting changes in trait mindfulness following psilocybin administration are positively associated with intensity of the mystical-type experience, suggesting that the acute phenomenology of psilocybin facilitates a shift in awareness conducive for mindful living. We furthermore show that higher pre-drug trait mindfulness is associated with reduced 5-HT_{2A}R binding in the right amygdala.

KEYWORDS

psilocybin, mindfulness, psychedelics, mystical experience, serotonin 2A receptor, [^{11}C]-Cimbi-36, Mindful Attention and Awareness Scale

Introduction

Psilocybin is a tryptamine alkaloid, naturally present in the *Psilocybe* genus of mushrooms, currently being researched as a promising therapeutic agent for a range of psychiatric disorders (Carhart-Harris and Goodwin, 2017; Andersen et al., 2021). In clinical studies, psilocybin shows immediate and sustained effects on depression (Carhart-Harris et al., 2016, 2018, 2021; Davis et al., 2021), obsessive-compulsive disorder (Moreno et al., 2006), anxiety and depression in terminal cancer patients (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016), alcohol abuse (Bogenschutz et al., 2015; Garcia-Romeu et al., 2019) and smoking (Johnson et al., 2014, 2017). With increasing evidence in favor of positive effects of psilocybin, it is crucial to explore potential associated psychological factors. A small (n = 10) study has recently demonstrated increases in trait mindfulness in healthy individuals 3 months following a psilocybin session with no related mindfulness-training (Madsen et al., 2020). Similarly, significant increases in trait mindfulness have been observed as soon as 24 h after psilocybin intake in experienced meditators compared to placebo (Smigielski et al., 2019a). Trait mindfulness can be defined as *"the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment."* (Kabat-Zinn, 2003, p. 145). It is positively associated with trait openness (Giluk, 2009), improved behavioral regulation (Keng et al., 2011) and positive bias (Kiken and Shook, 2011), and negatively associated with trait neuroticism (Giluk, 2009), emotional reactivity (Baer et al., 2006) and negative bias (Kiken and Shook, 2011), suggesting that higher trait mindfulness is an indicator of greater psychological health. Several techniques to evoke a state of mindfulness stem from Buddhist meditation (Kabat-Zinn, 2003; Bishop et al., 2004), and have been integrated as components of third-wave cognitive behavior therapy, such as Acceptance and Commitment Therapy (ACT) (Hayes et al., 2006), Mindfulness Based Cognitive Therapy (MBCT) (Segal et al., 2002) and Mindfulness Based Stress Reduction (MBSR) (Kabat-Zinn, 1990), so called mindfulness-based interventions (MBI's). Several researchers have postulated MBI as a framework for psychedelic drug administration due to similar phenomenology and psychological benefits that may act synergistically in combination (Heuschkel and Kuypers, 2020; Sloshower et al., 2020; Eleftheriou and Thomas, 2021). However, more empirical data is needed to gain a better understanding of how acute psychoactive effects of psilocybin are potentially associated with changes in trait mindfulness.

The psychoactive metabolite of psilocybin, psilocin, dose-dependently activates the serotonin 2A receptor (5-HT_{2A}R) (Vollenweider et al., 1998; Nichols, 2016; Madsen et al., 2019), alters cerebral functional network changes (Carhart-Harris et al., 2012; Madsen et al., 2021) and induces an altered state of consciousness characterized by three phases: ascent, peak and descent, lasting 4–6 h (Griffiths et al., 2011; Madsen et al., 2019; Stenbæk et al., 2020). The psilocybin-induced psychedelic experience has a unique phenomenology, including effects such as altered visual and auditory perception, audio-visual synesthesia, enhanced emotions and meaning-making and changes in sense of self (Preller and Vollenweider, 2018). Interestingly, when administered in medium-to-high doses (>12 mg), psilocybin can induce a highly meaningful experience (Griffiths et al., 2006, 2008) known as the mystical-type experience, characterized as an experience of unity with all that exists, a sense of awareness of the fundamental truths of reality, deepfelt blissful mood, transcendence of space and time and difficulty describing the experience with words,

termed ineffability (Stace, 1960; Pahnke, 1963; Barrett and Griffiths, 2018). Having a mystical-type experience during psilocybin administration has been associated with persistent positive effects (McCulloch et al., 2022) and increases in trait openness (Maclean et al., 2011) in healthy volunteers, as well as improvements in symptoms in psychiatric patient populations (Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016; Ross et al., 2016; Roseman et al., 2018; Garcia-Romeu et al., 2019). The psilocybin-induced mystical-type experience shares many phenomenological features with mindful states, including altered self-referential processing (Smigielski et al., 2019b). It is therefore possible that having a mystical experience in the context of psilocybin administration could be a catalyst for lasting changes in trait mindfulness.

We have recently reported a significant negative association between changes in neocortical 5-HT_{2A}R binding 1 week after psilocybin administration and changes in trait mindfulness after 3 months (Madsen et al., 2020), suggesting an involvement of 5-HT_{2A}R in trait mindfulness. We also found that lower pre-drug 5-HT_{2A}R binding, i.e., unstimulated by psilocybin, predicted the temporal unfolding of psychoactive effects of psilocybin, including greater intensity of the mystical-type experience (Stenbæk et al., 2020). 5-HT_{2A}R binding in selected frontolimbic brain regions has previously been positively associated to trait neuroticism (Frokjaer et al., 2008), a trait inversely related to trait mindfulness (Brown and Ryan, 2003; Giluk, 2009; Jensen et al., 2016). Given that 5-HT_{2A}R is critical for the described mind-expanding effects of psilocybin (Vollenweider et al., 1998; Stenbæk et al., 2020), it is conceivable that 5-HT_{2A}R may be involved in mindful and meditative states that are often also described as expanded states (Hölzel et al., 2011; Smigielski et al., 2019b). However, the association between pre-drug 5-HT_{2A}R binding and trait mindfulness has not yet been investigated.

In the present study, we evaluate the effect of psilocybin on changes in trait mindfulness from baseline to 3-month follow-up, and whether the mystical-type experience during acute psilocybin administration is associated with these changes in trait mindfulness. Lastly, we explore whether pre-drug 5-HT_{2A}R binding in neocortex and frontolimbic regions is associated with trait mindfulness. We hypothesize that: (1) Trait mindfulness will increase from baseline to 3-month following psilocybin administration, (2) The intensity of the mystical-type experience is positively associated with changes in trait mindfulness, and (3) Pre-drug 5-HT_{2A}R binding in neocortex and frontolimbic regions is negatively associated with trait mindfulness.

Materials and methods

Participants

The study included 39 participants who received a psychoactive psilocybin dose (>12 mg) and completed baseline and 3-month follow-up measures of trait mindfulness, as well as a post-session measure of the mystical-type experience. Of these, seven participants completed two psilocybin interventions with new baseline and follow-up measures, at least 12 months apart (mean months between interventions (SD) [range]: 21 (5) [12–28]). Thus, in order to increase power for the analyses, a total of 46 datasets were included in the analyses pertaining to hypotheses (1) and (2). For the analyses pertaining to hypothesis (3), 32 of the included participants also completed a pre-drug Positron Emission Tomography (PET) scan with the tracer [^{11}C]-Cimbi-36 for imaging of 5-HT_{2A}R binding in neocortex and frontolimbic regions (Ettrup et al., 2014, 2016).

All participants were recruited from a database of individuals volunteering to participate in human neuroimaging studies of psilocybin. Exclusion criteria included (a) present or previous psychiatric disorder in participant or immediate family, (b) present or previous neurological illness, severe somatic illness, or present medication that could affect the results, (c) non-fluency in Danish, vision or hearing impairment, (d) Present or previous learning disabilities, (e) current pregnancy or breastfeeding for women, (f) contraindications for MR-imaging, (g) alcohol or drug abuse, (h) allergy to the test drugs, (i) significant exposure to radioactivity within the past year, e.g., due to medical imaging, (j) ECG indicative of cardiac disease or use of medication causing prolonged QT-interval, (k) previous negative side-effects from hallucinogens, (l) use of psychedelics in the past 6 months, (m) blood donation less than 3 months before project participation, (n) hemoglobin <7.8 mM for women and 8.4 mM for men, (o) low plasma ferritin (<12 μg/L) and (p) bodyweight <50 kg. This was ensured through a complete physical and neurological exam, including ECG and blood screening for pathology, and a psychiatric screening, using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998).

Experimental procedures

Psilocybin interventions

Prior to the intervention day, participants met with the psychological support staff (one trained lead psychologist and one psychology trainee) to prepare for the psilocybin intervention, which included being informed about potential side-effects and safety precautions. On the intervention day, psilocybin was administered orally in 3 mg capsules with a glass of water based on a maximum weight-adjusted dose of 0.21 mg/kg (n = 12 sessions) or 0.31 mg/kg (n = 34 sessions). Of the 46 psilocybin interventions, 6 took place partly in a PET-scanner during acute effects (Madsen et al., 2019); 18 took place in a comfortable and private room

(Madsen et al., 2020), and 22 took place partly in a MR-scanner during acute effects (Madsen et al., 2021). The psychological support staff members were present with the participant throughout the intervention day to provide interpersonal support. All participants met with the psychological support staff the day after intervention for an integration session. All preparation and integration sessions were standardized across interventions and were conducted by the same lead psychologist.

Outcome measures

Mindful Attention and Awareness Scale

We used the Danish version of the Mindful Attention and Awareness Scale (MAAS) (Jensen et al., 2016) to assess the participants' trait mindfulness at baseline and 3 months after the psilocybin intervention. The MAAS is a self-report scale, comprising 15 items related to general tendencies of inattentiveness toward emotions, thought, activities and physical sensations in the everyday experience, rated on a six-point Likert scale from one (almost always) to six (almost never). Example items include *"I find it difficult to stay focused on what's happening in the present"* and *"I find myself preoccupied with the future or the past."* The total MAAS score is calculated as the mean of all 15 items. Higher scores indicate higher degrees of trait mindfulness. The MAAS has a unidimensional construct with excellent internal consistency (Cronbach's alpha for this dataset: baseline $\alpha = 0.86$, follow-up $\alpha = 0.90$) and good test-rest reliability (Brown and Ryan, 2003; Jensen et al., 2016).

Mystical Experience Questionnaire

Approximately 6 h after psilocybin administration on the intervention day, participants completed the Danish version of the 30-item version of the Mystical Experience Questionnaire (MEQ) (Barrett et al., 2015). The MEQ is a self-report scale to assess the intensity of mystical experience related to a discrete event, such as during acute psilocybin effects. Participants rated each item on a 6-point Likert scale [0 = none at all, 5 = extreme (more than ever before in my life and stronger than 4)] on four subscales: mystical (e.g., *"freedom from the limitations of your personal self and feeling of unity or bond with what was felt to be greater than your personal self"*), positive mood (e.g., *"experience of ecstasy"*), transcendence of time and space (e.g., *"loss of your usual sense of time"*) and ineffability (e.g., *"feeling that you could not do justice to your experience by describing it in words")*. The total MEQ score is calculated as the mean of all items.

Positron Emission Tomography and Magnetic Resonance Imaging

Thirty-two participants were scanned at baseline using High Resolution Research Tomography PET scanner (CTI/Siemens, Knoxville, USA) with an approximate in-plane resolution of 2 mm for 120 min after a bolus injection of [^{11}C]-Cimbi-36 tracer to reflect and image 5-HT$_{2A}$R binding (Ettrup et al., 2014, 2016). The scans were reconstructed into 45 frames (6 × 10 s, 6 × 20 s, 6 × 60 s, 8 × 120 s, 19 × 300 s). For the purpose of PET-image co-registration and segmentation, high resolution 3D T1-weighted and T2-weighted images were acquired on a 3T prisma magnetic resonance imaging (MRI) Scanner (Siemens, Erlangen, Germany), using either a 64-channel or a 32-channel head coil. Regional time-activity curves including cerebellum as a reference region were extracted, as previously described (Svarer et al., 2005), and kinetic modeling was done using the simplified reference tissue model (SRTM) to compute the regional non-displaceable binding potential (BP_{ND}) (Ettrup et al., 2014, 2016). Neocortical (a volume-weighted average of all cortical regions) [^{11}C]-Cimbi-36 BP_{ND} was chosen as our primary outcome region based on findings from our previous study (Madsen et al., 2020), the high expression of 5-HT$_{2A}$R within neocortex (Beliveau et al., 2017) and the high degree of inter-regional correlation across neocortical subregions (Erritzoe et al., 2010; Spies et al., 2020). As secondary outcomes for *post-hoc* analyses, [^{11}C]-Cimbi-36 BP_{ND} in frontolimbic regions [frontal cortex, left and right amygdala and left and right anterior cingulate cortex (ACC)] were chosen based on a previous study (Armand et al., 2022).

Data analysis

Psilocybin, Mystical Experience Questionnaire, and change in Mindful Attention and Awareness Scale

To evaluate the change in MAAS score from baseline to 3-month follow-up after psilocybin administration (Hypothesis 1) and its association with MEQ total score (Hypothesis 2), we used a linear mixed-effect model (LMM) for each hypothesis, as this model accounts for the repeated measures. To account for the seven participants who had completed two psilocybin interventions, participant-ID was included as a random effect. Baseline MAAS score was included as a covariate for Hypothesis 2, as magnitude of the change naturally is dependent on the baseline MAAS score due to the upper limit of the scale being six, and baseline MAAS has been associated to change in MAAS following a mindfulness-intervention (Shapiro et al., 2011). Although psilocybin dose and setting (Studerus et al., 2012) have been associated with acute psychedelic effects and positive psychological outcomes, inclusion of these as covariates in our model did not substantially affect the results, and were therefore not included in the final analyses. We report change in MAAS as the percentage change with a 95% confidence interval.

Post-hoc analysis of Mystical Experience Questionnaire subscales and change in Mindful Attention and Awareness Scale

In *post-hoc* analyses, we examined associations between change in MAAS and the individual MEQ subscales mystical, positive mood, transcendence of time and space, and ineffability, using the same LMM and under the same conditions presented in section "Psilocybin, Mystical Experience Questionnaire, and change in Mindful Attention and Awareness Scale."

Pre-drug neocortical [^{11}C]-Cimbi-36 binding and Mindful Attention and Awareness Scale

To evaluate the association between pre-drug neocortical [^{11}C]-Cimbi-36 BP_{ND} and MAAS score, (Hypothesis 3) we fit a linear regression model with [^{11}C]-Cimbi-36 BP_{ND} as independent variable and MAAS score as the dependent variable. Given that MAAS score is associated to age (Jensen et al., 2016) and body mass index (BMI) (Camilleri et al., 2015), these were included as covariates. Effects for the models are reported as unstandardized regression coefficients (β) with 95% confidence intervals (95% CI) and adjusted R^2 as a measure of variance.

Post-hoc analyses of pre-drug frontolimbic [^{11}C]-Cimbi-36 binding and Mindful Attention and Awareness Scale

In *post-hoc* analyses, we evaluated the associations between pre-drug [^{11}C]-Cimbi-36 BP_{ND} in the frontolimbic brain regions (total frontal cortex and right and left amygdala and ACC) and MAAS score. Covariates and procedures for reporting effects for the models were identical to those presented in section "Pre-drug neocortical [^{11}C]-Cimbi-36 binding and Mindful Attention and Awareness Scale."

Statistical significance and effect size

For Hypothesis 1, we conducted two significance tests: one with (n = 46) and one without the 10 participants from our previous study (n = 36) (Madsen et al., 2020), to demonstrate an independent replication. Cohen's d is reported as an expression of standardized effect size (Cohen, 1988) for Hypothesis 1. The threshold for statistical significance for Hypothesis 1, 2 and 3 was $p < 0.05$. For the *post-hoc* analyses, p-values were corrected for multiple tests using the Bonferroni method; four tests for the *post-hoc* analyses regarding the MEQ subscales, and five tests for the *post-hoc* analyses regarding pre-drug [^{11}C]-Cimbi-36 BP_{ND} in frontolimbic regions. For *post-hoc* analyses, p-values are reported both uncorrected (p_{unc}) and with a family-wise error rate correction (p_{FWER}) using a statistical threshold of $p_{FWER} < 0.05$. All statistical analyses were conducted using the statistical software *R (v4.0.5)*.

Results

Participant characteristics and descriptive statistics

Participant characteristics and descriptive data are summarized in **Table 1**. Previous psychedelic use covers prior experience with 5-HT_{2A}R agonistic psychedelics. A figure graphically displaying the change in each MAAS item score from baseline to 3-month follow-up can be found in **Supplementary Figure 1**.

Changes in Mindful Attention and Awareness Scale following psilocybin administration

We found a significant increase in average MAAS score from baseline to 3-month follow-up, both in the full sample (n = 46) (Cohen's d: 0.72; mean% change [95%CI]: 8.1 [5.1;11.1]; $p = 3.24 \times 10^{-6}$, **Figure 1**) and in the independent sample (n = 36) (Cohen's d: 0.71; mean% change [95%CI]: 7.5 [4.0;10.9]; $p = 1.0 \times 10^{-4}$). A graphical display of relation between baseline MAAS and change in MAAS is illustrated in **Supplementary Figure 2**.

TABLE 1 Participant characteristics and descriptive statistics.

Variables	Mean ± SD	Median	Range: min, max
Interventions n = 46			
Sex (% female)	37		
Previous psychedelic use (% yes)	37		
Age (years)	32.6 ± 8.69	29.8	24.2, 60.2
BMI (kg/m^2)*	24.5 ± 3.09	23.8	18.8, 33.2
Weight-adjusted psilocybin dose (mg/kg)	0.26 ± 0.04	0.27	0.15, 0.32
Actual psilocybin dose (mg)	20.2 ± 4.36	21	12, 30
Time from psilocybin intervention to follow-up MAAS score (months)	3.21 ± 0.55	3.10	2.55, 5.35
Baseline MAAS score	4.14 ± 0.6	4.2	2.33, 5.13
Neocortical [^{11}C]-Cimbi-36 BP_{ND}**	1.21 ± 0.220	1.17	0.870, 2.02

*For the participants that participated in two interventions, only BMI from the first intervention is included (n = 39), as only PET data from the first intervention was included in Hypothesis 3, where BMI was used as a covariate. **n = 32.

Mystical Experience Questionnaire and change in Mindful Attention and Awareness Scale

MEQ total score was significantly positively associated with change in MAAS score (% mean change per unit increase in MEQ [95%CI]: 3.1 [0.04; 6.0]; $p = 0.035$, **Figure 2**).

Post-hoc: Mystical Experience Questionnaire subscales and changes in Mindful Attention and Awareness Scale

Post-hoc analyses revealed a statistically significant positive association between change in MAAS score and the MEQ subscale mystical (% mean change per unit increase in mystical [95%CI]: 2.93 [0.75; 5.11]; $p_{unc} = 0.012$, $p_{FWER} = 0.049$). No other significant associations between change in MAAS score and MEQ subscales were observed after correction for multiple testing (positive mood: 3.40 [0.67; 6.13]; $p_{unc} = 0.019$, $p_{FWER} = 0.076$, transcendence of time and space: 0.48 [−2.57; 3.57]; $p_{unc} = 0.75$, $p_{FWER} = 3$ and ineffability: −0.13 [−3.01; 2.76]; $p_{unc} = 0.93$, $p_{FWER} = 3.72$).

Pre-drug neocortical [^{11}C]-Cimbi-36 BP_{ND} and Mindful Attention and Awareness Scale

The linear regression model showed a negative but not significant association between pre-drug neocortical [^{11}C]-Cimbi-36 BP_{ND} and MAAS score (β [95%CI], R^2: −0.55 [−1.48; 0.38], 0.0051; $p = 0.24$).

Post-hoc: Pre-drug frontolimbic [^{11}C]-Cimbi-36 BP_{ND} and Mindful Attention and Awareness Scale

Post-hoc analyses revealed a significant negative association between pre-drug right amygdala [^{11}C]-Cimbi-36 BP_{ND} and MAAS score (β [95%CI], R^2: −0.67 [−1.06; −0.28], 0.30; $p_{unc} = 0.0016$, $p_{FWER} = 0.008$, **Figure 3**). No other significant associations between [^{11}C]-Cimbi-36 BP_{ND} in frontolimbic regions and MAAS score were observed after correction for multiple testing (frontal cortex: −0.48 [−1.35; 0.38], 0.00015; $p_{unc} = 0.26$, $p_{FWER} = 1.3$), right ACC: −0.19 [−1.54; 0.17], −0.0047; $p_{unc} = 0.29$, $p_{FWER} = 1.45$, left ACC: −0.31 [−0.90; −0.28], – 0.0056; $p_{unc} = 0.30$, $p_{FWER} = 1.5$ and left amygdala: (−0.14 [−1.71; −0.89], −0.05; $p_{unc} = 0.78$, $p_{FWER} = 3.9$).

Discussion

We here demonstrate that psilocybin induces a significant increase in trait mindfulness of 8.1% from baseline to 3-month follow-up across 46 psilocybin sessions. As a novel finding, we show that participants who experienced a greater mystical-type experience exhibited a significantly greater increase in trait mindfulness at 3-month follow-up. We found no significant association between pre-drug neocortical 5-HT_{2A}R binding and trait mindfulness; however, *post-hoc* analyses of frontolimbic brain regions revealed a significant negative association between pre-drug 5-HT_{2A}R binding in the right amygdala and trait mindfulness.

The observed increase in trait mindfulness replicates and strengthens the results of our previous study, where psilocybin increased trait mindfulness for at least 3 months in 10 healthy volunteers (Madsen et al., 2020). These findings align with previous studies of psychedelic-induced mindfulness in healthy volunteers. Buddhist meditation practitioners show increased trait mindfulness the day after psilocybin compared to placebo (Smigielski et al., 2019a), and ayahuasca intake is associated with increased mindfulness 24 h after administration (Soler et al., 2016; Uthaug et al., 2018). More sustained effects have only been studied after 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) intake where trait mindfulness was higher 1 month after intake (Uthaug et al., 2019). Taken together, there is a growing amount of evidence suggesting that psychedelic substances promote an immediate and sustained increase in trait mindfulness in healthy individuals.

Although trait mindfulness is considered a stable human disposition, it can be enhanced through meditation and mindfulness-practice (Smigielski et al., 2019a). Our findings of sustained and increased trait mindfulness following psilocybin administration can be interpreted in relation to a previous mindfulness-intervention, where healthy individuals participated in an 8-week intensive MBSR course and on average experienced a 7% increase in trait mindfulness, compared to 1–3% in the inactive control groups (Jensen et al., 2012), indicating a significant increase following MBSR training. Another MBSR study reported a sustained 8% increase in trait mindfulness over 12-months in the treatment group, compared to the control group where both increases and decreases in trait mindfulness were reported, fluctuating up to 7% in each direction (Shapiro et al., 2011). These results suggest that trait mindfulness naturally fluctuates over time, but on average at a lower magnitude and without a clear pattern compared to what is observed following MBSR treatment and psilocybin intervention, the latter as suggested by the results from the current study.

Our findings support a positive association between the intensity of the mystical-type experience and increases in trait mindfulness, echoing previous studies that have attested to the importance of the mystical-type experience for lasting positive

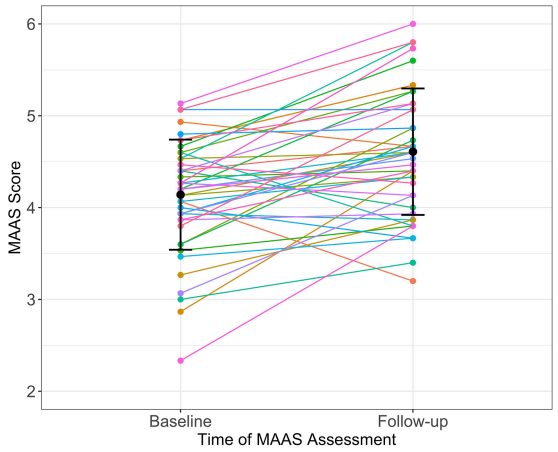

FIGURE 1
Change in Mindful Attention and Awareness Scale (MAAS) score following psilocybin administration from baseline to 3-month follow-up in the full sample (n = 46). Colored lines: Individual values; middle black dot: mean; error bar: SD. No participants had a total MAAS score <2. Maximum possible MAAS score = 6.

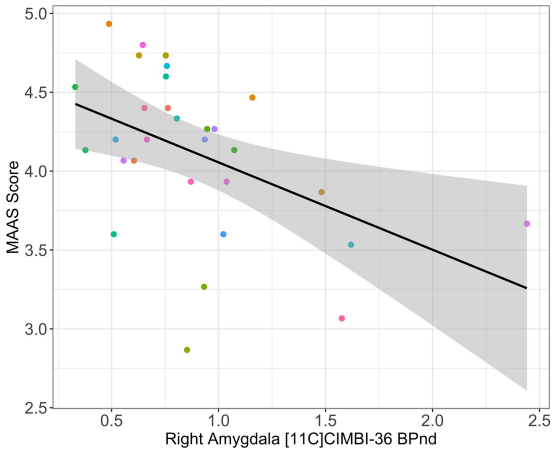

FIGURE 3
Pre-drug right amygdala [^{11}C]-Cimbi-36 BP_{ND} association with Mindful Attention and Awareness Scale (MAAS) score. Black line and gray shading: Estimated regression line and 95% confidence interval. Colored circles: Individual participants. No participants had a MAAS score <2 or >5. Maximum possible MAAS score = 6.

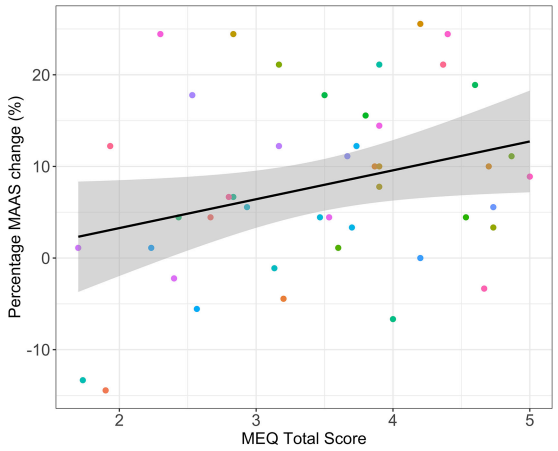

FIGURE 2
Mystical Experience Questionnaire (MEQ) total score association with percentage change in Mindful Attention and Awareness Scale (MAAS). Black line and gray shading: Estimated regression line and 95% confidence interval. Colored circles: Individual participants. No participants had an MEQ score ≤1.

psychological effects of psilocybin (Pahnke, 1963; Maclean et al., 2011; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016, 2018; Ross et al., 2016; Roseman et al., 2018; Garcia-Romeu et al., 2019; Smigielski et al., 2019a; McCulloch et al., 2022). In self-reported psilocybin accounts, healthy participants who have had a complete mystical-type experience (>60% on all subscales of the MEQ) describe feeling a universal bond, witnessing profound beauty and a great love for family (McCulloch et al., 2022). These themes of connectedness, bliss and unity with all things are also recounted in mindfulness practice, such as meditation (Hölzel and Ott, 2006; Barrett and Griffiths, 2018). Other notable parallels with meditation include the experience of ego-dissolution (Millière, 2017; Barrett and Griffiths, 2018; Millière et al., 2018) along with neurobiological similarities, such as reduced network integrity in the default mode network (Brewer et al., 2011; Carhart-Harris et al., 2014; Fox et al., 2016; Barrett and Griffiths, 2018). Furthermore, it has recently been demonstrated that both trait mindfulness and mystical-type experiences are associated with greater mental wellbeing, and that specifically psilocybin-induced mystical-type experiences alongside a mindfulness practice are associated with higher mindfulness and greater mental wellbeing (Qiu and Minda, 2022). It is possible that the subjective experience of merging with a "oneness" of all things together with a diminished focus on ego, at least when combined with a blissful or ecstatic emotional tone, allows for a shift in perspective that is conducive for psychological flexibility and mindful living. This is further supported by our post hoc finding of a significant positive association between the MEQ subscale "mystical" and change in trait mindfulness. Based on these initial findings, we encourage future research to study the possible complimentary effects of mindfulness-practice and psilocybin in clinical populations, as it may be a suitable therapeutic framework to maintain positive psychological effects of psilocybin treatment. It is also conceivable that intervention with psilocybin could be used to address barriers to MBI and potentially assist individuals who struggle with engagement in therapy.

In *post-hoc* analyses, we found a significant negative association between pre-drug 5-HT_{2A}R binding in the right amygdala and trait mindfulness. There is some pre-clinical

evidence to suggest an inverse coupling between available serotonin in the brain and 5-HT_{2A}R binding (Jørgensen et al., 2018), further supported by the downregulation of 5-HT_{2A}R binding following administration of serotonergic antidepressants (Sanders-Bush et al., 1989; Gray and Roth, 2001; Günther et al., 2009), also seen in depressed patients (Yatham et al., 1999). As such, it is possible that lower 5-HT_{2A}R binding in the right amygdala reflects increased serotonin, and that this is coupled to higher trait mindfulness. However, interpretation of this finding should be made with caution, as the time-activity curve fit for amygdala is typically noisy (Finnema et al., 2014), and we observed no other significant associations for neocortex or frontolimbic regions, including the left amygdala. Interestingly, fMRI studies support involvement of the right amygdala in mindful states (Farb et al., 2007) and trait mindfulness (Way et al., 2010), suggesting that the right amygdala may be more involved in mindfulness than the left amygdala. Future studies are needed to replicate the observed association between right amygdala 5-HT_{2A}R binding and trait mindfulness, and further explore the role of serotonin for individual differences in response to psychedelic administration.

Limitations

Our findings should be interpreted in light of the following limitations: Since we did not collect data in the time that elapsed between psilocybin intervention and 3-months follow-up, we cannot determine whether follow-up MAAS scores were affected by other life circumstances during this time period. Furthermore, although MAAS has shown high test-retest reliability and is a stable personality trait measure of mindfulness (Brown and Ryan, 2003; Jensen et al., 2016), this study is limited by its open-label design and not having a blinded control group (see Muthukumaraswamy et al., 2021 for discussion).

Conclusion

We demonstrate that trait mindfulness is increased in healthy volunteers at least 3 months following a single psilocybin intervention and that the self-reported mystical-type experience immediately following the psychedelic experience is positively associated with this lasting increase in trait mindfulness. We also show a negative association between pre-drug 5-HT_{2A}R binding in the right amygdala and trait mindfulness. These findings suggest that psilocybin and the mystical-type experience could have mindfulness-enhancing capacities, and may potentially work in synergy with mindfulness-based forms of therapies in a clinical setting.

Data availability statement

The datasets presented in this article are not readily available because of the General Data Protection Regulation (GDPR). However, data in the Cimbi database can be accessed by application (http://www.cimbi.dk/db). Requests to access the datasets should be directed to Peter S. Jensen, http://www.cimbi.dk/db.

Ethics statement

The studies involving human participants were reviewed and approved by the Danish Medicines Agency (EudraCT ID: 2016-004000-61, amendments: 2017014166, 2017082837, and 2018023295); and the Ethics Committee for the Capital Region of Copenhagen (journal ID: H-16028698, with amendments 56023, 56967, 57974, 59673, 60437, 62255, 74340, and 79042). This study was conducted in accordance with the Declaration of Helsinki. The participants provided their written informed consent to participate in this study.

Author contributions

AS collected the data, performed analyses, and wrote the manuscript. MM collected the data and provided feedback on the manuscript. BO provided statistical consultation. SA collected the data, assisted with the psilocybin interventions, and provided feedback on the manuscript. GK conceptualized the study, supervised the data collection, and provided feedback on the manuscript. PF collected the data, supervised the data collection, and provided feedback on the manuscript. DS conceptualized the study, assisted with the psilocybin interventions, and supervised the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

Data collected in the present manuscript was supported by the Innovation Fund Denmark (Grant Number 4108-00004B), Independent Research Fund Denmark (Grant Numbers 6110-00518B and 9058-00017B), and The Ester M. og Konrad Kristian Sigurdssons Dyreværns Foundation (Grant Number 850-22-55166-17-LNG). AS was supported through a stipend from The Novo Nordisk Foundation (Grant Number NNF20OC0066082). MM was supported through a stipend from Rigshospitalet's Research Council (Grant Number R130-A5324). BO was supported by The Lundbeck Foundation (Grant Number R231-2016-3236) and Marie-Curie-NEUROMODEL (Grant Number 746850).

Acknowledgments

We extend our sincere gratitude to Peter Jensen, Dorthe Givard, Drummond McCulloch, Lone Freyr, Agnete Dyssegaard, Josephine Torp, Gerda Thomsen, Svitlana Olsen, Annette Johansen, Catharina Messel, and Maria Zofia Grzywacz for help in various aspects of data collection and analysis. We are grateful to the University of Chemistry and Technology and the National Institute of Mental Health (Prague, Czechia) for production of psilocybin and Glostrup Apotek (Glostrup, Denmark) for encapsulation. We are grateful to The John and Birthe Meyer Foundation for the donation of the Cyclotron and PET scanner.

Conflict of interest

MM has received an honorarium as a speaker for Lundbeck Pharma and the Lundbeck Foundation. DS has received an honorarium as a speaker for the Lundbeck Foundation. GK has received honoraria as a consultant for Sanos and as a speaker for Sage-Biogen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer SL declared a shared parent affiliation with the authors to the handling editor at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.948729/full#supplementary-material

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frontiers | Frontiers in Psychology

TYPE Brief Research Report
PUBLISHED 17 November 2022
DOI 10.3389/fpsyg.2022.873455

Check for updates

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Psychology for Clinical Settings, a section of the journal Frontiers in Psychology

RECEIVED 10 February 2022
ACCEPTED 03 October 2022
PUBLISHED 17 November 2022

CITATION
Messell C, Summer L, Bonde LO, Beck BD and Stenbæk DS (2022) Music programming for psilocybin-assisted therapy: Guided Imagery and Music-informed perspectives. *Front. Psychol.* 13:873455. 10.3389/fpsyg.2022.873455

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Music programming for psilocybin-assisted therapy: Guided Imagery and Music-informed perspectives

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The psychedelic drug psilocybin has been successfully explored as a novel treatment for a range of psychiatric disorders. Administration of psilocybin requires careful attention to psychological support and the setting in which the drug is administered. The use of music to support the acute psychoactive effects of psilocybin is recommended in current guidelines, but descriptions of how to compile music programs for the 4–6h long sessions are still scarce. This article describes the procedural steps and considerations behind the curation of a new music program, the Copenhagen Music Program, tailored to the intensity profile of a medium/high dose psilocybin. The method of Guided Imagery and Music is presented as a music therapeutic framework for choosing and sequencing music in music programming and the Taxonomi of Therapeutic Music is presented as a rating tool to evaluate the music-psychological intensity of music pieces. Practical examples of how to organize the process of music programming are provided along with a full description of the Copenhagen Music Program and its structure. The aim of the article is to inspire others in their endeavours to create music programs for psychedelic interventions, while proposing that an informed music choice may support the therapeutic dynamics during acute effects of psilocybin.

KEYWORDS

music program, psilocybin, guided imagery and music, music therapy, psychedelic-assisted psychotherapy

Introduction

Music has been used in rituals across the world to achieve changes in consciousness throughout history, at times in combination with plants containing psychedelic compounds (Nettl, 2013). Literally translated from ancient Greek, psychedelic means "mind-revealing" (ψυχή = soul; δηλοῦν = to reveal) which is a name that hints to the therapeutic potential of

these compounds if administered with careful deliberation. The classic psychedelics include primarily compounds that stimulate the brain's serotonin system such as lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine and mescaline (Nichols, 2016). Of these, psilocybin, the prodrug of psilocin, is structurally similar to serotonin and produces its psychedelic effects through serotonin 2A receptor agonism (Kometer et al., 2012; Madsen et al., 2019). Psilocybin has been successfully explored as a novel therapeutic for a range of psychiatric disorders (Andersen et al., 2021) and is now tested in larger phase II studies of depression (e.g., ClinicalTrials.gov identifier: NCT03775200, C. G. I, 2022[1]). COMPASS Pathways is currently preparing a phase III trial testing psilocybin for treatment resistant depression. Recent clinical trials show promising results of treatment with psilocybin for patients with depression (Carhart-Harris et al., 2016, 2018a, 2021; Davis et al., 2021), addiction (Johnson et al., 2014; Bogenschutz et al., 2018, 2022), end-of-life anxiety (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016) and obsessive–compulsive disorder (Moreno et al., 2006). Although psilocybin is the drug under investigation in these trials, it is widely assumed that the external environment ("setting") and mind-set of participants ("set") modulates the acute and long-lasting effects (Carhart-Harris et al., 2018b).

Music has been recommended as an integral part of psychedelic sessions since the early psychedelic studies (Gaston and Eagle, 1970). Today music is still recommended as part of the psychedelic setting (Johnson et al., 2008) and the role of music is becoming more salient in psychedelic research (Barrett et al., 2018). It is currently unknown, whether alternative approaches, e.g., silence or nature surroundings can be used interchangeably with music, but since most psychedelic studies use music as part of the intervention setting, gaining more insight into the facilitating potential of music is important. A recent meta-analysis including ten studies concluded that music which resonates with the patient's experience supports self-exploration during the psychedelic experience (O'Callaghan et al., 2020). For example, liking the presented music is reported to promote safety and companionship (Belser et al., 2017; Noorani et al., 2018) and induce a sense of being on a personal journey (Gasser et al., 2014; Belser et al., 2017; Kaelen et al., 2018). Openness to and liking the presented music also correlate with the intensity of acute psychoactive effects of psilocybin and with better antidepressant treatment outcome (Kaelen et al., 2018), perhaps by enabling depressed patients to surrender and accept repressed emotions (Watts et al., 2017). These effects are likely compounded by the fact that psychedelic drugs themselves enhance the emotional and meaning-making response to music (Kaelen et al., 2015; Preller et al., 2017). Although music appears to be widely accepted as a central component in the psychedelic setting, the literature regarding appropriate choice of music for music programming in psychedelic therapy is surprisingly scarce. To gain a qualified perspective on the matter, researchers may look to the field of music therapy, which holds a wide body of knowledge regarding the therapeutic qualities of music and altered consciousness states.

As part of the early psychedelic research in the 1950's and 60's, music therapist Helen Bonny conducted research on the role of music in LSD sessions at Maryland Psychiatric Hospital (Bonny and Pahnke, 1972). In these sessions, she viewed the music as the primary mover of the therapeutic process, always present and actively influencing the patient (Summer, 1998). She and others found that music which matches the intensity of the drug effect could act as a non-verbal support with the capacity to facilitate relinquishment of control, emotional release, mystical experiences, and autobiographical insights (Eisner and Cohen, 1958; Gaston and Eagle, 1970; Bonny and Pahnke, 1972). Inspired by these early psychedelic studies, Bonny later developed the method of Guided Imagery and Music (GIM) (Bonny, 2002) after the prohibition of psychedelic drugs in 1970 (Oram, 2018). GIM is a receptive music psychotherapeutic method in which the patient listens to selected programs of classical music lasting 30–45 min, while exploring inner imagery with verbal guiding from the therapist (Bonny, 2002; Grocke, 2019). By use of relaxation techniques, the patient, who is laying down with eyes closed, is guided into a music-induced altered state of consciousness and invited to let the music *"take you where you need to go"* (Grocke, 2019, p.114). In GIM the music is understood to act as a co-therapist within the therapeutic triad of patient, therapist and music (Skaggs, 1992; Bonde, 2007, 43–74). Akin to the skilled therapist, music in GIM is understood to be a holding environment in which the music can regulate arousal and emotions (Grocke and Wigram, 2006; Koelsch, 2009), convey a sensed presence of an empathic 'other' (Summer, 1998; Levinge, 2015), facilitate embodiment (Beck, 2012; Bonde, 2017) and provide a sense of continuity and overall structure for experiences in altered states of consciousness (Lawes, 2017). We suggest that GIM may be a particularly relevant approach to consider when compiling a music program for use in psychedelic interventions. Based on the knowledge gained in GIM practice and from psychedelic research, we here describe our considerations and procedural steps for curating a novel music program for interventions with psilocybin.

With the intention of creating a novel music program for use in psilocybin sessions, i.e., the Copenhagen Music Program, which would accommodate a variety of cultural backgrounds, though primarily those of Northern Europe, we agreed on some overall criteria for the music program which were: (1) the music should reflect the intensity profile of a medium/high dose psilocybin, (2) the music should present cultural diversity of styles and genres, (3) vocal music pieces should avoid familiar languages, and (4) the music should avoid direct religious connotations. The procedural steps for creating the music program were inspired by (Bruscia, 2019) and will serve as the overall organisation of the article in four steps: (1) Setting up a structure for the music program, (2) Search and selection of music pieces, (3) Sequencing

1 https://clinicaltrials.gov/ct2/show/NCT03775200?term=psilocybin+phase2&type=Intr&cond=Depression&age=1&phase=1&draw=5&rank=13.

of music pieces for the music program, and (4) Indexing the intensity of music pieces in the music program. We hope that this format will provide a practical outline and inspire others in their endeavours to create music programs for psychedelic intervention.

Setting up a structure for the music program

To meet the first criteria for the music program, we wanted it to reflect the experience of a medium/high dose of psilocybin, as this dose is commonly used in psychedelic research. Ingestion of a medium/high dose psilocybin elicits profound changes in consciousness, which lasts around 4–6 h and unfolds through a dynamic process in several phases (Leuner, 1962; Preller and Vollenweider, 2016). Recently, this process was modelled empirically in a study of healthy volunteers, which revealed three overall experiential phases: (1) the Ascent phase; (2) the Peak phase and (3) the Descent phase (Stenbæk et al., 2021). These Ascent, Peak and Descent contours were also observed in physiological responses to psilocybin such as blood pressure and hormonal secretion (Hasler et al., 2004; Holze et al., 2022). The phenomenology of the experience is described to change through these phases as a gradual build-up of effects, including perceptual, autobiographical and psychodynamic effects at lower intensities, over symbolic existential effects with transient ego-dissolution to deep integral levels of transcendent states at higher intensities. (Leuner, 1962; Preller and Vollenweider, 2016). We therefore created a working template of the music program, organized it in these three overall phases and applied the average time period of each phase, as measured by Stenbæk et al. (2021). Based on the phenomenology described above, we then created sub-phases with specific music-psychological opportunities for progress through the overall phase. Sub-phases of the Ascent phase were named: Opening, Onset, Build to peak and Going inside, sub-phases of the Peak phase were named: Confrontation & Surrender, Plateau and Transcendence, and sub-phases of the Descent phase were named: Emotional release, Reflection & Integration, Acceptance & Relief, Celebration and Landing & Return. Inspired by Hevners Mood Wheel (Hevner, 1936), which is often used in GIM to evaluate the emotional expression of a piece of music, adjectives referring to the music-psychological qualities of each sub-phase were noted; for example, music pieces for the sub-phase Confrontation & Surrender were noted with the adjectives: expansive, challenging, intense, mystical, sacred and cosmic, and music pieces for the sub-phase Acceptance & Relief were noted with the adjectives: lyrical, tender, holding, affectionate, and heartfelt. The creation of sub-phases and descriptions of the music-psychological qualities were inspired by the work of Bonny and Pahnke (1972) and Preller and Vollenweider (2016). However, due to the scarce available data regarding the temporal unfolding of experiential content during a medium/high dose of psilocybin, the authors have partly based the descriptions of sub-phases on their own clinical experience. These descriptions should therefore be seen as propositions, which need to be empirically validated in future studies. For an overview of our description of sub-phases and their corresponding music-psychological themes together with exemplary music pieces for each sub-phase see Table 1.

Search and selection of music pieces

Based on our working template, we began the process of searching for music by focusing on the few playlists for psychedelic research, that are currently available. One playlist was created for psilocybin therapy at Imperial College, London (Kaelen et al., 2018; Kaelin, n.d.[2]) and consists of primarily neo-classical and ambient music with elements of jazz, classical and ethnic music. Two playlists were made for psilocybin therapy at Johns Hopkins University (Richards, 2003; Richards, 2015[3]; Strickland et al., 2020; Strickland, n.d.[4]) of which one consists of primarily Western classical music and the other primarily of overtone music. A last playlist that was made for psilocybin research at the Chacruna Institute included more indie, new wave and post-rock (Thomas, n.d.[5]). Apart from playlists for research, we listened to a variety of playlists made for psychedelic ceremonial work at retreat centres or within the psychedelic underground communities (i.e., Watts, n.d.[6]; Rasa, n.d.[7]), as well as a range of music programs made for GIM (Grocke, 2019; Bruscia and McShane (2014)). In our search for music, we primarily used music platforms like Spotify, ITunes and SoundCloud. Author 1 and 4 undertook the first selection of music pieces, of which each was categorized into one of the sub-phases. Each music piece that was deemed suitable according to the music-psychological qualities, underwent extensive critical listening for a range of specific details, such as the quality of sound in the specific recording and the musical performance, especially regarding presence, nerve, sensitivity, soulfulness and a general authenticity. In this respect qualities of singing voices and instruments were understood as important for the music to be engaging (Kaelen et al., 2018) and to embed qualities of an empathetic 'other' as described above (Summer, 1998; Levinge, 2015). We generally avoided well-known music- and vocal pieces with familiar language in order to offer a novel and curiosity-evoking, open experience with the music. Within the field of GIM,

2 https://open.spotify.com/playlist/6q0rnAIIxokcRlu6vRJPNX?si=6ed1a84816144904

3 https://open.spotify.com/playlist/5KWf8H2pM0tlVd7niMtqeU?si=188ef52ff5db4b77

4 https://open.spotify.com/playlist/40OOW1CBqejT3j0r56FDTS?si=481b6d13ecf04c0b

5 https://open.spotify.com/playlist/7yNhMh9EPndPBjle9Gx4Gx?si=b3b316cd0c7c413b

6 https://open.spotify.com/playlist/1LBcs5ACHGjtmRs4vAnmLh?si=ad4b0ff929384a1d

7 https://soundcloud.com/search?q=This%20Journey%20We%20Take

10.3389/fpsyg.2022.873455

TABLE 1 Phases and sub-phases of the Copenhagen Music Program.

Phase	Sub-phase	Example music description	Psychological theme	Descriptive adjectives
Ascent Phase	1A Opening	No. 2: A Fairytale Slow pace, expressive melody, lyrical, repetition of theme in beginning and end, middle piece has a more unpredictable character	Inviting the listener to begin letting go of control	Calm, melodic, inviting
	1B Onset	No. 6: Optimist Opening with drum, increasingly more dynamic and rhythmical with more unpredictable structure and harmonic tensions.	Inviting the listener to deeper awareness and movement forward	Increasingly more rhythmical
	1C Build to peak	No. 9: O Magnum Mysterium Catholic church chant, choral piece, multiple harmonic layers with a wide span between low and high pitch register, slow pace with unfolding crescendos, no clear pulse, but instead carried by breath. Harmonic lines that move smoothly between major and minor.	Inviting the listener into a sacred and lofty space	Expansive, slow, sacred, solemn
	1D Going inside	No. 11: Gorecki 3rd Symphony, mvt 1 Orchestral music and soprano, spiralling harmonic progressions with more complex and unpredictable structure, dramatic, forceful, intense, long opening and ending of bass and cello	Inviting the listener into unknown domains with opportunity to face inner conflicting material	Dramatic, forceful, dark, pushy, insisting, ambiguous
Peak phase	2A Confrontation & surrender	No. 15: Sacred Words of Liberation Deep male voices and chants, bells, no pulse, electronic "weird" sounds. A sudden fall in pitch, floating tones in keyboard	Inviting the listener into expanded awareness of self, time and space	Expansive, intense, challenging, mystical, sacred, cosmic
	2B Plateau	No. 17: Bach Komm süsser Tod Orchestral music with repeated motives in melody, slow pace, steady pulse, tenderness in musical performance	Inviting the listener to be held softly	Lyrical, affectionate, soft, holding
	2C Transcendence	No. 21: Ohm Namah Shivaaya Electronic Eastern instrumentation and deep male voice, drones and overtones, low pitch tones, harmonies that slide between quarter tones. Moving from no pulse to pulse. Repetitive with "dragged" pulse. Changing rhythmical patterns and tempo towards the end	Inviting the listener to experience transcendence	Sacred, powerful, opening, mystical, spacious
Descent Phase	3A Emotional release	No. 26. Barber Adagio for strings String quartet, slow pace, soft beginning, Stepwise ascending motion in melody, building in intensity that culminates in string choirs high register climax followed by a full silence. Slow ending with prolonged tones and slowly fading accompaniment.	Inviting the listener to experience and release emotions	Empathic, thoughtful, melancholic, emotional, lofty
	3B Reflection & Integration	No 32. Tveitt O Be Ye Heartily Welcome Arrangement for piano. Soft opening and ending, ascending movement in accompaniment, musical suggestions and melodic dialog. Crescendo in the middle section with hard and forceful phrases.	Inviting the listener to dialog with inner psychological material	Hesitant, questioning, strange, thoughtful, contrasting
	3C Acceptance & Relief	No. 38 Manukyan: Where is she Armenian duduk. Lament over drone fifth. Eastern European folk music. Music with slow pace and lyrical melodic phrases	Inviting the listener to find self-care	Lyrical, affectionate, tender, heartfelt, holding
	3D Celebration	No. 42. Jobarthe Saya Rhythmical music, African style, female solo voice (alto) with band incl. Kora, flute, bass and female choir Repetitive, predictable structure, steady pulse, slow pace	Inviting the listener to embody and celebrate the endeavours accomplished	Celebrative, rythmical, vocal, repetitious, engaging and joyful,
	3E Landing & Return	No. 60. Pärt Spiegel im Spiegel Slow pace, melody in violin and a three-note accompaniment by piano. The melody ascends and is then mirrored by a descending melody line returning it back "home" to the central pitch. Simple and predictable harmonic structure. The performance is sensitive and present, like a meditative state.	Inviting the listener to land safely back into normal consciousness	Increasingly more calm, soft, steady and predictable

The table shows an overview of phases and sub-phases in the music program, their corresponding music-psychological themes and descriptions of music features. For each sub-phase an exemplary music piece is shown to illustrate how the music corresponds to the music-psychological themes.

familiar languages are often avoided, as it may be experienced as too directive and thus distract the listener from experiencing the broader suggestions of the music's inherent qualities (Bonny, 2002).

Sequencing of music pieces for the music program

After critical listening to each music piece, we began the process of arranging the music pieces in meaningful sequences for the different sub-phases. Within the sequence of every sub-phase each piece of music would vary in regard to how its specific musical elements would serve the overall intent of the sub-phase; for example, the music could lead up to, prepare for, extend, give relief, add more variation or change direction from the overall music-psychological theme of a sub-phase (Bruscia, 2019, 401–12). The sequencing of music pieces involved a specification of the unique musical features and music-psychological quality of each selected piece in relation to the pieces surrounding it (Grocke, 1999; Bonde, 2007). To keep a record, the names of the music pieces and a description of their musical features and salient music-psychological qualities were noted in a table. To obtain a smooth transition between each of the music pieces, musical key, rhythm and sound in beginnings and endings were carefully examined and fitted together (Bruscia, 2019, 401–12), for example by connecting pieces in the same or related keys (according to the Circle of fifths) or by selecting pieces with the same basic note or one scale step up or down in modal music. Contrasts within and between music pieces and sections, such as instrumental/vocal, classical/electronic etc. were intentionally chosen to create a sense of opposing qualities, induce a sense of alertness or direct the listener in new directions (Bonny, 2002). In the same way that individual music pieces were carefully put together in sequences, sub-phases and overall phases were coordinated, until the program came together as a whole. To view the Copenhagen Music Program and the corresponding phases together with duration, tempo, key and genre of each music piece, see Table 2. The music program is available at: https://open.spotify.com/playlist/6QqL1JMtGAlw40kcMtBGDr?si=a47f1a017db74230 (Accessed January 15). After the first compilation of the music program by author 1 and author 4, all authors examined the music pieces and provided feedback both orally *via* online meetings and by commenting in the working template. During the process we repeatedly tested, revised and assessed the sequences to ensure that the original intention with the music program was met. This assessment also included approaching the music from a more affective-intuitive (Bonny, 1978) (as opposed to a cognitive, analytic) listening mode, by for example paying attention to subtle bodily and emotional reactions and by listening in an altered state of consciousness (Bonde, 2017, 269–277).

Indexing the intensity of music pieces in the music program

After the compilation of the music program, we applied a rating tool of music intensity developed in the field of GIM named the Taxonomy of Therapeutic Music (TTM) (Wärja and Bonde, 2014). The aim of applying this tool was to systematically explore whether the music program reflected the drug intensity profile of a medium/high dose of psilocybin (Stenbæk et al., 2021). The TTM consists of three prototypical music intensity profiles: (1) the Supportive, (2) the Mixed Supportive-Challenging, and (3) the Challenging. Each of these three main profiles is further divided into three sub-categories that express a continuum of intensity within the main profile. This makes it possible to rate a piece of music in one of nine sub-categories. The Supportive intensity profile consists of the following three sub-categories: (1) The supportive and safe field, (2) The supportive and opening field, and (3) The supportive and exploring field. The Mixed Supportive-Challenging intensity profile further consists of: (4) The explorative field with surprices and contrasts, (5) The explorative and deepening field, and (6) The explorative and challenging field, and the Challenging intensity profile consists of: (7) The rhapsodic field, (8) The field of metamorphosis and (9) The field of mystery and transformation (Wärja and Bonde, 2014). For a full description of music-psychological features of each of the three intensity profiles and their nine sub-categories with music examples, see Table 3.

In TTM, music intensity is understood as a compound feature of the music, including its degree of complexity, dissonance, mood and quality (Wärja and Bonde, 2014). The nature of the taxonomy is phenomenological, with each sub-category representing typical patterns of musical form, texture, dynamics and melodic-harmonic development, all elements strongly influencing the listening experience (Jacobsen et al., 2019). TTM merges music analysis with salient psychological features of the music, and thus relates to the music psychology of Kurth (1931). Intensity rating of the music pieces according to the TTM was undertaken by author 3, who noted the musical elements and psychological qualities of each piece of music in a table. Author 4 then examined the intensity ratings and in case of any discrepancies between author 3 and author 4, they would together with author 1 discuss the music piece in question in order to reach concensus. An overview of TTM intensity ratings of each music piece can be found in Table 2. Figure 1 shows the intensity profile of the music program upon a background of the three overall phases of psilocybin drug intensity.

Discussion

In this article we have described the curation of the Copenhagen Music Program by laying out a series of procedural steps and considerations rooted in music-psychological perspectives from the field of GIM. Overall, we found that these perspectives in GIM provide a language that unifies psychological concepts and musical analysis coupled with an understanding of how music can

10.3389/fpsyg.2022.873455

TABLE 2 The Copenhagen Music Program.

Phase	Sub-phase	*No.*	Music piece	Min.	Taxo-nomy	Key	Tempo (bpm)	Genre
Ascent Phase *Total time: 51:02 min.* .	1A Opening *Total time: 23:30 min.*	*1*	Pärt, A. (2019). Spiegel im Spiegel (violin and cello). [Recorded by S. Maer & S. Whitwell]. On *Classical chill: Cello*. ABC Classic. (Original work published 1978).	9:21	1	F Major	84	Classical
		2	Opsahl, J., & Opsahl, T. (2015). A fairytale. On *Unbroken dreams*. Heart to heart records.	4:31	2	G Major	92	Classical
		3	Økland, N., & Apeland, S. (2011). Sylkje-Per, variation. On *Lysøen (Hommage á Ole Bull)*. ECM.	3:58	2	D Major	54	Traditio-nal
		4	Horn, P. (1989). Shah Jahan. On *Inside the Taj Mahal I & II*. Kuckuck.	5:40	3	A Major	55 (fluent)	New age
	1B Onset *Total time: 17:02 min.*	*5*	Einaudi, L. (2019). Gravity day 1. (Recorded by L. Einaudi, F. Mecozzi & R. Hasa). On *7 days walking Day 1–7*. Universal music group.	5:27	3	A Minor	60	Contem-porary
		6	Keating, Z. (2010). Optimist. On *Into the trees.* Vertebrae productions.	5:01	3	Eb Major	71/138 (shift)	Contem-porary
		7	Keating, Z. (2010). Escape artist On *Into the trees.* Vertebrae productions.	6:34	3	D Minor	78	Contem-porary
	1C Build to peak *Total time: 10:30 min.*	*8*	Gjeilo, O. (2016). Tundra. On *Ola Gjeilo*. Decca.	3:35	3	Bb Major	71	Classical
		9	Lauridsen, M. (1997). O magnum mysterium. (Recorded by Shaw chamber singers). On *A Robert Shaw christmas: Angels on high*. Telarc.	6:55	5	D Major	74	Classical
Peak phase *Total time: 79:52 min.*	2A Going inside *Total time: 30:33 min.*	*10*	Elgar, E. (2015). Enigma variations, Op. 36: Nimrod. (Recorded by Royal philharmonic orchestra). On *Last night of the proms*. Philips.	3:46	5	Eb Major	80	Classical
		11	Gòrecki, H. (1992). Symphony no. 3, 1st movement, Lento. (Recorded by London Sinfonia, D. Upshaw). Nonesuch records.	26:47	6	E Minor	52	Classical
	2B Confrontation & surrender Total time: 30:19 min. .	*12*	Tchaikovsky, P. I. (1999). Hymn of the cherubim (From Liturgy of Saint John Chrysostom, opus 41). (Recorded by USSR Ministry of culture chamber choir). On *Universe 5*. Hearts of space.	7:36	9	Eb Minor	76	Classical
		13	Poulenc, F. (2014). Stabat mater doloroso, I. (Recorded by Capella Amsterdam, Estonian philharmonic chamber choir, Estonian national symphony orchestra). On *Stabat mater*. Harmonia mundi.	4:50	9	A Minor	72	Classical
		14	Pärt, A. (2010) Cantus *in memoriam* Benjamin Britten. (Recoded by Estonian National Symphonic orchestra). On *The very best of Arvo Pärt*. Emi.	6:48	9	A Minor	67	Classical
		15	Lama Gyurme & Rykiel, J.-P. (2007). Sacred words of liberation. On *The lama's chants - Roads of blessings/Songs of awe*. Last call records.	5:32	9	Eb Minor	62	New age
		16	Hopkins, J. (2018). Feel first life. On *Singularity*. Domino recording.	5:33	9	C# Major	71	Contem-porary
	2C Plateau *Total time: 9:29 min.*	*17*	Bach, J. S. (2016). Komm süsser Tod. (Arranged by L. Stokowski). (Recorded by Orchestre Métropolitain, Yannick Nézet-Séguin). On *Bonus track-Bach/Stokowski Choral 478*. Atma classique.	4:59	5	C Minor	70	Classical
		18	Purcell, H. (2006). Dido and Aeneas. When I am laid in Earth. Dido's lament, Z 626. (Arranged by L. Stokowski). (Recorded by Bournemouth symphony orchestra). On *Stokowski Bach transcriptions*. Naxos.	4:30	5	G Minor	73	Classical

(Continued)

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TABLE 2 (Continued)

Phase	Sub-phase	*No.*	Music piece	Min.	Taxo-nomy	Key	Tempo (bpm)	Genre
	2D Transcendence *Total time: 39:31 min.*	*19*	Von Bingen, H. (1997). O virtus sapiente (Arranged and recorded by Kronos quartet). On *Early Music (Lachrymæ Antiquæ)*. Nonesuch records.	4:32	5	E Minor	57	Classical
		20	Sawhney, N. (2015). Sacrifice. (Recorded by T. Tzarovska, J. Pook, V. Zivkovic, M. Pappenheim, & M. Yogeswaren). On *iTMOi (In the mind of Igor)*. Pook music.	6:16	6	F Minor	72	Contem-porary
		21	Russill, P. (2007). Om namah Shivaaya. On *Shakti – Tantric embrace (Shakti yoga)*. Relaxation company.	17:35	8	E Major	80/119	New age
		22	Haya Band & DaiQing, T. (2015). Ongmanibamai. On *Silent sky*. Wind music.	3:43	5	B Minor	73/101/121/71 (tempo shifts)	New age
		23	Anilah (2014). Calling the others. On *Warrior*. Not on label. https://www.youtube.com/watch?v=JUP_7jo6vlA	6:26	6	F# Minor	120	New age
Descent Phase *Total time: 208:37 min.*	3A Emotional release *Total time: 45:35 min.*	*24*	Hoppe, M. & Wheater, T. (1999). The waiting. On *Afterglow*. Heart of space.	4:15	5	G Minor	61	Contem-porary
		25	Richter, M. (2014). Mercy. (Recorded by H. Hahn & C. Smythe). On *In 27 pieces: The Hilary Hahn encores*. Deutsche Grammophon.	5:32	4	Bb Minor	91	Contem-porary
		26	Barber, S. (2004). Adagio for strings, opus 11. (Recorded by New York Philharmonic Orchestra, Leonard Bernstein). *On Barbers adagio and other romantic favorites for strings*. Sony.	9:56	6	Bb Minor	74	Classical
		27	Elgar, E. (2001). Sospiri. (Recorded by English chamber orchestra, P. Goodwin). On *Elgar Nursery suite, Dream children, Serenade, and other works*. Harmonia mundi.	5:07	5	F Major	76	Classical
		28	Pärt, A. (2006). Da pacem Domine. (Recorded by Estonia Philharmonic orchestra, P. Hillier). On *Arvo Pärt: Da pacem*. Harmonia Mundi.	5:43	5	D Major	84	Classical
		29	Garbarek, J. (1994). Parce mihi Domine. (Arranged by J. Garbarek and Hillier ensemble). On *Officium*. ECM new series. (Composed by Christobal de Morales).	6:42	2	Bb Major	81	Contem-porary
		30	Amar, A. (2006). Poem of the atoms II. On *Bab' Azîz:The prince who contemplated his soul (soundtrack)*. Naïve.	2:20	5	B Minor	69	Contem-porary
	3B Reflection & Integration *Total time: 11:27 min.*	*31*	Örvarsson, A., & Fang, S. (2020). *Engin Landamæri*. Flóra (Ost).	2:26	2	C Major	94	Contem-porary
		32	Tveitt, G. (1997). Velkomne med æra - Welcome with honour. On *Piano music - 50 folk-tunes from Hardanger, Op. 150 / 24-part inventions, Op. 2 Nos. 1–12*. Naxos.	4:01	4	G Minor	80	Classical
		33	Katchaturian, A. (1997). Gayane's adagio. (Recorded by Skt. Petersborg state symphony orchestra). On *Ballet music from Gayane, Spartacus, Masquerade*. Naxos.	5:00	6	F Minor	66	Classical

(Continued)

TABLE 2 (Continued)

Phase	Sub-phase	*No.*	Music piece	Min.	Taxo-nomy	Key	Tempo (bpm)	Genre
	3C Acceptance & Relief *Total time: 43:07 min.*	*34*	Arnalds, O. (2015). Reminiscence. On *The Chopin project*. Mercury classics.	4:28	5	C# Minor	56	Contem-porary
		35	Mahler, G. (1992). Symphony no. 5, adagietto. (Recorded by Polish national radio symphony). On *Mahler: Symphony no. 5*. Naxos.	12:07	5	F Major	80	Classical
		36	Elgar, E. (1997). Serenade for strings in E-minor, 2. Larghetto. (Recorded by Polish radio national symphony orchestra). On *The best of Elgar.* Naxos.	5:57	2	C Major	63	Classical
		37	Amar, A. (2014). Pour une femme. On *Mediterranean. A sea for all (film track)*. Long distance.	4:49	5	C# Minor	92	Contem-porary
		38	Manukyan, Y. (2000). Where is she. On *Armenian Duduk*. Karen studio/Believe SAS. https://www.melodlist.com/index.php?a=search&yti=i6TwTAA-7Qk	6:14	5	B Major	87	Traditio-nal
		39	A Filetta. (2015) Sumiglia. On *Songs and polyphony from Corsica*. Digimusikka.	4:12	5	C# Minor	70	Traditio-nal
		40	Kater, P., & Nakai, R. C. (2013). Offering. On *Ritual*. Mysterium music.	6:54	3	C Minor	80	Contem-porary
	3D Celebration *Total time: 38:19 min.*	*41*	Cissoko, A., & Goetze, V. (2012). Amanké Dionti. On *Amanké Dionti*. Mótema.	6:31	2	D Minor	79	Traditio-nal
		42	Jobarthe, S. (2020). Saya. On *Motherland - The score*. West African guild records.	3:53	2	C# Minor	91	Traditio-nal
		43	Dreamers' circus (2017). City gardens. On *Rooftop sessions*. GO´ Danish folk music.	5:06	2	G Major	81	Tradi-tional
		44	Santaolalla, G. (2014). De Ushuaia a Quiaca. On *Ronroco*. Not on label.	2:54	2	G Minor	71	Traditio-nal
		45	Curawaka (2018). He yama yo. On *Call of the wild*. Nixi music.	8:54	2	D Minor	67	New age
		46	Scheurenbrand, R. (2010). Yemanja. On *Viento Bueno*. Rainer Scheurenbrand.	5:37	2	G Minor	54	New age
		47	Arnal, M., & Barges, M. (2017). Ball del Vetlatori. On *45 cerebros 1 corazón*. Fina estampa.	5:24	2	C Minor	78	Traditio-nal
	3E Landing & Return *Total time: 70:09 min.*	*48*	Delius, F. (2002). Aquarelle (Lento). (Recorded by Royal Northern Sinfonia). On *English string miniatures, vol. 4*. Naxos.	2:12	2	A Minor	72	Classical
		49	Massenet, J. (1995). Sous les Tilleuls (from Scenes Alsaciennes). (Recorded by New Zealand symphony orchestra). On *Massenet orchestral suites.* Naxos.	4:59	2	Bb Major	63	Classical
		50	Ashana (2009). Soulmerge. (Recorded with T. Barquee). On *Jewels of silence: Meditations on the chakras for voice and crystal singing bowls.* Angelic tones/ Barkawitz music.	9:36	1	E Major	63	New age
		51	Portman, R. (2020). Much loved. On *Ask the river*. Node records.	4:22	2	E Major	64	New age
		52	Satie, E. (2016). Gymnopedie no. 1, lent et douloureux. (Recorded by Olga Scheps). On *Satie*. Sony.	5:57	2	G Major	80	Classical
		53	Saint-Saëns, C. (1998). The Swan (from Carnival of the Animals). (Recorded by Nadja Salerno-Sonnenberg). On *The most relaxing violon album in the world ever!* Virgin.	3:05	2	G Major	95	Classical
		54	Winther, J. (2015). Om. On *Mantra*. Unisound.	5:45	1	D Minor	62	New age
		55	Vasks, P. (2015). The fruit of silence. (Recorded by Latvian radio choir, S. Klava). On *The fruit of silence*. LMIC/SKANI.	7:27	2	Eb Major	73	Contem-porary

(Continued)

TABLE 2 (Continued)

Phase	Sub-phase	*No.*	Music piece	Min.	Taxo-nomy	Key	Tempo (bpm)	Genre
		56	Bach, J. S. (2015). Adagio from toccata, adagio and fugue in C. (Recorded by Sinfonia Varsovia). On *Bach Konzerte und Transkriptionen*. Deutsche Grammophon.	3:26	2	A Minor	62	Classical
		57	Gurdjieff, G. (2004). Prayer. (Recorded by A. Lechner & V. Tsabropoulus). On *Gurdijeff, Tsabropoulos: Chants, hymns and dances*. ECM new series.	3:50	2	F Minor	83	Classical
		58	Schultz, M., & Sangha, M. S. (2014). Calma y tranquilidade. On *Simplementes satsang: Cantos et mantra (ao vivo)*. Simplementes Yoga.	7:26	2	D Minor	70	New age
		59	Pepe, A. (2019). Felicia. On *Felicia*. IIP-DDS. https://music.youtube.com/playlist?list=OLAK5uy_kFWkTSGMAaWHwQY-tgf0XErNcshTTdGv4	2:15	1	G Major	61	Traditio-nal
		60	Pärt, A. (1999). Spiegel im Spiegel (violin and piano). (Recorded by A. Malter, & V. Spivakov). On *Arvo Pärt: Alina*. ECM.	9:49	1	F Major	77	Classical

The table shows a full overview of music pieces in the music program and their corresponding taxonomy ratings together with duration, tempo, key and genre of each music piece. The music program is a mix of genres: 43.33% Classical, 23.33% Contemporary, 15% Traditional (world/folk music), and 18.33% New age music. The Ascent phase is characterized by pieces in Major keys with an increasing tempo (average 66 bpm), and a mix of genres. The Peak phase consists of pieces from mostly classical genres in Minor keys, with an average tempo of 72 bpm, including two new-age pieces that use tempo shifts up to 121 bpm. A mix of Major and Minor keys and genres and a descending tempo (average 61 bpm) are prominent in the longer Descent phase, where most Traditional and Film Music pieces are included.

be experienced in altered states (Bonny, 2002; Grocke, 2019). We also became aware of important differences between selecting music for GIM and for a psychedelic music program. In GIM, music serves as the primary mover of the process, whereas music in a psychedelic session also supports and facilitates the effects of the drug. Therefore, unlike in GIM, the interaction between music and the drug has to be taken into consideration when compiling a psychedelic music program (Kaelen et al., 2015; Preller et al., 2017). This became evident, when we used the TTM to rate music pieces for the music program, where certain new age music pieces would be rated with medium intensity even though we had placed them in the end of the Peak phase (see Figure 1). For example, we would select music with "trance inducing" features such as repetitive rhythms, overtones or drones to support the listeners' experience of the intensity of peak psilocybin effects, by providing them with a musical "anchor" (the drone and rhythm) and a sense of spaciousness (the overtones) (Hall, 2015) (e.g., music no. 20: Sawhney (2015)[8]). In this sense the music was intended as a container of the drug effects and not as the primary mover of the process in that particular music piece. Importantly, TTM was created to assess the intensity of musical structures of classical music without intake of any drugs (Wärja and Bonde, 2014), which makes it suitable for GIM music programming. We suggest it as a valuable tool, which can be developed further for use in music programming for psychedelic intervention.

The method by which we rated the music pieces with the TTM can be criticised for not incorporating interrater reliability to substantiate the consistency of the ratings. As such it must be considered a tentative rating, that needs to be validated by other studies.

The temporal unfolding of phenomenological content with a medium/high dose of psilocybin is not well described (Stenbæk et al., 2021). Most of the available research focuses on retrospective summaries of the total psychedelic experience completed at the end of the session (e.g., Griffiths et al., 2011; Carbonaro et al., 2020). This impeded our ability to make empirically based decisions about music pieces at the more detailed level of sub-phases where we had to rely on more general phenomenological descriptions (Leuner, 1962; Preller and Vollenweider, 2016). More research is needed to inform these choices of music and we suggest that a neurophenomenological approach (Berkovich-Ohana et al., 2020) may be a good candidate for this type of temporal exploration of the psychedelic experience in future studies. We also see a need for randomised controlled studies evaluating the effect of music compared to no music on the unfolding psychedelic experience. Such knowledge would inform us about the role of music in a manner that controls for the effects of the drug.

Our approach to music programming for psychedelic interventions can be criticized for being too mechanistic and not taking the element of the therapeutic relationship and the patient's choice of music into account (Read and Papaspyrou, 2021). In such a more music-centred approach (compared to a more patient-centred approach) the psychological-metaphorical structures of a piece of music are treated as having inherent causal potential for certain psychological processes (Schneck and Berger, 2005). However, we emphasize that the effect of music must always be considered in relation to the listener's history,

8 https://open.spotify.com/track/7iO9HcAP57k4XzJdA4k5Ws?si=eda08294469b43f4

TABLE 3 A taxonomy of therapeutic music – with examples from the GIM repertoire.

Intensity Profile	Sub-category	Description	Music examples	Taxonomy rating
Supportive	Supportive and Safe	Music that is reliable and predictable with no or few surprises. It will take you by the hand and lead you gently. Simplicity in musical elements and form, perhaps a solo instrument and/or one or two supporting instruments. Light moods only.	Stefan Nilsson: Nr 17, Wilmas Tema. Jan Johansson: Bandura.	1
	Supportive and opening	Music that can open up to one or two 'tiny surprises'. Music with dialoguing instruments, possibly two different themes and at least two instruments.	Steve Dobrogosz: Mass and Chamber Music, Nr 13, Resting Place. Benny Anderssons Orkester, Nr 9, Sånger från andra våningen.	2
	Supportive and exploring	Music with some dynamic tension and complexity in texture and form. Gives further support for surrender and a possibility of exploring differences. Crescendos/decrescendos and accelerandos/ritardandos. Moderate harmonic tension.	Secret Garden: Papillon. Beethoven: Piano Concerto #5, Adagio.	3
Mixed Supportive-Challenging	The explorative field with surprises and contrasts	The music often presents a non-familiar soundscape, with surprising shifts in melody, harmony and specific instrumental texture. The musical course of events contains at least one major surprise, and there is moderate harmonic tension.	Bach: *Shepherd Song*. Respighi: *Gianicola*	4
	The explorative and deepening field	This is music that invites the listener into a welldefined emotional field, a certain mood or emotion, and holds the listener there, even though this can be challenging. The music is often in a minor or modal key, expressing a 'dark' atmosphere, typically through intense and expressive melody	Bach: *Mein Jesu*. Elgar: *Sospiri*. Mendelssohn: *5th symphony*, Andante.	5
	The explorative and challenging field	Music in this category offers some surprises and contrasts, often with a rather high degree of melodic or harmonic tension. The balance is often obtained by letting the piece begin and end in a calm and supportive character/quality. The profile can also be movement towards a climax.	Bach/Stokowski: *Passacaglia and fugue in D*. Debussy: *Sirenes*. Brahms: *Violin Concerto*, 2nd movement. Rodrigo: *Concierto de Aranjuez*, 2nd movement.	6
Challenging	The rhapsodic field	The music is a sequence of often unrelated (or loosely related) musical ideas, presenting many different moods, textures, tempi and timbres. Ideas/elements can be quite elaborated or even improvisatory.	Bach: *Toccata and fugue in D*. Wagner: *Siegfried's Funeral March*. Copland: *Appalachian Spring* (excerpt)	7
	The field of metamorphosis	Music is characterized by one or a few significant ideas that are elaborated in many different ways (shape, timbre, dynamics, tempo) and even transformed into something very different from the first form.	Ives: *The Unanswered Question*. Shostakovich: *5th symphony* (excerpt).	8
	The field of mystery and transformation	Music in this category cannot be generalised. However, it is often music that is intended to describe, express or facilitate transformative or mystic states of consciousness. The tempo is often slow, the mood predominantly dark, sombre or solemn.	Bach: *Crucifixus*. Rachmaninov: *Isle of the Dead*. Gorecki: *3rd symphony*, 2nd movement. Mahler: *Der Abschied* (excerpt from *Das Lied von der Erde*).	9

The table shows a full description of the three intensity profiles and their nine sub-categories in the taxonomy. Reprinted with permission from Bonde, L.O. and Wärja, M.

preferences and the cultural and social context of the listening experience (Summer, 2011; Bonde and Blom, 2016, 207–234). We do not understand the music effect as being causal in itself but view the role of the music as that of *inviting* the listener into a certain domain, which will be experienced in an individual manner by every listener (Bruscia, 2000). Importantly, a patient's reactions to the music during a session can at times be an expression of a conflict that holds therapeutic significance [akin to the process of transference to a therapist (Bruscia, 1998)], in which case the therapist can support and encourage the patient to stay with the music and engage the conflict (Bonny, 2002; Beck, 2012; Grob and Grigsby, 2021).

When working with ethnic minorities or racial trauma, some authors have suggested that the music choice can amplify intercultural power dynamics in the therapeutic relationship (Michaels et al., 2018). Recent studies suggest that individualized music selections may hold some promise (Kaelen et al., 2018; Strickland et al., 2020), and within GIM, culturally adapted music programs have been shown to engage listeners in exploring and reconnecting to their cultural roots

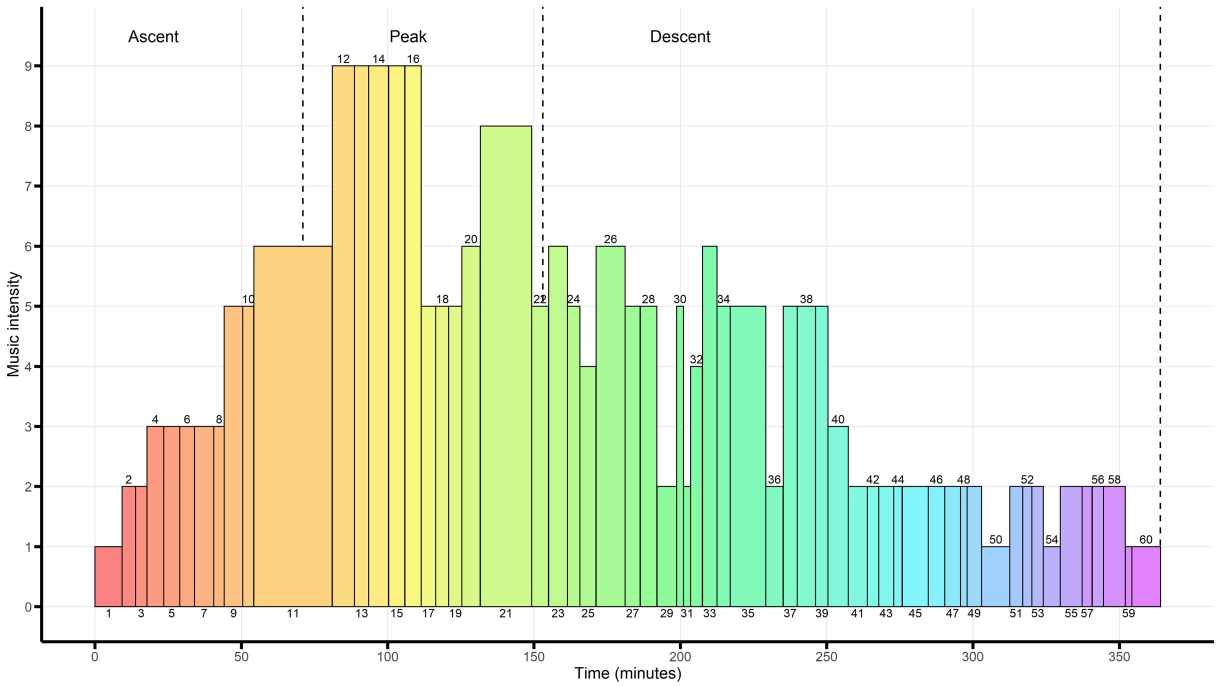

FIGURE 1
Intensity profile of the Copenhagen Music Program. Illustration of each of the 60 music pieces in the music program with intensity indicated on the y-axis and duration in time on the *x*-axis. Intensity of the music is measured by the Taxonomy of Therapeutic Music. Average time of the Ascent, Peak and Descent phases for a medium/high dose of psilocybin is indicated by the vertical dotted lines. Numbers in the figure refer to the place of each music piece in the music program. These numbers can also be found in Table 2 which provides a full overview of all the music pieces.

and identity (Swamy, 2018). However, the effect of using culturally adapted music programs in psychedelic-assisted therapy remains to be evaluated in future trials. If a therapist chooses to apply music from cultures foreign to them, it is advised that the therapist familiarize themselves with the function and cultural meaning of the music pieces, not to inflict unwanted associations in the listener (Short, 2005).

The Copenhagen Music Program was intended for possible use in psilocybin research, and although it was tailored to a medium-high dose of psilocybin, the procedures of curation can be modified and applied to music programming for other psychedelic substances, such as LSD, Ayahuasca or empathogens like MDMA.

Conclusion

The procedural steps and music psychological considerations behind the creation of a new music program, i.e., the Copenhagen Music Program, for psilocybin treatment was described in the current paper. Music selection was based on perspectives from GIM, and the TTM was presented and discussed as a possible assessment tool of music intensity. We found that GIM-perspectives provided a helpful framework for understanding the possible therapeutic role of music in psychedelic interventions. This approach may inspire others in curating music programs for psychedelic therapy and research. More music programs and theory developments are needed along with empirical testing of music programs to gain a better understanding of how music may complement and support psychedelic intervention.

Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

CM, DS, and BB contributed to the conception of the work and wrote the first draft of the manuscript. CM and BB conducted the first working template of the music program. CM, LS, LB, BB, and DS contributed to the analysis and interpretation of the individual music pieces and the final compilation of the music program, critically reviewed the manuscript and approved the

final submitted version. All authors contributed to the article and approved the submitted version.

Funding

The project was supported by The Independent Research Council Denmark (grant number 9058-00017A) and The Health Foundation (grant number 21-B-0358).

Acknowledgments

We gratefully acknowledge the assistance of assistant professor in biostatistics Brice Ozenne for technical and advisory support with the graphical representation of the music program.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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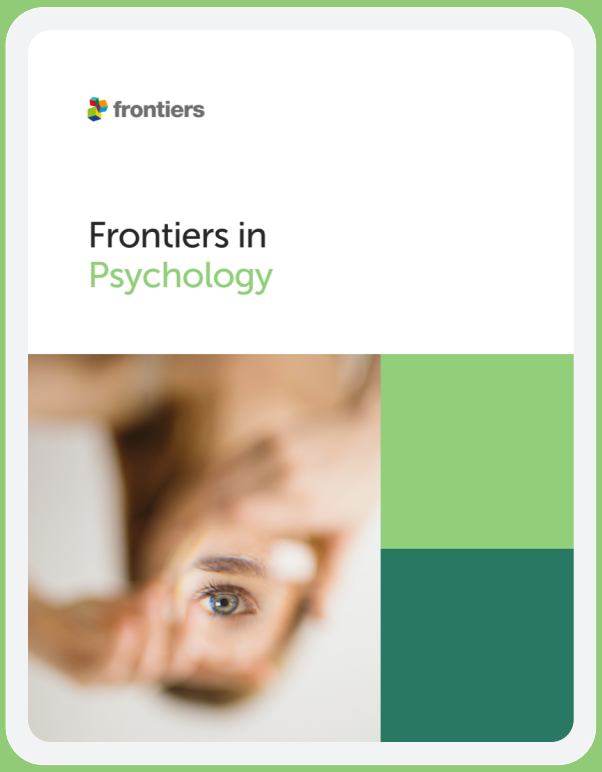

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