



Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame

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ABSTRACT

Psychedelic-assisted therapy is based on the premise that psychedelic substances can act as catalysts or adjuncts to psychotherapeutic processes. Recent clinical trials involving psychedelic-assisted therapy have generally employed a similar three-part structure consisting of preparation, support during the dosing sessions, and subsequent “integration.” However, the content of these sessions and the frame through which the therapists approach participants and understand the clinical process has thus far been inconsistent among studies. In designing a manualized therapy protocol for a small clinical trial of psilocybin-assisted therapy for major depressive disorder, our group sought to delineate an explicit and replicable, evidence-based model that intentionally builds upon both the neurobiological actions of the medication and the phenomenology of the drug experience. Having identified considerable concordance in proposed mechanisms of change between Acceptance and Commitment Therapy (ACT) and psilocybin therapy, we employed ACT as an overarching psychotherapeutic framework. We hypothesize that the psilocybin experience can provide direct experiential contact with ACT processes that increase psychological flexibility, and that these deeply felt experiences may in turn be reinforced during ACT-informed follow-up therapy sessions. In this paper, we describe the rationale for selecting ACT, areas of potential synergism between ACT and psilocybin-therapy, the basic structure of our treatment model, and limitations to this approach.

1. Introduction to models of psychedelic-assisted therapy

The classical psychedelics are a group of substances that produce characteristic alterations in cognition, perception, and emotion primarily through agonism of serotonin 5HT-2A receptors in the brain (Nichols, 2004). This set of substances includes lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), and mescaline among others. The term psychedelic, coined in 1957 by Humphrey Osmond, means “mind-manifesting” in Greek and refers to the capacity of these substances to broaden awareness of and interest in one's inner life (Osmond, 1957). Throughout the 1950s and 1960s, researchers investigated the therapeutic potential of psychedelic substances until their classification into the most restrictively regulated drug schedule of the United States Controlled Substances Act (Schedule I) in 1970, at

which point research slowed substantially (Belouin & Henningfield, 2018). In recent years, there has been a revitalization of interest in the therapeutic use of psychedelic substances and multiple lines of evidence suggest they have the potential to induce clinically beneficial changes in a variety of mental disorders (Garcia-Romeu, Kersgaard, & Addy, 2016).

While a variety of biological and psychological mechanisms of action for psychedelic therapy have been proposed, most researchers and therapists have operated under the assumption that the powerful subjective and experiential effects of psychedelic substances play an important role in therapeutic outcome, in addition to their direct pharmacologic effects. It is well-established that subjective effects are highly variable and seem to be strongly influenced by psychological and environmental factors, commonly referred to as “set and setting” (Leary,

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Metzner, & Alpert, 1995). “Set” refers to the mindset and intention of the individual prior to the experience. This includes their beliefs, hopes, fears, traumas, personality and temperament, as well as their expectations and fantasies about psychedelic experiences. In the context of clinical research, the participant's attitude toward the research setting, the medication, and the therapists, as well as expectations for relief also constitute important parts of the participant's set. “Setting” refers to the physical space and therapeutic environment in which one experiences the drug effects. This includes the therapists or guides, as well as factors such as music, artwork, and safety equipment. Most clinical research with psychedelics emphasizes the importance of set and setting to maximize safety, reduce the risk of harmful experiences, and enhance therapeutic response.¹

The term “psychedelic-assisted therapy” refers to a particular mode of using psychedelic substances in which the subjective and psychological effects of the drug play a significant role in the psychotherapeutic intervention. Traditionally, psychedelic-assisted therapy is comprised of three parts: preparation before the psychedelic dosing sessions, support during dosing sessions, and integration sessions afterwards. Preparatory sessions aim to accomplish several important tasks. Therapists develop therapeutic rapport with the participant and provide psychoeducation regarding the psychedelic experience and the therapeutic approach. Logistics for the dosing session are discussed and acceptable boundaries of interaction between the participant and the therapist are delineated. Participants are also assisted in setting intentions for their dosing sessions. Support refers to the largely nondirective stance taken by therapists while accompanying participants during the drug session itself. In recent psilocybin clinical trials, therapists have generally encouraged participants to have an inward directed experience and provided emotional support for engaging with difficult thoughts, sensations, or memories that arise. They also ensure safety and assist the participant in meeting any immediate needs. The integration phase usually begins the day after the dosing session and involves thoroughly reviewing the participant's experience during the dosing session and, in some cases, applying therapeutic techniques to reinforce particular aspects of the experience in order to sustain desirable patterns of thought and behavior. In other words, integration can be understood as the continuation of a therapeutic process that began during preparation sessions, and intensified during a psychedelic experience.²

While most clinical trials of psychedelic therapy have followed this basic model, the content of the preparation and integration sessions has varied considerably among protocols, based on the condition being treated as well as the therapeutic orientation of the researchers and therapists. Importantly, some studies have employed non-specific supportive psychotherapeutic models while others have incorporated elements of evidence-based, condition-specific therapies. An example of the latter is a study of psilocybin-assisted therapy for alcohol use disorder underway at New York University School of Medicine, which integrates elements of Motivational Enhancement Therapy into the familiar structure of preparation and integration sessions (Bogenschutz & Forcehimes, 2017). Numerous forms of psychosocial interventions could potentially be compatible or adaptable for use in psychedelic-assisted therapies, provided there is some theoretical synergism with the pharmacologic treatment to produce desired therapeutic outcomes.

In contrast, supportive models of psychedelic therapy are not linked to particular therapeutic orientations, nor do they target the specific disorder being treated. Instead, they provide containment, safety, and clear guidelines to help participants navigate the psychedelic

experience. Thus, the clinician is not referred to as a “therapist” but instead is named a “sitter,” “guide,” “facilitator,” or “monitor.” Some large-scale clinical trials of psilocybin treatment for major depressive disorder currently being implemented are employing nonspecific models of “psychological support” (Carhart-Harris et al., 2016). While this decision reflects research priorities in drug efficacy trials aiming to isolate drug effects from therapy effects, it also relates to the reality that it is not clear “how best to integrate the psychedelic experience into treatment models designed to have specific therapeutic effects, for example, to ameliorate the symptoms of a specific disorder” (Bogenschutz & Forcehimes, 2017). While we do not question the possibility that psychological support models may facilitate healing experiences with the potential for internally generated self-repair, we see numerous compelling reasons to employ an explicit therapeutic modality in the psilocybin-assisted treatment of research participants with major depressive disorder.

First, we feel that an important therapeutic opportunity is lost when a condition-specific treatment modality is not employed in the overall course of psychedelic therapy for moderate to severe diagnosed mental disorders. Major depressive disorder is a complex, vexing, chronic condition that is best understood in neuroscientific and cognitive and behavioral and social dimensions. Thus, the notion that a non-specific, supportive psychosocial container is the best method to address such a complex clinical situation seems highly specious, and reinforces a “magic bullet” approach to psychedelic therapy. Whatever changes that spontaneously emerge from the intense psilocybin experience will inevitably be met with deeply ingrained patterns of thinking and behaving. These are unlikely to be permanently erased by even the most intense psychedelic experience. Setting the groundwork for the psychedelic experience to reveal certain types of psychological processes and insights during preparatory sessions and reinforcing understandings of content that emerges along specific therapeutic lines may amplify and lengthen the duration of effect. As we will discuss, this is our intention for including ACT as a therapeutic frame in our study.

Second, failure to outline a coherent therapeutic approach with standardized therapy procedures presents a problem for controlled research. Without selecting and implementing a particular therapeutic approach, variability between study therapists' styles and interventions goes unaccounted for, as each is likely to employ his or her own intuitive therapeutic modalities at different times and in different ways with different participants. Thus, we believe it is more scientifically rigorous to proactively outline a therapeutic approach and structure, acknowledging there will be some inevitable variability in session content, rather than to refrain from delineating these variables at all.

Third, we concur with the NIH-endorsed approach that research “interventions to change health behaviors ought to be guided by a hypothesis about why the behavior exists and how best to change it” (Nielsen et al., 2018). Most psychotherapies provide answers to both of these questions. In the case of major depressive disorder, we have a panoply of theories regarding etiology and treatment, reflecting the evident truth that depression can be understood meaningfully within many different discourses (Parker, 2005). For these reasons, at the very beginning of our study, we deliberated on several empirically studied depression treatments for our therapists to employ during the course of the study.

2. Selection process of therapeutic modality

We began the process of constructing a therapy manual for psilocybin-assisted therapy of depression by studying several manualized therapies for depression that both had an evidence base and conceptual overlap with psychedelic therapy. We specifically sought a therapeutic approach that would be facilitated by the effects of the psychedelic dosing sessions and also offer a structure for the preparation and integration sessions. The therapeutic modalities considered were: a) Weissman and Klerman's Interpersonal Psychotherapy (IPT) for

¹ See Johnson, Richards, and Griffiths (2008) for guidelines for maximizing safety and minimizing risk in human research studies with psychedelic substances.

² In this paper, we use the terminology “integration sessions” and “follow-up sessions” interchangeably.

Depression (Klerman, Weissman, Rounsaville, & Chevron, 1994); b) Frankl's Logotherapy (Schulenberg, Hutzell, Nassif, & Rogina, 2008); c) Mindfulness-Based Cognitive Therapy for Depression (Segal, Williams, & Teasdale, 2018); and d) Acceptance and Commitment Therapy (Zettle, 2007).

Our process involved outlining the following key factors for each modality: the etiology of depression (how the causes of depression are understood), the therapeutic mechanism(s) (how the therapy intends to relieve depression), targeted outcomes, and the therapeutic approach. Finally, we reflected upon how each modality may or may not relate to core phenomenological aspects of psychedelic and “mystical-type experiences” (see MacLean, Leoutsakos, Johnson, & Griffiths, 2012; Studerus, Gamma, & Vollenweider, 2010).

This process led us to ultimately select Acceptance and Commitment Therapy as our modality of choice. IPT generally conceives of depression as a result of problems in role functioning, role transition, or interpersonal deficits. We chose not to include it in our model because it is predominantly focused on external circumstances and actions. Logotherapy is based on the idea that the search for meaning is at the core of human suffering and that loss of meaning is a central factor in psychopathology. While meaning-making is an important process in psychedelic integration, we did not prioritize this approach as we felt its intense focus on meaning and language might inadvertently reinforce depressive patterns of thought and behavior. Mindfulness-Based Cognitive Therapy focuses on present moment awareness, acceptance of all that arises in the mind, non-judgment of self, and self-transcendence. All of these elements seemed congruent with how the psilocybin experience may alleviate depressive cognition. However, ACT was selected because it contains these elements in addition to a behavioral approach consisting of exploration of personal values (often lost in depression) and values-based action (also often deficient in depression). The remainder of this paper will explore the conceptual overlaps between ACT and psychedelic therapy, and how these may be harnessed in the treatment of depressive disorders.

3. Overview of Acceptance and Commitment Therapy

ACT was developed through the integration of radical behaviorism with experiential and existential approaches intended to target transdiagnostic drivers of psychological distress. The FEAR acronym describes the common targets that ACT is oriented toward: “fusion, evaluation, avoidance, and reason giving” (Hayes, Strosahl, & Wilson, 2003). The common human experience of over-reliance on thoughts and beliefs over direct experiences (i.e., fusion), the evaluation of our experiences as wanted or unwanted, and attempts to avoid both external and internal (e.g. thoughts, feelings, memories) antecedents of unwanted experiences can all amplify and create the experience of suffering. Within the context of a culture that values the pursuit of positive emotions over a life lived in accordance with one's values or a sense of deeper meaning (Ryan, Huta, & Deci, 2008), attempts to control or avoid unpleasant internal states become a major source of unhappiness and psychological distress (Hayes, Strosahl, & Wilson, 2011). Though derived within the behavioral tradition, there are a number of parallels that have been noted between ACT, mindfulness interventions, and Buddhist philosophy (Hayes, 2002), including the concept of an *observer mind* or *transcendent self*, separate from the content of the mind or conceptualizations of the self, that can be experienced. In ACT, such transcendent experiences are considered to arise from amplified contact with the learned experience of the verbal relations I-you, here-there, and now-then (McHugh, Stewart, & Almada, 2019).

The central treatment target of ACT is the development of psychological flexibility, cultivated through six core processes: present-moment awareness, acceptance of one's experiences, defusion from the literal belief in one's thoughts, values clarification, the identification of specific behaviors in the service of those values (committed action), and contact with a flexible experience of the self (self-as-context) (Hayes

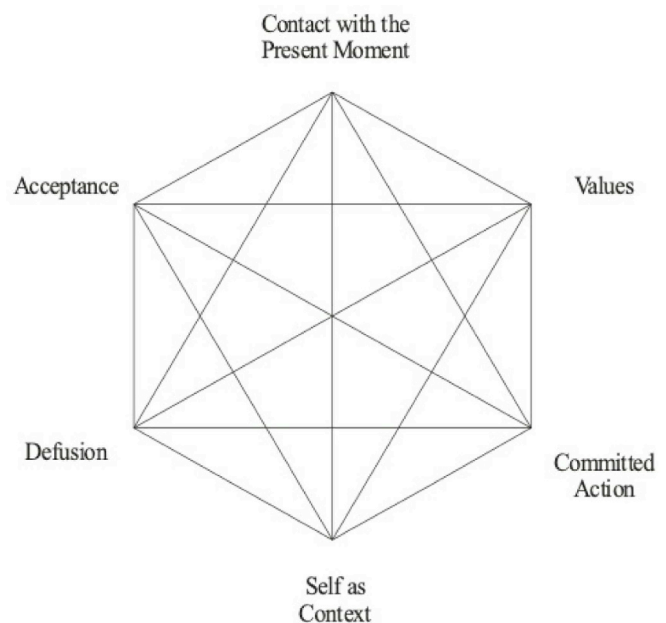


Fig. 1. The ACT Hexaflex. Copyright Steven C. Hayes. Used by permission.

et al., 2011). This “hexaflex” model is outlined in Fig. 1. In contrast, psychological inflexibility can be seen as functionally related to a range of psychological problems, including depressive, anxiety, substance disorders, and eating disorders (Levin et al., 2014). Within the framework of treating depression, it can be helpful to consider that experiential avoidance behaviors are better described as *experiential escape*; rather than attempting to control contact with unwanted experiences, the internal aspects of depression, such as guilt, shame, or painful memories of loss, lead to attempts to escape painful internal experiences that are already present (Zettle, 2007). A detailed description of how the processes of psychological inflexibility manifest in depression is beyond the scope of this article. However, as a whole, this lens offers a highly valuable description of problems encountered in depressed patients in a discourse that is humanistic and of higher heuristic value than DSM-5 descriptive diagnostic criteria; it offers a construct that describes the effects of depression on thinking and behavior in ways that are amenable to specific psychological interventions. Moreover, the evidence base for ACT in the treatment of depression is growing and several studies demonstrate that it is equally effective to traditional cognitive behavioral therapies (Forman, Herbert, Moitra, Yeomans, & Geller, 2007; Zettle, 2015).

4. Rationale: why ACT in psilocybin-assisted therapy of depression

In this section, we will describe how we conceived of ACT principles as complementary and synergistic with those of psilocybin therapy. First, we will discuss how ACT and our conception of psilocybin therapy share several key differences from traditional pharmacological approaches to depression (Sloshower, 2018). In the current era of biological psychiatry, mental illnesses like depression, schizophrenia, as well as addictions, are often conceptualized as brain diseases resulting from aberrant neural circuitry and chemical imbalances. To address brain-based pathology, psychiatrists primarily prescribe medications and deliver other interventions, such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS), that target brain circuits, levels of neurotransmitters, and neuroreceptors. In this model, the patient is positioned as a passive recipient or consumer of such treatments, tasked only with adhering to the treatment regimen and reporting their response. Additionally, conventional pharmacological approaches to

depression primarily target signs and symptoms of depression, but do not address underlying psychological, emotional, social, and spiritual causes of depressive suffering.

ACT, like most psychotherapies, differs from pharmacologic approaches in several important ways. First, it actively engages the participant in the process of recovery. For instance, patients engage in mindfulness practices, values clarification exercises, as well as behavioral activation. Second, ACT does not explicitly set as its goal the amelioration of symptoms of depression or any other specific condition. Rather, ACT targets the more complex construct of psychological flexibility as discussed above. Part of increasing psychological flexibility involves acceptance of internal and external discomfort, which perhaps paradoxically for some patients, involves decreased avoidance of unpleasant thoughts and emotions, and instead, fully experiencing them with openness and acceptance. The desired outcome is to live a full, meaningful life. Doing so may indirectly lead to a reduction of depressive symptoms.

Similarly, we conceive of psilocybin-assisted therapy as also requiring the active engagement of participants in their own healing. We question the view of psychedelic therapy as a “magic bullet” intervention, requiring only the safely contained dosing of the medicine by the suffering participant. Certainly, psychedelic substances may have beneficial pharmacological effects that are independent of set and setting or therapeutic approach. For instance, recent studies suggest that psychedelics can alter functional connectivity in a manner that disrupts stable spatiotemporal patterns of brain activity and increases communication between brain regions that are usually isolated (Carhart-Harris et al., 2014; 2012; 2017). Additionally, the research study of which the ACT protocol described here is a part³ is further investigating the hypothesis that psilocybin induces a transient neuroplastic brain state (Ly et al., 2018). While these pharmacological effects may inherently confer some degree of symptom relief or benefit, we suggest that the full potential of psychedelic therapy is more likely to be unlocked when the participant is actively engaged in a multifaceted therapeutic process of interrupting deep-seated pathological patterns of thought and behavior through integrated neurobiological and psychosocial intervention. This biopsychosocial approach (Engel, 1980) is especially important when working with chronic depressive pathology characterized by deeply ingrained rigid self-criticism, hopelessness, experiential avoidance of pain, and abandonment of valued actions. Thus, it is our hypothesis that psilocybin-assisted therapy of depressive disorders can confer more meaningful and longer lasting benefits by thoughtfully infusing ACT principles into the course of psilocybin therapy.

In order to achieve this, we constructed our therapy protocol according to the theory that the experience of moderate to high doses of psilocybin, with preparatory priming and psychoeducation, can provide direct experiential contact with the ACT processes known to increase psychological flexibility (McCracken & Gutiérrez-Martínez, 2011) and that these deeply felt experiences may in turn be reinforced during ACT-informed therapy sessions. For example, the intensity of the psychedelic experience may bring the participant directly and forcefully into contact with the present moment via all the thoughts, sensations, emotions, and memories that arise. These experiences are generally perceived as occurring beyond conscious control, often as a stream or flood of consciousness.⁴ Participants are encouraged to surrender to their experience during drug sessions, or to “trust, let go, and be open” (W. A. Richards, 2015). The release of tension that may be experienced when this is done can serve as a deeply felt experience of the ACT principle of acceptance. Another aspect of psychedelic experience is the

alteration of self-perception towards an experience of unity, or at its extreme, ego dissolution (MacLean et al., 2012). This may allow the experience of self-transcendence; an experience of the self that is larger than a familiar depressive identity, and thus, not as strongly identified with depressive cognition and self-critical, pessimistic, ruminative narratives. From this spacious vantage point, the participant may have an intensely felt experience of self-as-context in which the self is perceived as distinct from the thoughts that arise in the mind. Finally, it is possible for psychedelic therapy to assist people in gaining clarity of their values and priorities in life (Swift et al., 2017). The experience may reveal areas of life that have been neglected, aspects of self-care that need to be addressed, or how interpersonal relationships might be improved. Thus, there are many potential areas of synergism between ACT and psychedelic experience.

Of course, not all of these processes and experiences will emerge clearly in every psychedelic experience for every individual, and study participants with long standing depressive disorders may have particularly entrenched problems of psychological inflexibility. This suggests that ultimately, we may find that multiple psilocybin sessions are optimal for the treatment of major depressive disorder. It also speaks to the important role of preparatory and follow-up psychotherapy sessions to support the effects of the psilocybin dosing sessions. Integration sessions are almost universally recommended in psychedelic therapy protocols as a means of both making sense and creating new meaning out of the experience, and helping positive changes and insights carry forth into day to day life. While psychedelic integration is widely discussed as part of psychedelic therapy, it remains vaguely conceived, undertheorized, and may lack an operational relationship to the problem being treated. It is often a non-specific mixture of supportive listening and encouragement to engage in introspective practices, such as journaling, meditation, and spending time in nature. In the context of our study, ACT offers a framework for integration sessions (as well as preparatory sessions), which we will describe in the following section. We believe that having such a template allows therapists to meaningfully engage with familiar depressive negativism, pessimism, self-criticism and despair as they may arise during the integration period.

In summary, we propose that ACT and psilocybin therapy create a synergism as both foster the core principles of psychological flexibility. It is our hypothesis that embedding psilocybin therapy within an ACT framework may amplify the response and lengthen duration of improvement from depression by actively engaging the participant in making changes to his or her patterns of thinking and behavior. We believe these changes may be enhanced through the combined neurobiological effects and psychological experiences during psilocybin sessions, followed by active reinforcement by the therapists.

5. Constructing the therapy manual: how ACT is incorporated into the structure of psychedelic therapy

In constructing our therapy manual, we maintained the familiar structure of preparation, support, and integration sessions used in other psychedelic therapy protocols, but infused ACT perspectives, principles, and interventions into the sessions in a variety of ways.

5.1. ACT-based clinical formulation

While depressive and psychedelic narratives can be understood through a variety of different discourses, in our protocol, ACT provides a primary mode of understanding the nature of depressive thoughts, feelings, and behaviors, as well as participants' responses to psychedelic experiences. During preparatory sessions, therapists are instructed to listen to participants' histories of depression through an ACT lens, noticing examples of cognitive fusion, experiential avoidance, loss of values or other examples of psychological inflexibility. In this way, they begin to understand the participant's narrative along these ACT dimensions and identify which ACT processes on the hexaflex model are

³ Please see National Institute of Health (2018) for more information on clinical trial NCT03554174.

⁴ The organization of this emergent experience occurs at a level of consciousness that is outside awareness, and is a source of many speculative discourses.

Table 1

Sequence of therapy sessions contained in treatment protocol and ways ACT was employed in each session.

Session Information	Session Goals and How ACT is Employed
Preparatory Psychoeducation Session #1 (2 hours)	Establishment of therapeutic alliance. Therapist listening to participant's narrative of depression and treatment history to understand patterns of psychological inflexibility that are most prominent. Psychoeducation regarding the psilocybin experience, grounding techniques including diaphragmatic breathing, therapeutic boundaries (e.g. touch) and safety measures. Intention setting for medication session #1.
Medication session #1 (at 1 week)	ACT-based clinical formulation continues as therapist listens to emergent narratives and notes instances of psychological flexibility and inflexibility, especially present moment awareness, self-as-context, and experiential avoidance. In line with supportive stance during medication sessions, no significant ACT interventions or feedback provided.
Debriefing session #1 (1–2 hours, day after medication session)	Elicit complete narrative of participant's experience during medication session. Identify and explore aspects of the participant's narrative that engage with core ACT principles, as well as instances when they moved toward or away from psychological flexibility.
Debriefing session #2 (1–2 hours, 1 week after medication session)	Further review and reflection of participant's medication experience and what changes have taken place since. Begin the process of values clarification by discussing the participant's completed Valued Living Questionnaire. Discuss relative importance of valued domains of living and how they are or are not living in accordance with their values.
Preparatory Psychoeducation session #2 (2 hours, at 4 weeks)	Psychoeducation regarding the cognitive processes and behaviors that are problematic in depression from ACT perspective (i.e. cognitive fusion, experiential avoidance, reason-giving etc.). Induce “creative hopelessness” and suggest depressive patterns can be changed through an interactive process between the principles of ACT and the experience with psilocybin. Teach mindfulness practice. Intention setting for medication session #2.
Medication session #2 (at 5 weeks)	Same as medication session #1
Debriefing session #3 (1–2 hours, day after medication session)	Elicit complete narrative of participant's experience during medication session. Explore aspects of the experience in relation to ACT principles discussed previously. Consider use of metaphors derived from psilocybin experience or from ACT (i.e. house and furniture metaphor) to aid in understanding of the principles, such as self-as-context.
Debriefing session #4 (1–2 hours, 1 week after medication session)	Further review and reflections of participant's medication experience and changes that have taken place. Continue values clarification with focus on putting values into action; Consider use of the ACT Matrix, and shifting towards a more directive behavioral approach helping the participant define exactly what actions they can take to start living in accordance with their values.
Follow-up sessions #1 and #2 (2 and 4 weeks after medication session #2)	Continue to explore insights gained from the psilocybin experience and assess for changes in psychological flexibility. Consider introducing the ACT hexaflex and explore how the dosing and therapy sessions brought each ACT process to light. Reinforce relevant ACT concepts and encourage successful behavioral changes and committed actions taken. Review mindfulness practices and other concrete ways the study experience can be translated into lasting changes. Termination discussions and planning for post-study follow up care.

sites of potential change for the individual. The participant also completes the Valued Living Questionnaire (Wilson, Sandoz, Kitchens, & Roberts, 2017) at baseline, which is reviewed by the therapist for later discussion. During dosing and debriefing sessions, therapists pay attention to instances when the participant's experience either moved them toward or away from psychological flexibility. Cases of the former can serve as deeply felt reference points for more flexible and “workable” ways of thinking and behaving, which can guide the therapeutic approach during the integration period. Conversely, instances in which the participant avoided experiences of the present moment, or specific emotional states or self-concepts, can point to particular areas of the ACT hexaflex that would benefit from increased attention during follow-up sessions. Thus, ACT-based clinical formulation occurs throughout all therapeutic encounters with the participant, guiding therapeutic approach and assessment of progress in an iterative manner.

5.2. ACT-based clinician intervention

Holding an ACT formulation of the participant's difficulties and values in mind, therapists can provide feedback and use other

interventions to target particular areas of the ACT hexaflex that need more attention, such as values-based goal setting, defusion from unworkable negative thought constructs, and overcoming experiential avoidance. For example, several of our depressed participants expressed deeply held negative beliefs regarding their self-worth. In this case, the therapist may examine the ways that the participant is conflating a depressive thought with an absolute truth (fusion) and the resulting impacts on their behavior. During debriefing and follow-up sessions, therapists may evoke moments from the psilocybin sessions to reinforce lived experiences of increased psychological flexibility. For example, the therapist might say, “remember how you told me about how you were calmly watching a stream of shapes, colors, and images move through your mind for several minutes during your dosing session? That is the kind of mindful attention we hope to cultivate through everyday mindfulness practices.” One participant in our study presented with an obsessive tendency to try to articulate himself perfectly during social interactions, often resulting in avoidance and social isolation. During his dosing session, however, he became very playful with his language and body movements. The therapist was able to remind him of this openness and freedom from fear with the hope of decreasing his experiential avoidance of future social interactions.

5.2.1. Didactic explanations

There are several points in the protocol in which the therapist directly teaches and explains ACT principles to the participant. This occurs during preparatory sessions as a means of priming the participant to register elements of the psilocybin sessions as reflecting ACT-defined shifts in thinking, behavior, and awareness of values. It also may occur during follow-up sessions, as a way to provide useful tools for the participant to solidify understanding of ACT principles for self-directed, ongoing work toward psychological flexibility after their time in the research study concludes.

5.2.2. Experiential exercises

While didactic explanations of ACT principles provide a cognitive understanding of problematic patterns and potential remedies, it is also critical that participants *experience* psychological flexibility on a deeper level or derive their own understandings of the principles. We hypothesize that the psilocybin experience can provide this to some degree, especially with priming, but we also implement ACT consistent metaphors, mindfulness practices, and worksheets to deepen this experience. For instance, we use metaphors to help convey the concepts of fusion and self-as-context. We use worksheets to help participants clarify their values, as well as the “ACT Matrix” (Polk & Schoendorff, 2014) to help participants discover how their internal experiences impact their ability to engage in values driven actions. For the purposes of standardization in research, we selected a handful of metaphors, worksheets, and exercises to include in our protocol, however these could be flexibly employed by ACT trained clinicians in other contexts. Table 1 outlines the sequence of therapy sessions in our treatment protocol and some of the specific ways that ACT is employed in each session.

6. Therapist training

Once the therapy manual was completed, we devised a training program for study therapists. All therapists recruited for the study are licensed clinicians with extensive clinical experience treating patients with depression. Most had significant experience or familiarity with principles of both mindfulness and cognitive behavioral therapy, but limited experience with ACT specifically. The objective of the training program was to introduce them to core principles of both psychedelic therapy and ACT, and to train them to implement our therapy protocol. The training program consisted of pre-assigned didactic videos and readings, including *ACT Made Simple* (Harris, 2009) and the study therapy manual, followed by four day-long sessions. These in-person sessions consisted of close reading and discussion of the therapy manual, didactic teaching, and role plays. Day 1 of the training focused on essential elements of psychedelic therapy. Day 2 was spent reviewing core principles and techniques of ACT and how these are used in the therapy manual. Days 3 and 4 focused on role plays and experiential exercises, including a day long intensive retreat led by a peer-reviewed ACT trainer. Role-play scenarios provided therapists an opportunity to practice using ACT interventions and supporting participants through challenging psychedelic experiences. We consider the process of integrating the principles of ACT into psychedelic therapy to be an iterative project requiring ongoing case supervision and refinement of the protocol. Thus, regular peer case supervision sessions are being conducted with a therapist who has extensive experience conducting psilocybin-assisted therapy in a research context.

7. Discussion

The model presented here represents our best attempt to design a rational and effective therapy protocol to accompany a small clinical trial of psilocybin-assisted treatment of depression. We sought to design a bespoke therapy model that incorporates evidence-based treatment principles and intentionally builds upon both the presumed

neurobiological actions of the medication (i.e. heightened neuroplasticity and altered functional connectivity) and the phenomenology of the drug experience in order to achieve more efficacious, long lasting effects. In so doing, we hoped to create a true medication-assisted psychotherapy in which the experience of the drug sessions represents the pivot-point around which the rest of the therapy revolves. It is important to highlight that this is a different concept than conventional combination or sequential therapy, which combines an antidepressant medication with a course of evidence-based psychotherapy, such as Cognitive Behavioral Therapy. In typical combination treatment models, the drug treatment and psychotherapy occur independently of one another; the content and messaging of the two therapies are generally unrelated and each could be conducted separately, even with different providers. This is not the case in psychedelic-assisted therapy, in which the two elements cannot be separated. The protocol we designed would not make sense without the medication, as each session is specially designed to either prepare the participant for the drug experience, or to transform the content of the drug experience into longer lasting changes in patterns of thoughts and behaviors. Clinically, we know that combined treatments - psychotherapy and medication - are generally more effective in treating depressive and anxiety disorders than medication alone (Cuijpers et al., 2014). We hope that our approach of rationally combining pharmacology and psychotherapy will be an important future direction for mental health treatment.

7.1. Limitations

While our limited experience using this treatment protocol with research participants suggests it holds promise, there are a number of important limitations to our approach. First, we are not currently conducting a trial comparing our approach to psilocybin treatment with psychological support only. Thus, we cannot make any definitive claims that the integration of ACT is actually more effective. We are however in the process of collecting qualitative data and self-report measures of mindfulness, changes in values, cognitive flexibility, personality, and quality of life, which we hope will shed light on which aspects of our therapy protocol are effective or helpful to participants. Another limitation is that our therapists are not highly experienced ACT practitioners and received modified training in ACT, as described above. We have now conducted two rounds of therapist training and have modified the training program, yet the optimal approach in training therapists for this work remains an open question. Particularly in research settings, utilizing tools to monitor adherence to the therapeutic model would be an important future step. Additionally, our protocol does not include the full range of possible ACT interventions. This limitation is inherent to this therapy protocol being designed for a small, placebo-controlled, within subject crossover clinical trial. For scientific reasons, we attempted to standardize the therapy protocol and provide a relatively consistent approach throughout the protocol and to each participant. For reasons related to feasibility, the number of therapy sessions was constrained and we suspect that more preparatory and follow-up sessions would be optimal. Similarly, therapy sessions in our study are conducted largely by a single therapist,⁵ as opposed to the two-therapist model used in some other psychedelic therapy protocols. As a result of these limitations, we accept that we are providing a limited form of ACT and that there are alternative, possibly superior ways that ACT could be integrated with psychedelic therapy.

7.2. Cultural considerations of ACT-facilitated psychedelic therapy

Another important potential limitation of the approach outlined here is its untested cultural relevance and acceptability among people

⁵ A study physician is also present for all experimental drug sessions and takes part in some preparatory and debriefing sessions.

of color and other marginalized and oppressed groups. This issue pertains to psychedelic therapy and research in general (Michaels, Purdon, Collins, & Williams, 2018) and to aspects of ACT in particular. The behavior analytic roots of ACT do not preclude a deep understanding of cultural contexts and histories of clients belonging to oppressed or stigmatized groups (Hayes & Toarmino, 1995) and preliminary evidence suggests that ACT may be effective with different ethnic groups (Woidneck, Pratt, Gundy, Nelson, & Twohig, 2012). Nonetheless, a number of core concepts and practices in ACT need to be utilized with caution and thoughtfulness when working with oppressed and stigmatized groups.

Due to a variety of cultural factors, people of color may not seek treatment until problems are severe, and most communities of color have taboos against sharing problems outside their community (Chapman, DeLapp, & Williams, 2018). Mental health literacy and self-stigma of help-seeking may also vary among cultural groups, and some people may not consider their difficulties as signs of a mental disorder as defined by Western psychiatry and psychology (Cheng, Wang, McDermott, Kridel, & Rislin, 2018). To use ACT effectively with people of color, therapists must be aware of these factors and account for them in order to build rapport with clients. At the onset of treatment, clients of color may expect therapists to provide expert advice to help them resolve urgent problems. Therefore, a non-directive approach could be experienced as frustrating, unhelpful, and invalidating. For this reason, a clear explanation of the mechanism of treatment is essential, especially when using a modality like ACT whose therapeutic concepts may seem foreign, mysterious, or counterintuitive. For instance, the idea of “acceptance” may be misinterpreted as a need to continually accept inequitable and hurtful treatment from others, rather than noting and allowing whatever responses are experienced as a result of such treatment. Marginalized individuals must be validated in their intersectional realities before acceptance can take place. Further, among people of color, the idea of “commitment” may be experienced as an extension of racist cultural assumptions about an unwillingness to be accountable. “Committed action” could then be more neutrally described in terms of identifying small steps to live a fuller or more meaningful life in line with participant-suggested values, eliminating any implied link with a lack of commitment and retaining the meaning of this mechanism within ACT. In sum, therapists should take care to use the language of ACT flexibly; the concepts can be described in a number of ways, and ACT protocols for topics such as chronic pain routinely excise the use of the word “acceptance” while retaining the principles in practice (McCracken, 2005).

Caution must also be used when introducing mindfulness exercises, such as meditation, as this may be misconstrued as engaging in a competing religious practice, resulting in ambivalence or refusal to engage in such activities. Fortunately, formal meditation is only one of many ways to establish contact with the present moment and is not a necessary component of ACT. All faiths have some type of contemplative practice, and it may be best to first gain an understanding of a participant's religious beliefs so that mindfulness exercises can be made congruent with their existing religious practices and worldview.

Finally, the ACT therapeutic frame permits participants to make contact with difficult internalized experiences, like racism. However, if this occurs prematurely or is encouraged in an inappropriate manner, they may feel alienated, invalidated, or drained, thereby decreasing therapeutic rapport and opportunities to deepen psychological flexibility. This exemplifies the importance of diversity training when doing this kind of therapeutic work. Therapists should be well practiced and comfortable discussing issues of racism and oppression with clients, and they should have a ready response for how ACT can be useful in navigating, resisting, and healing from the effects of discrimination. For example, a therapist can highlight that a client could accept distressing emotional responses to racism and still view their life circumstances as unacceptable (Sobczak & West, 2013).

8. Conclusion and future directions

Two of the most intriguing aspects of psychedelic-assisted therapy are imagining the ways it may be helpful across a range of psychiatric (and possibly medical) conditions and the impact it might have when integrated with existing psychosocial therapies. In general, pharmacotherapy and psychosocial therapies have existed in separate discourses from one another with mind treated as distinct from brain. As discussed in the previous sections, psychedelic-assisted therapy welds these into a single intervention with neuroscientific mechanisms and lived experience informing and actually creating one another. Intriguingly, this opens up the possibility of deepening the effectiveness of numerous treatments, and rendering certain treatment resistant conditions more responsive to intervention.

As a field, psychiatry and psychology are at an early stage of imagining how psychedelic states of consciousness may have ameliorative effects on different types of therapies for various conditions. Many questions exist about how psychedelic therapies work and how to implement them, for different individuals, with different conditions, in an optimal way (i.e. dose and frequency of medication and therapy, use of music, individual versus group administration etc.). Thus far, positive outcomes in trials of psychedelic-assisted therapies have been correlated with “mystical-type” subjective effects, suggesting a mediating role of mystical-type experiences in psychedelic-assisted treatment (Garcia-Romeu, Griffiths, & Johnson, 2014; R. R.; Griffiths, Richards, McCann, & Jesse, 2006; Ross, 2018). However, it remains unclear exactly how such experiences convey a therapeutic effect. In this paper, we link aspects of psychedelic experience with specific psychotherapeutic processes that lead to greater psychological flexibility. Thus, we would suggest that increased psychological flexibility may mediate the relationship between mystical type experiences and therapeutic response. This would help account for the preliminary efficacy of psychedelic-assisted therapies across a range of mental health disorders, as many demonstrate aspects of psychological inflexibility: the cognitive rigidity and behavioral restrictions so prevalent in obsessive compulsive disorder and autism spectrum disorder, as well as the constriction in thinking and emotion that are commonly observed in anorexia nervosa. Compulsivity and behavioral rigidity are obvious in substance use disorders, as well as behavioral addictions.

As large scale efficacy trials for psilocybin treatment proceed with the aim of rescheduling the substance for medicinal use, we believe it is critical to engage in lively and thoughtful discussions about how these substances can be combined creatively and effectively with psychotherapeutic processes and other healing modalities to optimize outcomes for patients. We hope this paper offers a cogent starting place for this discussion and look forward to iteratively refining our model based on expert and participant feedback and clinical experience.

Declarations of interest

None.

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