YALE MANUAL FOR PSILOCYBIN-ASSISTED THERAPY OF DEPRESSION

Authors
Jeffrey Guss, MD
Robert Krause, DNP APRN-BC
Jordan Sloshower, MD, MSc

Contributors
Ryan Wallace, MD, MPH
Monnica Williams, PhD
Sara Reed, MA
Anne Dutton, MA, LCSW

Yale Manual for Psilocybin-Assisted Therapy of Depression
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For information, write to Dr. Jordan Sloshower: Jordan.Sloshower@yale.edu

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TABLE OF CONTENTS

PART I: THEORETICAL FOUNDATION FOR PSILOCYBIN-ASSISTED ACT THERAPY IN TREATMENT OF DEPRESSION

1. Introduction	I.1
2. Therapist Foundation	I.12
3. Set And Setting: Therapist Preparation	I.13
4. Prior To The First Session With The Therapists	I.18

PART II: PSILOCYBIN-ASSISTED THERAPY MANUAL AND DESCRIPTION OF SESSIONS

5. Introduction	II.1
TABLE 1: Overview of Therapy Session Sequence + Ways to Employ ACT	II.4
6. Psychoeducation session #1 (2 hours)	II.6
7. Experimental sessions #1 & #2 (8 hours)	II.19
8. Debriefing sessions #1 & #2 (1-2 hours)	II.25
9. Psychoeducation #2 (2 hours)	II.29
10. Debriefing session #3 (1-2 hours)	II.35
11. Debriefing session #4 (1-2 hours)	II.38
12. Follow-up sessions #1 & #2 (1 hour each)	II.40
13. Limitations	II.42
APPENDIX A: Therapist Self-Care	II.44
APPENDIX B: Psilocybin	II.46
APPENDIX C: References	II.48

PART I

THEORETICAL FOUNDATION FOR PSILOCYBIN-ASSISTED ACT THERAPY IN TREATMENT OF DEPRESSION

1. INTRODUCTION

1.1 Goals of This Manual

The Yale Manual for Psilocybin-Assisted Therapy of Depression provides researchers and therapists with methods, structure, and areas to consider regarding the use of psychedelic-assisted therapy in the treatment of Major Depressive Disorder (MDD). In particular, this manual illustrates a mode of utilizing Acceptance and Commitment Therapy (ACT) as a therapeutic framework for psilocybin-assisted therapy of depression.

This manual is intended for use with participants in an approved clinical trial who have provided their informed consent. In this manual, the people who participate in the experimental psychotherapy sessions are referred to as "participants" rather than as "patients" or "subjects." The manual is intended for use in conjunction with an approved study protocol, contained in a separate document, describing the study design. The design of the study for which this manual was developed involves several experimental ("dosing" or "medicine") sessions with associated preparatory and integrative therapy sessions. The number and order of sessions presented here is particular to this trial.

We consider the process of integrating the principles of ACT into psychedelic therapy to be an iterative project requiring ongoing case supervision and refinement or adaptation of the protocol. As such, the number and order of sessions may be adapted, based on the needs of other research studies. Additionally, certain aspects of the manual may be adjusted to meet the needs of different studies. However, elements of the manual designed to ensure the safety of the participant(s) or therapists should be followed. Because of the adaptable nature of the information presented in this document, the authors have adopted a mostly suggestive tone, using words like "should" or "may" in describing activities. In instances where certain practices or standards must be observed to ensure safety, the authors have chosen a directive tone, using words like, "will" or "shall."

The specific goals of this manual are to:

a. Delineate the essential elements of research-based, psychedelic-assisted therapy for individuals suffering from Major Depressive Disorder, including establishing and maintaining proper set and setting.
b. Delineate theoretical and clinical approaches drawn from Acceptance and Commitment Therapy (ACT) as a platform that offers a model for understanding and depression and treating the psychological rigidity/inflexibility that is common in MDD.
c. Provide guidelines to therapists for use of this model regarding: preparation sessions (psychoeducation), dosing (experimental) sessions, and integration (debriefing and follow-up) sessions.
d. Educate therapists regarding self-care practices that support this work.
e. Educate therapists regarding inclusion and exclusion criteria, screening procedures and consenting procedures.
f. Define basic criteria required to function as a study therapist.

1.2 General Elements of Psychedelic-Assisted Therapy

The term "psychedelic-assisted psychotherapy" refers to a particular mode of using psychedelic substances in which the effects of the drug, both biological and psychological, play a significant role in facilitating a psychotherapeutic intervention. This intervention begins before the first psychedelic dosing session occurs, and continues after the final dosing session. While most clinical trials using psychedelic therapy have followed the basic preparation, support, and integration 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 writing the protocol. Nonetheless, psychedelic-assisted therapies have certain common recognizable features. This therapeutic modality places significant emphasis on set, setting, preparation, integration, the creation of a supportive therapeutic container to focus and frame the effects of the psychedelic drug, and the creation and maintenance of a strong therapeutic alliance.

Traditionally, psychedelic-assisted therapy is comprised of three parts: preparation for the dosing session, support during the dosing session, and integration following it. Preparatory sessions, occurring prior to the medication session, aim to accomplish several important tasks. Therapists must develop therapeutic rapport with the participant, gather information about the participant and their history, and provide psychoeducation regarding the psychedelic experience, the therapeutic approach to be used, and expectations of the participant's active collaboration in the process. Additionally, the sessions seek to clarify the participant's expectations of the medication session. We explain the logistics of the session (how long it will last, the type of music to be utilized) and delineate acceptable boundaries of interaction between the participant and the therapist, as well as safety measures. Support in this context refers to the affirming, largely nondirective stance taken by the therapists during the experimental drug sessions. In psilocybin trials, therapists generally encourage

participants to focus their mind inward during dosing sessions. Therapists provide emotional support and encourage the participant to engage with difficult thoughts, sensations, or memories that arise. They also assist the participant by meeting any immediate needs for comfort or safety. The integration phase usually begins the day after the dosing session; it involves reviewing the participant's experience during the dosing session thoroughly and, in some cases, applying therapeutic techniques to reinforce particular aspects of the experience so they foster sustained desirable patterns of thought and behavior. In other words, integration continues the therapeutic process that began during preparation sessions, and intensified during a psychedelic experience. The role of the therapist is to facilitate the integration process and help consolidate the newly developed mindset, including the actualization of insights and initiation of behavioral changes that foster recovery from depression.

It is a well-established principle that subjective effects from psilocybin administration are highly variable and are strongly influenced by psychological and environmental factors, commonly referred to as "set and setting" (Leary, 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 and the therapists, themselves. 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, environment and context in which one experiences the drug effects. This includes its inhabitants (therapists or guides), as well as factors such as music, artwork, and safety equipment. The relationship with the therapists is a primary determinant of the setting. Given the influence of all these factors on the participant's experience, most research with psychedelics emphasizes the importance of set and setting to maximize safety, reduce the risk of harmful experiences, and guide therapeutic response. Guidelines for maximizing safety and minimizing risk in research studies with psychedelic substances have been published (M. Johnson, Richards, & Griffiths, 2008). Recent clinical trials with psilocybin have demonstrated that its use is remarkably safe when conducted in a safe, therapeutic environment in which individuals are adequately prepared for the experience.

1.3 Theoretical Considerations of Psilocybin-Assisted Therapy for Depression

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 and Cognitive Behavioral 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. 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 is consistent with, and determined by, research priorities 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).

In "psychological support only" models, the clinician is not referred to as a "therapist" but instead is named a "sitter," "guide," or "monitor." Such nonspecific models sometimes evoke the notion of an "inner healer" that abides within the psyche of the individual person and is unleashed or brought forward by the psychedelic medicine. The job of the guide, then, is to "hold space" for this natural healing process of the individual to unfold. We do not question the possibility that a self-regulating process with some potential for internally generated self-repair may be a part of psychedelic efficacy. Likewise, we also employ a nondirective approach during psilocybin dosing sessions themselves, trusting that whatever content and processes that arise will be of therapeutic value, in an analogous manner to free association in the psychoanalytic situation. However, we see numerous compelling reasons to employ a therapeutic modality with an explicit theoretical orientation in the 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, that is, one which idealizes and fetishizes the molecule itself as the active agent that is internally powerful, isolated from its social and cultural contexts. Whatever changes emerge from an intense psilocybin dosing experience will inevitably be countered by deeply ingrained patterns of thinking, feeling and behaving and are unlikely to be permanently reconfigured by even the most intense psychedelic experience.

Setting the groundwork for the psychedelic experience to occur with a specific change intention, during preparatory sessions, and then reinforcing that approach during integration can help direct the psychedelic experience in ways that are known to be therapeutic for depression. As we will discuss later, this is our explicit intention in utilizing ACT as a therapeutic frame in our study. While efficacy trials of psychedelics may minimize the role of formal psychotherapy in order to separate drug effects from psychotherapy effects, we argue that the "support only" approach puts participants at risk for receiving suboptimal treatment.

Second, failure to specifically outline a coherent therapeutic approach with standardized and theorized therapy methods presents a problem for controlled research. Without a therapeutic approach being defined, much of what the sitters or guides do or say goes unaccounted for and leaves hidden the role of their therapeutic attitudes, fantasies, desires and fears. We do not believe that "psychological support" can be provided in a truly neutral manner; this ignores the existence of unconscious processes, unspoken consciously held attitudes, beliefs and emotions that live under the obfuscating blanket concept of bland and non-intrusive "support." The supportive interactions of monitors are likely to contain more than neutral space holding, especially while working with and bearing witness to the suffering of significantly depressed participants, with the therapists operating in a highly complex setting with their own deeply held relationship dynamics regarding psychedelics. In any scenario, each study therapist is likely to employ their own intuitive therapeutic modalities at different times and in different ways with different participants, even without an intention to. Thus, we believe it is more scientifically rigorous to proactively outline a therapeutic approach and structure, acknowledging there will be some reasonable variability in session content, rather than to refrain from delineating these variables at all and imagine that "non-specific support" is a specific, controlled intervention.

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.

1.4 Development of This Psychedelic-Assisted Therapy for Depression

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 at least some 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 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).

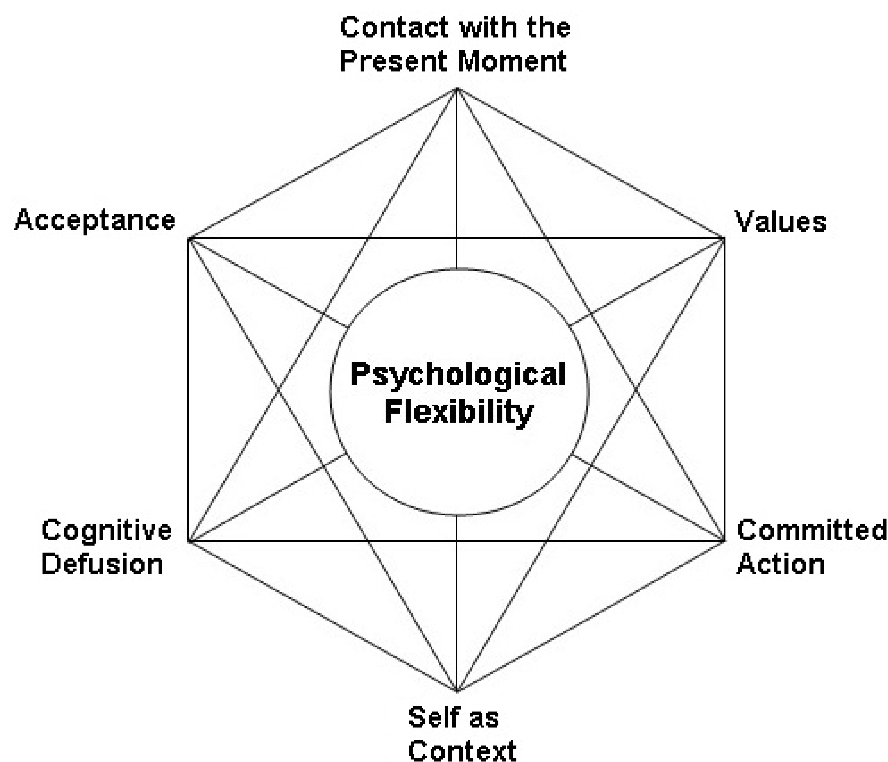
Our process involved outlining these key factors for each modality: the etiology of depression (how the causes of depression are understood), the therapeutic mechanism(s) (how the therapy intends to relieve depression), targeted outcomes (in addition to improvement of depressive symptoms), and the therapeutic approach (how the therapist engages with the patient). Finally, we reflected upon how the therapeutic modality may or may not relate to psychedelic experience and possible psychological mechanisms of psychedelic therapy.

Of the four modalities that were studied, two emerged as best suited for integration with psychedelic therapy in the treatment of Major Depressive Disorder: Acceptance and Commitment Therapy (ACT) and Mindfulness Based Cognitive Therapy (MBCT). Mindfulness-Based Cognitive Therapy had many positives, with a focus on non-judgmental acceptance of self, acceptance of all that arises in the mind, a focus on the present moment, and self-transcendence. All of these elements are represented in ACT, which offers, in addition, exploration of personal values (often lost in depression) and the need for values-based action (also, often missing in depression). Thus, ACT provided the most conceptual overlap with existing traditional approaches to psychedelic therapy as well as matching our intuitive notions of how psychedelic therapy may be beneficial in the treatment of depression.

1.5 Acceptance and Commitment Therapy in Psilocybin-Assisted Therapy for Major Depressive Disorder

ACT was developed through the integration of radical behaviorism and experiential/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 a careful focus on 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 et al., 2011). This "hexaflex" model is outlined in the figure below.

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 experiencing these unwanted experiences (the internal aspects of depression, such as guilt, shame, or painful memories of loss) we see an attempt to escape painful internal experiences that are present, leading to their persistence, rather than their elimination (Zettle, 2007). A detailed description of how the processes of psychological inflexibility manifest in depression is beyond the scope of this manual. 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)

1.6 Why Utilize ACT in Psilocybin-Assisted Therapy for Major Depressive Disorder?

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, in ACT, patients are required to 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, it 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 postulate that psilocybin-assisted therapy requires 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, with the magical appearance of an "inner healer" to do the necessary repair work. Certainly, psychedelic substances may have beneficial pharmacological effects that are independent of set and setting or therapeutic approach. 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). Our research study, which includes the ACT protocol described here[1], actively investigated 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 via 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. The ACT model involves helping patients learn skills to: a) be in the present moment, b) develop a more flexible experience of the self (self-as-context) rather than be fused to a particular personal narrative (self-as-content), c) disengage from attempts to control thoughts and emotions and instead, observe and accept them as they are (acceptance and defusion), d) to clarify values that have been lost through depression and then, e) engage in values-based action.

The intensity of the psychedelic experience may bring the participant directly and forcefully into contact with the present moment via the highly intense thoughts, sensations, emotions, and memories that may arise. These experiences are generally perceived as

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[1] Please see (National Institutes of Health, 2018) for more information on clinical trial NCT03554174.

occurring beyond conscious control, often as a stream or flood of consciousness.[2] 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, Leoutsakos, Johnson, & Griffiths, 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 occur 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, multiple psilocybin sessions may be required for the successful treatment of Major Depressive Disorder. It also speaks to the important role of preparatory and integration or 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 meaning out of the experience, and helping positive changes and insights carry forth into day-to-day life. While psychedelic integration has become a buzzword in psychedelic communities, it remains somewhat vaguely conceived, undertheorized, and, in general, longs for an operational relationship to the problem being treated. It often centers 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 template for use in integration sessions, as well as preparatory sessions with individuals who suffer from depression, which we will outline in the following section. We believe that having such a template will allow therapists to more successfully engage with a participant's familiar depressive negativism, pessimism, self-criticism, inactivity and despair as they may arise during integration sessions that follow the psilocybin dosing day.

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

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 a specific way, in making changes to their patterns of thinking and behavior. We believe these changes are a co-creation of neurobiological effects, psychological experiences, and effects of the container (ACT, the therapists and our culture) during psilocybin sessions, followed by active reinforcement by the therapists.

Note: Much of this section was adapted from Sloshower et al. (2019).

2. THERAPIST FOUNDATION

2.1 Essential Therapist Background

Therapists involved in our study were required to have:

a. An up-to-date license to practice as a psychiatrist, psychologist, master's prepared social worker, or psychiatric nurse, and
b. At least 5 years' experience treating psychiatric patients in a clinical setting.

Experience in conducting psychodynamic as well as cognitive-behavioral therapies was viewed favorably, as was experience with altered states of consciousness, including yoga, mindfulness practices, holotropic breathwork, hypnosis, flotation tank work, etc.

2.2 Therapist Training

Therapists in our research study received specialized training in treating depression with psilocybin-assisted ACT therapy. 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 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.

<u>Training methods may be adapted to suit other research studies and may include:</u>

- Attending supplemental trainings given by MAPS, California Institute of Integral Studies' psychedelic psychotherapy program
- Attending ACT trainings
- Consultation and supervision with ACT practitioners

3.0 SET AND SETTING

"…the unconscious mind is often terribly frightening; we have made much of its contents unconscious because we want nothing to do with it. It takes a strong heart, honesty, and a desire to learn and face one's problems in order to enter the dark areas of our suppressed inner self. Nothing is more helpful than the presence of a kind, loving, understanding person thoroughly familiar with the dark regions of the mind - a companion who is confident of his ability to help one navigate and resolve those regions that have been an enormous burden in the past, a person who knows the wonder of being free. The willingness to surrender to the experience and allow such resolution to proceed often results in the most valuable kind of learning about one's repressed feelings, hidden values, compulsions and aspirations, and inappropriate behavior."

~ Myron Stolaroff, The Secret Chief Revealed (2004)

3.1 Set: The Inner World of The Participant

"Set" and "setting" are concepts used to describe what the participant brings to the psychedelic situation and what they find there. "Set" refers to the conscious and unconscious parts of the individual leading up to the experience. This includes their beliefs, hopes, fears, traumas, personality and temperament, as well as their expectations and fantasies about psychedelic experiences and the therapists, themselves. In the context of clinical research, the participant's attitude toward the research setting, the medication, cultural attributions to psychedelics, the relationships with the therapists, as well as expectations for relief also constitute important parts of the participant's set.

We do not know what traits will lead people to have specific kinds of experiences, but through this study, we asked: what do people who experience major depression bring to the psychedelic experience? How can an ACT-based formulation guide the therapeutic process? Does the experience of psilocybin therapy help promote psychological flexibility?

3.2 Setting: The Outer World of The Participant

"Setting" refers to the physical space, environment, and context in which one experiences the drug's effects. Setting includes elements such as music, artwork, safety equipment, hospital, city, and state, etcetera and inhabitants of the space (therapists and participant). The participant's relationship with the therapists is a primary aspect of the setting.

The current standard in clinical psychedelic research is to create a warm, inviting, and private environment where participants can feel comfortable and safe to experience the medicine's intense effect and express themselves freely. To make study rooms more comfortable, researchers often decorate with plants, fresh flowers, artwork, warm colors, and homey furnishings (see Johnson et al. 2008 for general guidelines).

Each therapist will bring their unique combination of training and perspectives to their encounters with the participant. This includes their identity as a therapist, personal history with depression (or not), personal experience with psychedelics (or not), and experience treating patients experiencing major depression. Therapists also carry their own experiences, transferences toward the study, feelings about their home institution, transferences between therapists, and transferences between disciplines and the psychedelic community. We encourage therapists to be mindful of how their life experiences affect their emotional presence in the clinical sessions.

While one particular psychotherapeutic school of thought does not exist for psychedelic therapists, all of the practitioners in our study had significant experience working in traditional psychiatric and psychotherapeutic contexts, and training in a blend of psychodynamic and cognitive-behavioral approaches. Most had experience with mindfulness practices, including the use of mindfulness in psychotherapy. Our approach combines each therapist's background with applied ACT/MBCT principles. In this approach, it is important that all therapists receive training in treating depression from a modified ACT and MBCT point of view. This is the primary psychological framework the therapists consciously, mindfully offer.

3.3 Preparing the Physical Setting

Establishing a safe and therapeutic physical setting and mindset for the participant requires that the therapists take an active role in creating the environment. Ensure the space is conducive to the therapeutic psilocybin experience and supports the participant's ability to engage fully in their internal experience.

If possible, choose a physical setting that is private, free from interruption, and has minimal external stimuli. Make the room comfortable and, to hide or remove anything that would impart a hospital room feeling. Our study, located at the West Haven VA hospital,

utilized an office space with a couch made up like a bed, pleasing artwork, and plants (see photos). We avoided religious iconography in favor of nature imagery.

The ability to play prerecorded music through speakers as well as headphones is integral to creating the setting. The deliberate and thoughtful selection of music will affect the participant's perceptions of the setting (see the section on music below).

Although a homey feeling matters, do make the participant aware of all safety equipment in place for medical monitoring. This generally includes a blood pressure and pulse monitor and locked areas for protocol materials and records. Maintaining physical safety includes providing access to treatment for possible reactions to the medicine during or immediately after each treatment session. Most reactions can be dealt with through supportive care. However, to ensure the participant's emotional comfort and physical safety, review the use of ***rescue medications*** with the participant as described in Part II, Section 6.9.

Only conduct psychedelic-assisted therapy in a setting where Basic Cardiac Life Support (BCLS) is immediately available and Advanced Cardiac Life Support (ACLS) can be summoned reasonably quickly in the unlikely event of an acute medical problem.

During psychedelic-assisted sessions, therapists should ensure participant's physical safety by providing adequate cautions when patients move about the room or ambulate. This includes assisting participants getting to and from the bathroom, and helping participants to remain hydrated during the test day. The setting thus includes the presence of drinking water, electrolyte-containing beverages or juices, and small snacks.

3.4 Preparing Social Support Following Medication Sessions

Following a dosing session, discharge the participant from the treatment setting only in the company of a designated support person, such as a family member or friend who

understands the research project and the participant's involvement with it. The therapists need to meet or at least speak with this individual during the preparatory period prior to dosing. The therapists should assess the suitability of the support person for these tasks, which include safely accompanying the participant home, providing a safe, non-intrusive, supportive environment, responding to participant needs, and notifying the therapists of any problematic developments that need evaluation or discussion. The support person should receive education regarding the nature of the study, common and rare side effects or after effects that might emerge and advice on how to be most helpful. The support person should also be provided with contact information for both therapists and investigators as well as any other emergency contact numbers. See ***departure requirements*** in Part II, Section 6.9 for more information.

3.5 Planning for the Therapeutic Use of Music

Research into the specific types and forms of music most conducive to psychedelic-assisted therapies is still in its infancy and varying styles of music have historically been used in studies employing psychedelic-assisted therapies; from western classical music to Indian ragas to rock to ambient soundscapes. The role of the music, regardless of style, is to provide guidance and emotional support for a wide range of emotions throughout the session. Other general points relating to music used in psychedelic studies include:

- The playlist is crafted in such a way as to reflect and complement the psychedelic experience.
- Participants are encouraged to utilize the music to facilitate their journey, but should have the ability to decrease the volume or turn the music off, if they desire.
- Headphones are an ideal way for the participants to listen to the music as they create an internal experience with the music. Speakers may simultaneously play the music in the study room, thereby providing a valuable point of connection between therapist and participant during the session.
- Eye masks are generally available to participants, again to facilitate inward exploration and contemplation.

The music playlist we used in our study was created specifically for a phase 1 clinical trial at Imperial College London of psilocybin treatment for depression by Mendel Kaelen, PhD. Doctor Kaelen has conducted seminal research on the use of music in psychedelic-assisted therapies (see Kaelen et al., 2018). In developing this playlist, he considered more than the music, thinking also about the entire soundscape the organization of the playlist would create and the ways songs transition into each other.

In order to control variables across dosing sessions and between participants, we used the same playlist for all experimental sessions in the study. However, one could argue that listening to a novel selection of music during each session would more accurately control between dosing sessions for a given participant, as the experience of re-listening is different

than hearing for the first time. Another viable and more culturally considerate approach would be to develop a standardized method for customizing the music to each participant based on their cultural background and preferences.

3.6 Relationship with Therapists as Setting: The Therapists' Commitments

The therapist's responsibility is primarily to establish a well working therapeutic alliance, to support the participant's honest expressiveness, and utilize ACT treatment principles. The therapists work to support the participant's openness, self-acceptance, willingness to take action, and increased psychological flexibility. They attempt to engage with a participant's depressive way of thinking and living and access/teach strategies for change. In helping to accomplish these goals the therapist acts as empathic listeners, trustworthy guides, facilitators of self-transcendence, and also, unavoidably, each brings their own unique way of working with patients.

Psychedelic medications can have profound emotional and physical effects. To foster a therapeutic mindset and contribute to a collaborative therapeutic rapport, the therapist and participant prepare for each experimental session through numerous specific agreements discussed prior to the session:

1. The therapists commit to providing adequate preparation time and focused attention to the treatment during preparatory, dosing, debriefing and follow-up sessions.
2. Therapists and participant agree on boundaries regarding touch. Any sexual or erotic touch is explicitly forbidden. The participant is asked to agree to refrain from self-harm, harm to others, and harm to property. Participants also must remain appropriately clothed throughout the session. The participant is asked to agree to follow the therapist's recommendations regarding safety.
3. At least one of the therapist or sitters will be present in the room at all times throughout the entire psychedelic-assisted session. Both therapist and sitter commit to remain in the room with the participant throughout the psychedelic-assisted sessions except for brief periods for restroom breaks or other such needs.
4. Along with the supervising physician, the therapists will assess the participant to determine mental status and stability to leave at the end of the dosing session.
5. The therapists commit to being available by phone or text throughout the course of the study for emergency.
6. The therapists accept the extensive time commitment that may be required (exceeding the expected length of dosing sessions) should the participant need additional support.

4. PRIOR TO THE FIRST SESSION WITH THERAPISTS

4.1 Screening and Consent

The study investigators and study research staff conduct the screening and consenting process. For our study, the therapists did not participate in these sessions. It is worth noting that establishing a trusting rapport with the participant begins with the first contact made; this includes all screening and consenting conversations as well as sessions with therapists. Thus, the investigators, study physicians, and research staff are part of the rapport building process.

The screening and preparatory period is the time to gather participant history and to begin establishing an effective therapeutic alliance. It provides an important opportunity for the therapists and study staff to address the participant's questions and concerns, and to prepare the participant for psychedelic-assisted sessions by familiarizing them with the logistics of the sessions and the therapeutic approach that will be used, as well as establishing a tone of gentle concern, professionalism and organization. This should be done with the intention of helping the participant feel a sense of safety and comfort in the therapeutic setting. It is also an opportunity to model attitudes that will be important during psychedelic-assisted sessions, such as unhurried pacing, open ended curiosity about the participant's present moment experience (including their somatic experiences), respect for the participant's boundaries and innate wisdom about their own healing process. In clinical research, there are quite a number of questionnaires and forms to be completed, especially during the preparation period. Study staff should strive to have the necessary forms completed while still allowing time to foster a therapeutic setting and deepen the therapeutic alliance.

4.2 Prerequisites and Contraindications

Prior to enrolling in the study, participants will be given written information about the clinical trial. Participants will be given ample time to ask questions and discuss the meaning and ramifications of informed consent with staff prior to signing the Consent Form.

4.3 Commitments from The Participant (Part of the Consenting Process)

1. The participant agrees to:

    a. Attend all preparatory therapy and follow-up sessions,
    b. Complete the evaluation instruments, and
    c. Comply with dietary and drug restrictions.

2. Participants are not required to complete the study; they may withdraw consent and leave the study at any time, except during a medicine dosing session. Follow-up assessments may be performed if a participant drops out, but has not withdrawn consent.
3. The participant will be required to agree that they will remain within the treatment area until completion of each session. This means they cannot leave until the study physician and the therapists have affirmed the participant's readiness and stability to leave. (The therapists will assess the participant for signs that the psychedelic effects of the medication have ceased. The therapists and study physician will clinically assess the participant's ability to leave safely and function without medical supervision.)
4. Participants must commit to refrain from self-harm during the study, to communicate suicidal ideation to their therapists or seek emergency room care if self-harm is imminent. If they cannot make this commitment, they will be excluded from the study and referred to active clinical assessment and treatment.
5. Participants should be aware that clinical trials of psychedelic-assisted therapy often generate attention from the media. While such communication always remains the participant's choice, we encourage the participant to complete the study before engaging in public/media discussions of their experience. We encourage each participant to discuss this decision with the therapists, in order to emotionally prepare for the experience of being interviewed by the media and its aftermath.

PART II

PSILOCYBIN-ASSISTED THERAPY MANUAL AND DESCRIPTION OF SESSIONS

5. INTRODUCTION

Part II outlines the content and goals of each participant encounter as designed for this particular clinical trial. In constructing our therapy protocol, we maintained the familiar structure of preparation, support, and integration sessions used in other psychedelic therapy protocols. However, we infused the sessions with ACT perspectives, principles, and interventions in various ways. Practitioners who use this manual to guide other research or clinical practice may find adding sessions or renaming sessions makes sense.

The overall goal of combining psilocybin-assisted therapy for depression with ACT is to provide a therapeutic framework that will enable participants to alter patterns of cognition and behavior that characterize depression, while increasing values-based active engagement in the world. Fostering these two types of change (which characterize psychological flexibility) through the interactive effects of the therapy and the medication sessions is the central hypothesized mechanism for change and improvement from depressive symptoms. In this manual, this approach is implemented through ACT-based Clinical Formulation and ACT-based Clinician Intervention during the psychoeducation, experimental, and debriefing/follow up sessions.

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 sites of potential exploration and 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 these particular areas that might 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 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 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 perfectly during social interactions; this often resulted in anxious avoidance and social isolation. During their dosing session, however, they became very playful with their language and body movements. The therapist reminded them of this openness and freedom from fear with the hope of decreasing their experiential avoidance of future social interactions. The important part was not "making the participant wrong" for having a fixed belief about themself, but rather reinforcing their direct experience of playfulness and ease of expression.

Didactic Explanations

At several points in the protocol, the therapist directly teaches the participant about ACT principles, including during:

- Preparatory sessions, to prime the subject to register elements of the psilocybin sessions as reflecting ACT-defined shifts in thinking, behavior, and awareness of values; and
- Follow-up sessions, to help the participant solidify their understanding and implementation of ACT principles in their ongoing work toward psychological flexibility (after conclusion of their time in the research study.)

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 to connect their experience with the concepts. We hypothesize that the psilocybin experience can provide this to a significant degree, especially with priming. However, we also implement ACT consistent metaphors, mindfulness practices, and worksheets to deepen this experience. 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 to employ ACT in each session.)

Table 1: Overview of Therapy Session Sequence + Ways to Employ ACT in Each Session

Session Name	**Session Overview and Ways ACT is Employed**
Preparatory Psychoeducation Session #1 (2 hours)	Therapist aims to establish therapeutic alliance through: • 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, therapeutic boundaries (e.g., touch) and safety measures; • Teaching grounding techniques including diaphragmatic breathing; • Assisting the participant in setting an intention for medication session #1.
Medication Session #1 (at 1 week)	• In line with supportive stance during medication sessions, the therapist does not provide significant ACT interventions or feedback. • 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.
Debriefing Session #1 (1-2 hours, day after medication session)	• Therapist elicits complete narrative of participant's experience during medication session. • Identify and explore aspects of the participant's narrative that engage with 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)	Therapist and participant continue to review and reflect on the participant's: • Psilocybin experience, including any emotional, mental, or lifestyle changes that followed the dosing session. • Values, by discussing the participant's completed Valued Living Questionnaire, and relative importance of valued domains of living. • Experiences living in accordance with or not living in alignment with their values.

Preparatory Psychoeducation Session #2 (2 hours, at 4 weeks)	• Conduct psychoeducation regarding:
	    o The cognitive processes and behaviors that contribute to depression from an ACT perspective (i.e. cognitive fusion, experiential avoidance, reason-giving etc.);
	    o How depressive patterns can be changed through an interactive process between the principles of ACT and the experience with psilocybin; and

	○ Mindfulness practice. • Through this process, the therapist aims to induce "creative hopelessness." • Assisting the participant in setting an intention 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)	Therapist elicits complete narrative of participant's experience during medication session, exploring: • Aspects of the experience in relation to ACT principles discussed previously. • 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)	Using the ACT Matrix if helpful, therapist and participant continue to review and reflect on the participant's medication experience and changes that have taken place, to explore: • What the participant values most; • How to put their values into action. Therapist may shift towards a more directive behavioral approach to help the participant to define precise 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)	Therapist continues to explore and reinforce; • Insights gained from the psilocybin experience while assessing for changes in psychological flexibility; • How the dosing and therapy sessions brought each ACT process to light, using the ACT hexaflex; • Relevant ACT concepts • Successful behavioral changes and committed actions taken; • Mindfulness practices and other concrete ways the study experience can be translated into lasting changes. Therapist leads termination discussions and plans for post-study follow up care for the participant.

6. PSYCHOEDUCATION SESSION #1

When people see some things as beautiful,
other things become ugly.
When people see some things as good,
other things become bad.

Being and non-being create each other.
Difficult and easy support each other.
Long and short define each other.
High and low depend on each other.
Before and after follow each other.
~ Lao Tzu, Tao Te Ching

By this point, the participant has completed the screening and consenting stages and is meeting their primary psychedelic therapist(s) for the first time. The tasks described in this section need to be accomplished during the first Psychoeducation Session, which lasts about two hours, or during the preparatory period leading up to the first dosing session. Due to practical and logistical study design reasons, during our study, we covered all of the tasks in one lengthy session. However, this content may be covered more effectively over the course of several preparatory sessions.

6.1 Internal Agenda for Therapists During Psychoeducation Session #1

6.2 Building Rapport and Therapeutic Alliance

6.3 Review the Structure of Today's Session

6.4 Evoke and Listen to The Participant's Lived Experience of Depression

6.5 Evoke and Listen to The Participant's Lived Experience of Psychopharmacologic Treatment

6.6 Understand The Participant's Preconceptions About Psychedelic Experiences

6.7 Listen for ACT "Misdemeanors" and Begin Constructing an ACT-Based Clinical Formulation

6.8 Intention-Setting

6.9 Educate The Participant Regarding Psilocybin Dosing Sessions

a. common experiences with psilocybin script
b. difficult experiences script
c. ski slope script
d. therapist interventions script
e. grounding techniques scripts
f. rescue medications
g. practical guidance and safety instructions script
h. departure requirements

6.10 Lead The Participant Through an Eyeshade and Headphone Trial

6.11 Discuss Questions and Details Regarding Arrival at the Dosing Session

6.1 Internal Agenda for Therapists During Psychoeducation Session #1:

Explicit education of the participant regarding the common cognitive and behavioral problems seen in depression will not occur until the Psychoeducation Session #2. However, during Psychoeducation Session #1, therapists will observe carefully which of these are most prominent for this participant, where strengths lie, and which particular psychological patterns seem most amenable to intervention. The therapists will also note where resilience and creativity may lie.

<u>Cognitive Fusion</u>

Does the participant experience thoughts, words, and language as if they were factually, absolutely true? The thought "I am a worthless person" may be experienced and believed as if it were true in some absolute sense. "I am so depressed that I cannot move" is experienced as truth when it is actually a metaphor for the experience of depression. "My life is worthless" or

"I cannot do anything right" are taken at face value, rather than as thoughts that come and go and are not accurate representations of a permanent reality. "I am a depressive" or other thoughts indicating that depression comprises their core identity are examples of cognitive fusion. This intense vulnerability to internally generated pain (my thoughts are hurtful to me, I am my thoughts, I am what I think and feel), once experienced as painfully true, may then result in experiential avoidance.

Experiential Avoidance

This refers to attempts to avoid or change thoughts, feelings, memories, physical sensations and other internal experiences through:

Thought suppression: trying not to think painful thoughts, suppression, distraction
Rumination: obsessing over events, memories, narratives in a stereotyped, repetitive way that solves nothing but serves to preoccupy the mind, or
Behavioral avoidance: social withdrawal, not taking action that might trigger depressed feelings or thoughts.

Experiential avoidance is maintained through negative reinforcement: it relieves pain in the short run but is associated with persistence or even worsening depression in the long run. For instance, "If I don't get off the couch and go to that party, I won't feel like a loser when no one wants to dance with me" leads to temporarily reduced discomfort from staying in a safe place, but more long-term depressogenic isolation and impaired social functioning.

Reason-Giving/Rumination: Searching for reasons that one experiences depression does not change the condition. In fact, searching for reasons can lead to persistence or exacerbation of the condition. This is especially true with historical events that "caused" the depression. Since no one can change the past, identifying an event that caused the depression can lead to the conclusion that recovery from depression is hopeless. For example: "My childhood trauma caused this depression, and nothing can change what happened then. Therefore, my situation is hopeless." Exploring such reasons, as if that exploration might ameliorate symptoms, is contraindicated in this approach.

Our protocol involves focusing on the relationship between the symptom and its current contextual implication.

Self-Discrepancy: Failing to live up to one's own (high) expectations and feeling like a failure generates depression. When applied to the outside world, this is useful (the house is messy, I'd prefer it neat; I will clean and vacuum and achieve that goal). This is not useful with internal assessments such as, "I am depressed because I am a terrible person, therefore I must become a good person." Internal assessments that reflect unrealistic, grandiose, or even modest self-expectations typically generate depressive cognition when not met.

Willingness vs. Desire: A common promise in psychopharmacologic treatment is that the medication treatment will *make* the individual *want* to do things, have desire, and be happier through correcting a chemical imbalance. This implies that passivity, patience and surrender to the treatment are the primary role expectations for the participant/patient. The willingness to take action to change one's life is explicitly evoked in ACT (commitment), and the passive wish to feel better solely through the medication's action is confronted as a untenable proposition. While this step (confrontation) is not addressed in Psychoeducation Session 1, the therapists take care to observe the balance of activity and passivity in the participant's narrative and behavior in session.

6.2 Building Rapport and Therapeutic Alliance

The therapist's manner of welcoming a new patient into treatment, introducing themself, and cordially beginning the process of building rapport will inform this part of the therapeutic process. The therapist may ask the participant about their experiences during the screening and consenting process, or invite the participant to ask about the experience of coming to the sessions. Including only experienced clinicians in the study will enable the principal investigator and study physician to trust the therapists to find the most effective way to make each participant comfortable and welcome.

<u>Specific approaches include:</u>

- Asking about the participant's experience in the research so far,
- Active listening: asking for elaboration and details to evoke specificity,
- Nodding and non-verbal sounds of understanding and empathy,
- Accepting whatever is said as the participant's lived truth,
- Empathizing with expressed affect, anxiety about being in the study, fears of failure in the study, and
- Admiring the courage and strength that allows the participant to carry on living in the face of such suffering and despair.

6.3 Review the Overall Structure of Today's Session:

Describe the things that will be covered in today's session. For example:

"First, we'd like to get to know you, your life and what things are like for you right now. We'd like to learn about your experience with depression, and what your depression treatments have been like for you. Then, we'll talk about how this psilocybin-assisted therapy treatment works and how it is different from the usual psychopharmacological treatment of depression. After that we will give you a detailed description of the psilocybin sessions. At the end, we'll give you a chance to try out the eyeshades and earphones that you'll use during the session and we'll review our schedules for all the remaining sessions that are part of the study. Sound good?"

6.4 Reviewing The Participant's Lived Experience of Depression

During the preparatory session or period, the participant is invited to describe how depression expresses itself in their life. The goal here is for the participant to speak freely, without structure from the therapist, and to feel truly heard and supported in telling their own story, however it emerges. The therapist's role is to offer empathy for the pain and suffering that the participant shares, while carrying out the *Internal Agenda* described above. The emphasis is not on accurately acquiring a psychiatric history (which has already been done) but in learning the psychological and behavioral patterns that define depression for this individual. If concerning new information emerges, for example if the participant reveals a history of self-injurious behaviors, bulimia, dissociative episodes, or similar experiences, move to a structured approach. Finding out when such experiences began, how frequently they occur(red), and the severity of the behaviors or episodes will be an appropriate intervention. Following this session, consult immediately with the principal investigator and study physician. The team may need to reconsider the person's eligibility to participate in the study.

6.5 Reviewing The Participant's Lived Experience of Psychopharmacology Treatment

Participants in this study are likely to have had several courses of treatment, experiencing numerous medications, medication combinations, possibly ECT or TMS or ketamine, and to have worked with a variety of mental health practitioners. These experiences may have left an overall transference towards treatment that is likely to be intense and unique for each person in the study. The participant may feel strongly that a psilocybin experience is their only and last hope; thus, the participant may idealize the study and feel desperate to participate. This may make it challenging for the participant to be genuine with the therapist, therefore it is valuable for therapists to explore the participant's history with psychiatric treatments in an accepting but neutral way. *Colluding with the idealization of psilocybin would be very problematic here.* However, awareness of the participant's emotional valence toward psychopharmacology as a disappointing part of their treatment history may be helpful in understanding the relationship with psilocybin and the psilocybin study.

6.6 Understand The Participant's Preconceptions About Psychedelic Experiences

Ask participants about their preconceptions, expectations, and learning history about psychedelic experiences and psilocybin. Elicit their concerns and hopes. Ask about their experiences in youth, including with marijuana, and about their conversations with friends who have had psychedelic experiences. Explore the participant's responses to Michael Pollan's book, *How To Change Your Mind* (2019) or other media representations of psilocybin therapy they have seen.

6.7 Listen for ACT "Misdemeanors" and Begin Constructing an ACT-Based Clinical Formulation

During preparatory sessions, therapists will listen to the participant through an ACT lens, noticing examples of cognitive fusion, experiential avoidance, loos 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 sites of potential exploration and change for the individual.

6.8 Intention-Setting

> *"Having an intention is akin to having a compass aboard a sailboat. When we enter the vast ocean of expanded consciousness, there can be waves and storms, placid waters, gentle breezes, or intense winds. Having our sail raised high and compass in hand gives is a point of reference to return to, and a direction to pursue"*
>
> *~ Bourzat & Hunter, 2018*

Intention is an important aspect of the participant's 'set' going into the experimental session. In this portion of the psychoeducation session, the therapists introduce the concept of intention setting, elicit any initial intentions, and encourage the participant to think about and solidify their intention between now and the dosing session.

Sample dialogue: "An intention is a statement of one's motivation or direction. Why are you here? What do you want for your life out of this experience? We believe that your intentions play a large part in creating your experience. We hope that the medicine and talk-therapy sessions will help you adjust the habitual thoughts and behaviors that foster your experience with depression, so you can make positive changes in your life. We do not know how the medicine session will unfold for you or just what needs to happen in the medicine session to bring about such changes. Setting your intention will help keep you on track during the dosing session, so you can get the answers and insights you need."

6.9 Educating The Participant About Psilocybin Dosing Sessions

Although some of the following will have been discussed with study staff during the consent process, it is crucial to ensure the participant understands this material. It is also valuable for this information to come from the lead study therapist. We suggest using the following scripts, or similar, when imparting this information to the participant:

a. Common Experiences with Psilocybin Script

We recommend covering the following points of psychoeducation with the participant regarding the range of experiences that may occur during a psilocybin session:

- Psilocybin is a “classical” hallucinogen that can cause profound changes in sensation, perception, thought processes, emotions, your experience of time, the nature of reality and of the self. The effects may range from very mild to very strong.
- Psilocybin alters perception. You may experience visual distortions or illusions, strong visual imagery and rarely true hallucinations. Towards the beginning of a session, you may experience cascading geometric forms and colors.
- You may see things from a radically different perspective. For instance, you may find yourself in a different reality, as if you were or are living in another time or place. You may even feel you are ceasing to exist, going crazy, or are becoming an animal, plant or other organism. Such changes may feel confusing or disturbing at times, but may also contribute to strong spiritual or mystical/transcendent experiences.
- The experience with psilocybin therapy may help you make significant positive changes in your life, but it is not a magic cure for anything. For instance, you may have psychological insights about yourself or others. These insights alone will probably not help your experience with depression unless you translate their impact and teaching into your day-to-day life and make conscious changes in the way you think and behave.
- We encourage you to take an attitude of curiosity and acceptance toward everything that happens during your session. Whatever comes up has some kind of meaning or wisdom that you can learn from, even if this meaning is not immediately obvious. It is not uncommon to feel as though your thoughts and perceptions are coming more swiftly than you can process them. We encourage you to fully allow all your emotions and perceptions, good and bad. Let memories, images, and body sensations arise. Accepting and feeling these deep and sometimes difficult emotions is the path toward being able to change your deep-seated patterns of fear, powerlessness, guilt, and shame.

b. Difficult Experiences Script

- This medicine may cause periods of physical or emotional discomfort.
- Physically, you may experience periods of nausea, chills, anxiety, or panic. Your blood pressure may become somewhat elevated, and we will be monitoring this. Remember: although the psychological effects may feel extreme, the physiological risks of this medicine are extremely low.
- You may have bizarre sensations and experiences, and you may experience frightening images or thoughts. These may alternate rapidly. This is normal and does not mean anything is wrong. The effects will end and present no major risks to the body. It is best to embrace these experiences as they occur and seek to learn from them.
- We encourage you to “go with” or surrender to difficult experiences rather than fight them. Approach rather than flee; accept rather than reason away, lean into whatever comes up, including any impulse to run away. Strive to stay with the experience and explore it, allow yourself to be curious about what is emerging in your experience. Trust. Let go. Be open.
- What we are asking you to do is difficult, counterintuitive and not anyone’s typical pattern. It is natural to avoid negative or uncomfortable emotions and experiences. Don’t be

surprised if, during the session, we remind you to allow or even move toward the uncomfortable sensation or thought.

- There are methods for grounding and calming yourself, if you would like to use them. We will teach you several strategies before the end of today's session.
- If you are having difficulty of any kind, please let us know. We may be able to help you by providing reassurance, support, redirection or therapeutic touch (if you give permission for that).

c. Ski Slope Script

We have just covered a lot of information about psilocybin experiences and you may be wondering why having such an experience could be useful in treating depression. One way to think about this is that, in some ways, the mind is like a ski slope with many paths. Thoughts may start on one path, then veer in another direction. You may return to the top of the mountain and try a new thought pathway. But rumination is similar to skiing down the same path repeatedly—once you go down that one path a few times, you are more likely to go down that way again and again. Each time you do, you deepen the grooves, making it harder to turn onto a new path. In depression, people often ski down well-established ruts of thinking, feeling, and behaving. Their cognition is repetitive and inflexible.

We can think of psilocybin treatment as providing a fresh coating of snow on the mountain. With fresh powder, you have much more freedom to ski anywhere (a greater ability to think freely and tolerate a broader range of emotions). The psilocybin therapy experience can help you find new, different paths down the mountain, finding new terrain and new sights (and a sense of yourself as freer).

d. Therapist Interventions & Grounding Techniques Script

During the preparatory and integration sessions, we will have a free exchange of ideas, and ample time for conversation and discussion. During the medicine session, we invite you to take an inward journey. You can work *with* this medicine to co-create your experience. We encourage you to collect experiences and save discussion about them for later review and reflection. We will be in the room, and will check in with you if you seem to be in distress. However, for the most part, we will not seek contact with you unless you reach out to us for assistance. Please feel free to let us know if you become concerned with anything you are experiencing. You may also ask for contact at any time, either verbally or by gesturing to us, and we will always be present to help you.

e. Grounding Technique Script 1: Abdominal Breathing

- If you are feeling tense, anxious or overwhelmed during the session, abdominal breathing may be helpful.
- Direct your attention to your breathing, the sound, the feeling, the bodily experience.

- Focus on moving air with your diagram rather than your chest muscles. Imagine a balloon in your stomach connected to tube passing through your chest to your mouth. Send air through the tube to inflate the balloon, then deflate the balloon.
- With each exhalation, let go and allow tension to leave your body.
- Detailed instructions:

    1. Sit or lie flat in a comfortable position.
    2. Put one hand on your belly just below your ribs and the other hand on your chest.
    3. Take a deep breath in through your nose, and let your belly push your hand out. Your chest should not move.
    4. Breathe out through pursed lips as if you were whistling. Feel the hand on your belly go in, and use it to push all the air out.
    5. Do this breath cycle 3 to 10 times. Take your time with each breath.
    6. Notice how you feel at the end of the exercise.

f. Grounding Technique Script 2: Therapeutic Touch

- It can be helpful to establish physical contact with one or both of your therapists.
- If you agree, we may offer to hold your hand, foot, or shoulder in order to make contact with you.
- Consenting process: We would like to check with you now to see what kinds of touch you are comfortable with and under which circumstances you would like us to make physical contact. We can make physical contact with you only when you request it or use a certain gesture, or we may offer this to you if it seems like you're having a difficult time. In either case, you may always change your mind and let us know you do not want to be touched at any time. You also should feel free to signal your wish to end the touch if you desire. You may also request contact with one or the other therapist, if you prefer. Do not worry about hurting anyone's feelings; please be direct in asking for what you would like.
- We will only touch you with your advance permission. Do you give us permission to make physical contact with you during the session? Are you okay with us initiating the touch or would you prefer to be touched only when you request it? You are, of course, invited to change your answer to this question at any time.
- (If participant agrees) You may request this at any time during your medication session if you think it would be helpful. Pay attention to your inner signals regarding what is right or desirable or comfortable for you. If you cannot speak and would like physical contact, raise your hand or gesture towards us to communicate this.

Note to Therapists: If participants are experiencing ongoing physical discomfort during the dosing sessions or have significant somatic symptoms during any therapy session, it may be useful to practice the following, Awareness of Body Sensation exercise. If time permits, this may be practiced with the participant during the preparatory period.

g. Grounding Technique Script 3: Awareness of Body Sensation Exercise

- When you are experiencing strong emotion that is causing you to feel you like you are falling, this mindfulness practice can help you regain a sense of balance.
- As you are lying on the couch, arrange your body in a comfortable position, turning your attention to your body at that moment. We feel emotions in our body: perhaps a heaviness in the heart when we are sad, or maybe a tightness across the jaw when we are angry. Where in your body do you feel that emotion?
- *Pause to allow experience*.
- People sometimes report feeling emotion in the gut or stomach or chest and other places as well—in the throat or behind the eyes, for example. Notice the location where sensation is most vivid for you at this moment. Purposefully rest your attention here.
- *Pause*.
- As you attend to sensations in this part of your body, bring awareness to their specific qualities, with sincerity but without a drive for perfection. For example, you may be noticing heaviness, pressure, tension, heat or coldness, fluttering, vibration or some other sensation. Some sensations are hard to describe. That's OK – no need to put them into words. Stay with the sensation from moment to moment, as best you can.
- *Pause*.
- *This next part should be done for a minimum of 10 minutes, up to 20 minutes, repeating the instructions periodically. Cue participant to attend to or refocus on their sensation(s) every 1 - 2 minutes, more frequently in the beginning and gradually reducing frequency and using fewer and fewer words, interrupting their process as little as possible.*
- When you notice your attention has wandered, gently return it to the sensations in your body. This is especially important if you notice yourself lost in thinking about the events or circumstances connected to the emotion.
- *Pause*.
- *Wait at least five minutes before giving the following instruction:*
- Notice if the sensations shift. They may grow weaker or stronger, or shift in location. Sensations may spread out, or shrink, or change in some other way. Whatever happens, continue resting your attention on the sensations, moment after moment after moment.
- Now, we have come to the end of the practice. As you feel ready, let your attention expand to include a sense of your body as a whole, the sounds in the room, and anything else that is here right now.

This can be followed by a brief inquiry into the experience of the participant, focused breath work, or some other grounding practice. You may also choose to ask participants about their experience of this practice during the debriefing session.

h. Rescue Medications

Review with the participant the rescue medications that will be available during the session and the indications for their use. These medications and their indications will have been discussed once during the consent process.

1. Emphasize that use of rescue medication will generally be a last resort, and that other strategies, such as relaxation exercises, will be tried first to manage anxiety or elevated blood pressure.
2. Reiterate that these medications are available to ensure the participant's safety if needed.
3. Explain that for the most part, using any rescue medications will be a joint decision, not a unilateral decision. However, in the case of an unresolvable difference of opinion, the participant must accept the clinical judgment of the study physician and therapists.

i. Practical Guidance and Safety Instructions Script

- Think of the experimental session as a multi-day experience. Minimize stress for a few days before the session and especially the day before. Spending some time in nature can help reduce stress. We also recommend reducing time on the phone or Internet. Abstaining from heavy and spicy foods is a time-honored way to prepare for spiritual experiences. You will be in the best position to benefit from the session if you are refrain from consuming alcohol and other intoxicants for one week before the session.
- We also suggest not working the day after the session, or at least having a light schedule. It is helpful to have time to reflect on what happened during the session and you may want to take some time to recover from the intensity of the session.
- On the day of the session, please arrive well rested, although you may have some difficulty sleeping the night before and this is normal. The most important thing is to be ready to devote yourself fully to the experience of the session for the full 8 hours.
- We encourage eating a light, low fat breakfast either before your arrival or at the lab. We will have light snacks, such as granola bars and crackers, as well as water and ginger ale available to you throughout the day if you become hungry. You will also have the opportunity to order a sandwich for lunch.
- Wear loose fitting comfortable clothes, such as sweat pants, t-shirt, yoga pants, etc. Dress in layers, as it is common to have fluctuations in feeling warm or cold during the course of the medication session. Please also bring a change of clothes just in case. We invite you to bring photos, small artwork, or any objects that you feel will be supportive of your process during your session.
- On the day of the session, arrive at 8:00 a.m. to complete final questionnaires, urine toxicology, and urine pregnancy test (if indicated).
- After you take the study medication, you are required to stay in the clinic for at least six hours and until you are deemed safe to leave by study staff. Leaving before being cleared

by study staff could be dangerous. **We need a clear commitment from you that you will stay in the study facility for the full duration of the session (minimum 6 hours) until you are cleared to leave by study staff.**

- We can change the light, temperature, volume of music, and provide additional blankets. Just ask, and we will do whatever we can to make you comfortable.
- Vital signs will be checked every 30 minutes for the first 2 hours, then hourly. We may ask how you're doing during these blood pressure checks; otherwise, we will generally not intrude unless you initiate contact or appear to be in distress.
- If you feel emotional, need to laugh or cry, express yourself, or move your body, please go ahead. Emotional release is normal, expected, and welcome in the session, unless your behavior threatens your safety, or the safety of other people or the study environment. We will let you know if your behavior is causing any concern and work with you to find a safe way to express yourself.
- Nausea and stomach ache may occur. Vomiting is rare, but we will have a basin available just in case.
- After about 6-7 hours, we anticipate that the effects of the medication will have almost worn off completely. At that point, we will ask you to complete some questionnaires.
- **After the session:** After you arrive home, please take some time to write down everything significant that you can remember from the session. Some of these memories and sense impressions can fade very rapidly. Don't worry if some parts of your session are difficult to recall. We will go over your experience the next day at your debriefing session. Don't feel any obligation to be sociable the night after your session. You may prefer to keep your experience of the dosing session private, even from people who care deeply and want to hear about what happened. If you wish to talk about your experience, limit discussions to people who know what you've been doing and are close to you.

j. Departure Requirements

- The participant will arrange a companion or support person to come at the end of the dosing day and accompany them home. That person will be contacted ahead of time by study staff and invited to join the end of the preparatory session in order to assess competence and appropriateness for their role, provide psychoeducation and invite questions. If they cannot attend the session in person, they must be contacted by phone (this will be the responsibility of study staff/physician rather than the therapist). The support person will be educated regarding:
    1. Basic structure of the study
    2. Range of possible after effects:
    3. Headache, common, treated with ibuprofen. 200 mg po
    4. Infrequent: changes in mood, confusion, anxiety, insomnia.
    5. Rare effects: paranoia, panic, suicidality.
    6. Methods for reaching the therapists and/or Study Physician

- The support person will be asked to come to the study area to meet the participant and therapist team upon conclusion of the session. They will be provided an information sheet containing contact information for study staff in case any concerns arise.

The authors gratefully acknowledge the use of work by Bogenschutz & Forcehimes, (2015) in this section.

6.10 Eyeshade, Music Trial and Introduction to the Physical Space

If possible, the therapists will give the participant an opportunity to adjust and try on the eyeshades that will be used in the dosing session, as well as listening to a few minutes of the music playlist. At the same time, they will offer the participant an opportunity to recline on the sofa or armchair they will use during the medication session. (Note: if this is not done during preparation, it can be done prior to dosing during the experimental session).

6.11 Ending: Questions, Recap of Details for Arrival for Session

Offer an opportunity to ask questions, confirm details for arrival at dosing session and companion pick up.

7. MEDICATION SESSIONS #1 & #2

7.1 General Guidelines and Overview for Medication Sessions

Each session will last up to eight hours. Prior to the participant's arrival, ensure the room will be fully devoted to that day's dosing session exclusively. Except in case of emergency, no other persons should enter the room. Prepare the room to create a safe, warm, private atmosphere, using the checklist below.

Two study staff will be present for the entire experimental dosing session, except for bathroom breaks. The participant's therapist will be the primary person making interventions, and a study physician will be the second sitter. There will always be a study physician available and the support of nursing and research staff is also available as needed, for instance to assist with vital signs collection and completion of scales and assessments.

The sessions begin when the participant arrives and completes the assessments scheduled for that morning. Researchers and nursing staff check blood pressure and pulse to make certain that they are in an acceptable range for proceeding with the dosing. Perform urine toxicology, and if the participant is a woman of childbearing age, conduct a pregnancy test.

<u>Session preparation checklist (gather and prepare items the morning of the session)</u>

- Room decor: art, plants, flowers, food etc.
- Sheets, blankets, pillow
- Water-resistant sheet below cotton sheets in case of incontinence
- Emesis basin
- Standardized music system ready with ambient speakers
- Eyeshades
- Lamps and comfortable lighting
- Art materials
- Air purifier
- Blood pressure machine or manual sphygmomanometer, as decided
- Psilocybin or placebo medication
- Rescue medications, PO and IM
- Monitor rating forms and vital sign forms as required

7.1.1 Check-In

Researchers and nursing staff greet the participant and give standard medical/psychiatric assessments:

1. Check blood pressure and pulse for appropriateness for dosing,
2. Evaluate the participant for suicidality (a therapist will conduct an emergency assessment and make a referral, if needed),
3. Conduct urine toxicology and, if appropriate, a pregnancy test, and
4. Ask the participant about any changes in their medications.

Given that a lot of information was covered during preparation, we have found it useful to briefly review the following items with participants before they ingest the medication:

1. Expectations for test day (minimum 6 hours, cannot leave the floor, will have at least one person in room with them at all times)
2. Orient to bathroom location and procedure (participant to let us know if they need to use the restroom and, will be escorted)
3. Trial of eyeshades and headphones (adjust eyeshade straps, headphone volume)
4. Food: mention snacks available, take lunch order in advance
5. Review trip instructions, such as attitude of curiosity and acceptance to whatever arises, lean into experience rather than run away, 'trust, let go, be open'
6. Review techniques for dealing with distress (focus on the breath, asking therapists for support)
    a. Reconfirm consent for supportive physical contact, as well as assuring participant they can say no to these interventions at any time without offending therapists
7. Review participant's intention(s) for the session
8. Personal items brought by the participant will be available to them through the session.
9. Vital signs will be monitored at 30-minute intervals for the first two hours, then hourly.
10. Rescue medication will be available in the nearby research lab as detailed in the study protocol. After approximately five hours, art supplies may be offered to the participant.
11. Final reminder that participant can ask therapists to help them with any needs as they arise

7.1.2 Dosing

After the supervising physician clears the participant for the dosing session, the therapists have reviewed all preparatory information, and the participant is feeling ready, the therapists will offer the participant the study medication. In line with actively engaging participants in their own recover and promoting the sense that the patient is taking this

medication and embarking on the experience as a matter of their own choice, we offer the medication in a dish or vessel so that the participant can pick up the capsule and take it on their own accord (i.e. we are not directly administering the medication). The therapists will invite the participant to drink an entire cup of water to help the capsule dissolve fully in the stomach. After ingestion, the participant usually will want to speak for a few minutes prior to lying down and putting on eye shades and headphones. If the participant has not already done so by 30 minutes post-dosing, they should be encouraged to lie on the couch and begin turning their focus inward. Remind them that, if they feel comfortable to do so, putting on the eyeshades will facilitate their inward focus.

Guidelines for therapist actions/attitudes during session

Principles of non-intrusive presence

The in-session therapist will maintain an attentive but non-intrusive presence. Interactions with the participants should be supportive and non-intrusive, and therapists should not attempt any significant type of psychotherapeutic work, except in addressing extremes of emotion or behavioral disruption. There will be an opportunity for brief check-ins during vital sign monitoring. As a rule, the therapist will not engage with the subject during the session except in a supportive manner when sought by the subject or if the participant appears in significant distress.

Responding to invitations to talk

If the subject requests engagement with the therapist, the therapists shall listen and respond in a supportive manner. After a few minutes, the therapist should gently suggest the participant resume an inward-directed focus, including the optional use of headphones and eyeshades. If the participant resists the suggestion, continue to work with them in a supportive and compassionate manner until they are ready to resume an inward focus. Note such instances as they may represent experiential avoidance or other important processes to be discussed during debriefing. Note that dialogue may naturally be more substantial towards the end of the session, as the medication is wearing off. As some sessions are placebo sessions, it will be more challenging to not engage in significant conversation, but therapists should attempt to conduct all experimental sessions in a similar manner if the context is a clinical trial.

Responding to intense, painful affect states

The therapists will gently encourage the subject to “lean in” or “go towards” intense or difficult affective states, rather than try to avoid or diminish them.

Responding to agitation or restlessness

The therapist will encourage breathing exercises and grounding techniques, as described above. If these are not helpful, the participant will be invited to sit up, take off the eyeshades and make visual contact with the therapists and the room. The therapists may offer reassurance that such states are to be expected and are likely to be short lived.

Responding to requests for contact

The therapist will keep in mind the subject's stated boundaries regarding touch and as appropriate will respond to requests for physical contact.

Responding to marked agitation

If the subject displays significant or marked agitation and previously mentioned interventions fail, the therapist will consult with the physician regarding the possible administration of benzodiazepine or antipsychotic medication. Medical intervention will be utilized only when agitation is persistent, and no other means to help relieve the agitation are effective.

Responding to marked, persistent paranoid reactions

If the subject presents with significant persistent paranoia the therapists must strive to remain calm and present. The therapist should reassure the subject that they are safe and offer a reminder that they have taken a powerful medicine that is affecting their thinking. It is useful to remind the participant that their experience will end within [x] hours and symptoms they are having will likely resolve quickly.

Responding to urge to undress or move about the room

If the subject begins to undress or expresses a desire to undress, the therapist will remind them of their commitment to remain fully dressed. If necessary, this will become a firm instruction. If the subject desires to move about the room, the therapist will encourage the participant to enjoy this activity briefly, and return to sitting or lying on the couch before too long.

Therapist's role/attitude/frame-of-mind during psychedelic-assisted sessions

The therapist's calm attentive self-awareness benefit both them and the participant during the dosing sessions. An empathic presence during the session will offer the best support to the participant. In so doing, the therapist encourages the participant to stay present with their inner experience, and they create a safe environment that fosters willingness to remain open to new, challenging perceptions that may arise.

The intensity of the therapeutic experience for the participant is affected by the therapist's capacity to remain calm in the face of highly intense emotion and expressiveness.

The processes of "reperceiving" and radical self-acceptance need to be modeled by the therapists in order for the participant to have the best chance of learning these skills. When needed, the therapists may offer assistance to the participant in managing difficulty or confusion, while fostering the awareness that the participant's relationship with the medicine is the primary source of healing.

The therapists hold in mind any intentions for the session that the participant has identified during preparatory sessions, while also allowing for additional, perhaps unexpected, psychic material to emerge. They also consider individual psychological factors that may impact the therapeutic relationship (transference and countertransference) and seek to offer specific interventions that will be best suited to that particular individual, at that point in time.

7.1.3 First Narrative Telling (15-60 minutes)

Toward the end of the session, the participant will be invited to talk about the experience they just had, the emotions it evoked and their in-the-moment reflection on their journey. The therapist will focus on eliciting phenomenology, rather than interpreting or guiding this report. Notes will be taken by one of the therapists, which are normally given to the participant to take home as a memory aid. It is valuable to use the principles of "active listening," namely: asking open ended questions, inquiring for details and associations, avoidance of "why" questions and supporting a free-flowing report that isn't concerned with logic, rationality or productivity. This may last between 15 minutes and an hour depending on the participant. Following this (or during it) the participant will be offered water, juice, fruit and snacks to satisfy hunger and facilitate the return to ordinary consciousness.

7.1.4 Departure

About 6-7 hours after ingestion of the study medication, the majority of psilocybin effects are likely to have abated and the participant should be capable of sitting up, ambulating, conversing, and eating. They will be asked to complete any questionnaires that are part of the study. After all assessments, narratives and eating are complete, the supervising physician, in collaboration with the therapist, will assess the participant's safety for discharge from the clinic. The time from ingestion to discharge from the treatment room will be a minimum of 6 hours. So, if ingestion occurs at 9 am, the discharge will be 3 pm or later. Assessment of readiness to leave the treatment setting entails performing a mental status exam, assessment of physical safety (vital sign stability, coordination, steadiness of gait) and inquiry into any lingering effects of the medication (visual illusions, unusual beliefs, paranoia, thought processes and content, mood and insight). If cleared for discharge, the participant will be released to their companion. The next days' debriefing session, which has already been scheduled, is confirmed. The therapist ensures both the participant and the support companion have both therapist and study staff telephone numbers.

7.2 Medication Session #2

The second experimental session occurs five weeks after this one and can be conducted according to the same guidelines as described in this section.

The authors wish to acknowledge the excellent standard of care offered by Michael Bogenschutz and Alyssa Forcehimes, and to thank them for permission to use many elements of their therapy manual for psilocybin assisted therapy of alcohol dependence (Bogenschutz and Forcehimes (2015).

8. DEBRIEFING SESSIONS #1 AND #2

8.1 General Guidelines for Debriefing Sessions

Each debriefing session lasts one hour. The primary goal of debriefing sessions is to offer support for the participant's reflections on the medicine session. Therapists accomplish this by asking open-ended questions about the session, intended to elicit the introspective, interpersonal, spiritual or noetic insights that occurred during the session that the participant may otherwise forget or have difficulty verbalizing. Eliciting such insights may provide important clues to changes in behavior, thought, or relationships that may be intimately related to the participant's depression. Therapists will support the participant's narrative expression of their experience, and emphasize this over making interpretive interventions.

A critical related goal for therapists during debriefing is to listen for (during debriefing #1) and explore (during debriefing #2) aspects of the participant's narrative that are consistent with core ACT principles: cognitive defusion, acceptance, transcendent self, values, and action.

Thus, the therapists' agenda during debriefing is to hold an open, affirming manner while listening to the psilocybin experience, and simultaneously contextualizing the participant's narrative through core ACT principles.

8.2 Debriefing Session #1

This session takes approximately one hour and occurs the day after the first medication session.

8.2.1 Open Narrative

The therapists should use the following script or cover the following content using their own style:

- "Today the main goal is to talk about your medication session. We are interested in learning how the session affected you, what you experienced, and most importantly, how it has affected your thinking and ideas about your experience with depression."

- "Can you tell us everything you remember about your session, from beginning to end? What happened? What did you see? What did you hear or feel? What happened in your body?"
- "Did anything happen that was difficult or challenging for you? Did you experience periods of negative emotion, fear, sadness, depression, or terror? Did images emerge that were hard to bear? Have any of these persisted; have any of these gotten worse since the session?"
- "What have you been thinking and feeling since the session? Do you notice anything different about your usual depressive thoughts, beliefs, attitudes, or emotions?"
- "How have you been sleeping and eating since yesterday's session? What was it like coming here and seeing us (the therapist and support person) today? How did family contacts feel since yesterday's session?"
- "How are you feeling emotionally today?"

8.2.2 Session #1 Ending

As the debriefing session comes to a close, the therapist performs a mental status exam and safety assessment to evaluate for worsening mood, passive or active suicidal ideation, paranoia or confusion, persistent hallucinations, illusions, or delusions. If acute safety concerns are identified, the therapist should notify one of the study physicians to determine a plan and assess the need for further evaluation. If no acute safety concerns are identified, the therapists close the session by confirming the next appointment, and restate their availability by phone.

8.3 Debriefing Session #2

This session takes one-to-two hours and occurs one week after medication session #1. The overall goals of the second debriefing session are similar to the first but include an exploration of the role of **personal values** in recovering from depression. This debriefing session will be divided into two sections.

In the first part of the session therapists will help the participant integrate the content and process of the medication session, and their experiences during the following week.

In the second section of Debriefing Session #2, the therapists review the participant's Valued Living Questionnaire (VLQ) and values clarification list, in order to help the participant further clarify their personal values. The therapists will use the results of the participant's previously completed VLQ (done the day before first experimental session) to conduct a sincere exploration of values lost, values forgotten, values retained, and how values have changed. This may require more active exploration on the therapist's part than has been the case, as loss of values and loss of awareness of values is a common experience in depression. Not only will values be clarified, but also past activities that have demonstrated those values

will be identified and explored (preferably with humor, warmth and kindness). Please note that while we utilized the VLQ as a standardized way of exploring values in our study, numerous other ACT tools and worksheets may be utilized for this purpose. The session may conclude with a metaphor to highlight important topics if appropriate.

The therapists may use the following questions to facilitate the discussion with the participant:

Debriefing of Medicine Session Script:

- "How have you been since our last session? How is your mood, your sleep and appetite? What have you been doing?"
- "Have you noticed any changes in important relationships in your life? Work? Family life?
- Where has the medicine session of (one-two-three) weeks ago been in your thoughts and emotions? Do you think of it often? When you do, what comes to mind? Do you feel its impact still being with you or does it feel like it's faded? Do you notice any changes in how you think or how your emotions express themselves?"

Values Clarification Script

- "The day before your dosing session, you completed something called a Valued Living Questionnaire. Do you remember doing that? We'd like to take some time to discuss that with you."

The therapists bring out the Valued Living Questionnaire results and give a copy to the participant. After allowing the participant to review the results, they ask the participant to respond to their feedback, which will fall along these lines as the therapist tries to help the participant clarify:

- Which values matter most to you?
- Which values do you feel most attached to?
- Which values used to be expressed in your daily life but got lost to depression?
- Which values were imposed by others, not chosen, and need to be retired?
- Values from your childhood or early adulthood have you lost touch with?
- Which values used to be important, but now are unimportant?
- Which values have been impeded by depression?
- How has living with depression led to important values being neglected or discarded?

Having gathered the participant's feedback to the VLQ, the therapists review the experience of assessing their values with the participant.

- “As we go through this exercise, what do you feel? What memories are triggered? Are you surprised at what came up for you in the questionnaire?”
- “How did these values (family, creativity, loyalty, recognition) show up during your medicine experience? Does today's conversation make you think about how you might reconnect with these values as you move forward? How do you see your experience with depression affecting your life in terms of these values?”

8.3.1 Session #2 Ending

a. Confirm the safety and stability of the participant.
b. The participant may leave the session on their own, provided no worsening depression symptoms have emerged. If the participant has experienced worsening symptoms of depression during the debriefing session, conduct a full mental status examination and safety assessment in conjunction with the study physician, and develop an appropriate follow-up plan.
c. Confirm scheduling for the next sessions: Psychoeducation #2, Dosing #2, Debriefing #3 and Debriefing #4

9. PSYCHOEDUCATION SESSION #2

The second psychoeducation session takes approximately two hours and occurs four weeks after the first medication session. The purpose of this session is to introduce the participant to ACT principles: the thoughts and behaviors (cognitive processes, actions) that are problematic in depression can be changed through an interactive process that links the principles of ACT and the effects psilocybin.

9.1 Checking In

Check in with the participant about their progress since the last session as in previous sessions.

9.2 Differentiating the Traditional Psychopharmacology Model of Depression Treatment from This Psychedelic-Assisted Therapy Model

Briefly introduce the participant to the basic distinction between a traditional *passive* pharmacologic approach to depression treatment versus the more *active* integrated medication and psychotherapeutic approach being offered in this study.   This is important as patients may not only be accustomed to the pharmacologic paradigm from prior medication trials, but also may have unrealistic beliefs that psilocybin will cure them, like a 'magic bullet.' The basic principles are as follows:

a. In traditional psychopharmacology model for depression, depression is seen as a medical illness, which exists in the brain.
b. The doctor (or other MH practitioner) diagnoses the condition, explains it as such to the patient, and prescribes medication.
c. The patient's role is to report symptoms honestly, accept the doctor's diagnosis and treatment recommendation.
d. The medicine, then, is the active agent, which works to change the brain chemistry. Hopefully, improved mood, altered thought patterns, and behavioral activation follow over the coming weeks.
e. In psilocybin-assisted therapy for depression, the participant is invited to be a more active agent in changing their patterns of thinking and behaving.
f. The experience of the medicine and the relationship with the therapists are used to facilitate these changes in thinking and behaving.

g. The medicine may have a profound effect in facilitating these changes, but it will likely not accomplish them on its own, and if it does, such changes are unlikely to persist without active engagement on the participant's part.
h. The therapists seek to facilitate the active utilization of the medicine experience and the therapy in bringing about meaningful changes in the participant's way of life (not simply in reducing feelings of depression).

Another key distinction is that traditional pharmacologic approaches attempt to directly ameliorate depressive symptoms – i.e. take the pill and the symptoms will hopefully get better. However, in ACT, we are actually trying to improve **psychological flexibility**, which is the ability to be present in the moment with full awareness and openness to our experience, and to take action guided by our values. In other words, "ACT assumes that a) quality of life is primarily dependent upon mindful, values-guided action, and b) this is possible regardless of how many symptoms you have – provided you respond to your symptoms with mindfulness" (Harris, 2009).

9.3 Psychoeducation Regarding Psychological Processes in Depression

The purpose of this segment of the psychoeducation session is to induce "Creative Hopelessness," or the acceptance that the participant's normal, instinctive ways of fighting depression are, in fact, sustaining it. Here, the therapist uses didactic explanation to help the participant understand how, we believe, the ACT plus psilocybin combination therapy approach works. *In our study, therapists used the following framework to structure the discussion:*

"We are going to teach you what the field of psychology has learned about depression, namely, how the minds of people with depression commonly work. It's not about understanding WHY you're depressed, but about understanding HOW the depressed mind works and changing that. In fact, focusing on WHY leads to a continuation of depression, not an amelioration of it. This is counterintuitive, but true. As I discuss some of these points, I want you to think about the ways in which they may or may not apply to you. Some may feel more relevant to your particular experience than others. Some of what we discuss may in fact feel off-base or may challenge some of the ways you have been coping with depression for a long time.

"We hope what we're going to describe here will give you some new ways to think about depression. We anticipate that the medicine sessions will help you to feel these new ideas on a deep emotional level."

The following types of depressive thinking and behaving often accompany or exacerbate depression. Using the suggested language below, the therapist should explain the types of depressive thinking and behaving and provide some examples of each.

Cognitive Fusion

"In plain language, cognitive fusion 'means getting caught up in our thoughts and allowing them to dominate our behavior' (Harris 2009). 'In a state of cognitive fusion, we're inseparable from our thoughts: we're welded to them, bonded to them, so caught up in them that we aren't even aware that we are thinking… Defusion means separating or distancing from our thoughts, letting them come and go instead of being caught up in them.'"

The therapist gives some examples of cognitive fusion in the abstract or recounts a clinical moment from their previous sessions with the participant, sharing an example of cognitive fusion that they observed in the participant. For example, the participant may say: "I know I'm not really a worthless piece of garbage, but I FEEL like I am." This is an opportunity to a) differentiate thoughts from feelings/emotions and b) bring in the ACT concept of cognitive defusion. The therapist might inquire what it actually feels like when they think they are a piece of garbage. Is there an associated bodily sensation? What is the impact on them when they have that thought? How does this thought affect the participant's relationship with the outside world? Do not try to convince the participant that they are not a worthless piece of garbage, rather that the thought is simply one thought among many others, and that it has a particular impact on them. (This ties into the next concept of workability.) Our goal is to reduce the power of the thought to guide behavior, not remove the thought. The bottom line in this section is to introduce the idea: I am not my thoughts; thoughts arise and pass away, arise and pass away, and I can observe that happening.

Introduce the concept of **workability**: The issue is not whether thoughts are true or false, but how they get in the way living life in a full, meaningful way in accordance with abiding values.

Experiential Avoidance

Explain the concept of experiential avoidance to the participant. We suggest simply using the term "avoidance", rather than the more technical term "experiential avoidance."

"Painful thoughts and feelings are extremely uncomfortable. To escape the pain, the mind may avoid experiences in one of two ways: **internal avoidance** and **external avoidance.** Internal avoidance is characterized by avoiding painful emotions or thoughts and trying to make them go away, either by suppressing them or trying to fix them through understanding (reason giving)."

Here, the therapist offers examples of internal experiential avoidance that they've seen in the weeks of working with this participant. This invokes **creative hopelessness**, showing that the participant's attempts to alleviate their depression, although understandable, have been not only ineffective, but may actually be perpetuating it. This may not be easy for them to take in, and you may see resistance or distress as familiar strategies for blunting pain are

challenged. This is where **acceptance** of emotion can be put forward as part of their healing process. Acceptance refers to opening up and making room for painful feelings, sensations, urges, and emotions, rather than struggling, resisting, or getting overwhelmed by them.

External Avoidance: The therapist explains the term 'external avoidance,' and if possible, gives examples of places where this particular participant has demonstrated external experiential avoidance. It might be valuable to explain why giving up experiential avoidance is so difficult: it works, but only in the short run. Not doing something anxiety provoking leads to a reduction in painful emotion, and then, a deeply felt reinforcement for not taking action in the world. Yet studies show that prolonged experiential avoidance is associated with persisting or even worsening depression because it reinforces isolation, passivity, withdrawal and hopelessness about the ability to change.

Reason-giving/explaining why: The therapist explains that exploring narratives about the past and what "caused" the depression are not part of this therapy. This does not mean that those narratives are false or trivial, but they are not as relevant to solving the problem of depression, even though they may have caused it. Reviewing these narratives over and over is not helpful as they can limit us from having a rich, full, meaningful life.

Willingness to act in valued directions: The therapist explains the difference between willing and wanting, and introduces the idea that how the participant feels about doing something doesn't have to determine whether they actually do it. They may not want to do something, but can still be *willing* to do it. Saying "I'm going to do it *only if I feel like it,*" is very problematic, perpetuates depression, and is the opposite of willingness.

The therapist tries to help the participant recognize that while there is one voice in their head that says, "I cannot go to the gym because I am immobilized by my depression," or, "I would go to the gym BUT I feel depressed, tired etcetera," they can find another voice that says, "I can go to the gym even though I feel tired and depressed." The therapist suggests a new narrative, which might be: "I can feel depressed AND go to the gym." This is the principle of 'And not But.'

9.4 Mindfulness Metaphors and Mindfulness Practice

In order to provide participants with the experience of contacting the present moment, we encourage and teach a concentration type of mindfulness practice that seems suited to the particular participant we are working with.

To introduce the concept of mindfulness, the therapist may consider offering a metaphor if that seems helpful, such as the "Sky and the Weather Metaphor" (Harris, 2009, p. 175). Introducing the concept of The Transcendent Self/Self-As-Context may also be appropriate here.

The therapist asks about the participant's prior experience with mindfulness and meditation, learning about any existing practices they maintain or have tried in the past. We want to encourage regular practice of a mindfulness or meditation at this point, which will form one means of integration after the dosing session and after their study participation ends. If the participant already practices a form of mindfulness and wishes to continue practicing that, then the therapist should gain a better understanding of that practice and set goals for regular practice. If the participant does not yet have a mindfulness practice or wishes to learn a new one, the therapist should help them learn a new one, based on their knowledge and assessment of the participant.

Examples of mindfulness practices

a. Breath awareness practices (counting breaths, following breaths, ratio breathing)
b. Touch points: awareness of the points of your body that contact the environment or themselves
c. Sound Awareness
d. Mantra meditation

It may be helpful to guide the participant through the mindfulness practice while in the session. A sample set of breath awareness instructions are as follows:

1. Find a comfortable seated position. If on the floor, use a pillow under your buttocks. Sit in cross legged position, or, if it's comfortable, in lotus position or half lotus position. If on a chair, sit on the forward 6 inches or so of the chair with your feet flat on the floor.
2. Maintain good posture. Do not slump or make the back rigidly upright.
3. Pick a point about 4 feet ahead of you on the floor. Softly rest your gaze on this point. Keep your eyes half open and half closed. If your eyes are open fully, you will be too easily distracted; if they are closed, you will too easily go to sleep or daydream.
4. Rest your hands in your lap, one on top of the other, thumbs touching. They should just touch. If they separate you may be drifting or falling asleep. If they press together you may be thinking too hard.
5. Become aware of your breathing. Breathe through your nose if you can. For every inhalation, count silently "one," then breathe out. On your next inhalation, count, "two," and so on until "ten." Once you reach "ten," start over.
6. Now here's the challenging part. If you think of any thought at all besides the number you intend to count, start over. Do not be surprised if you cannot make it to 10 or even to 3 for quite some time.
7. When thoughts come into your mind besides the number you intend to count, observe the thought, put it aside, and return to counting.
8. It is common for the thoughts to be random: things you need to do, things you have done, lists, things from a long time ago, song lyrics, and perhaps, thoughts of things you regret. Whatever they are, observe them for a moment, put them aside and return to counting.

9. You may become aware that you are frustrated by the difficulty of the task. That is ok. Observe the frustration then put it down and return to the counting.
10. Before you start, decide how long you will sit. Do not stop before that time is up. Even if you feel that you are making no headway at all. Sit with that.
11. Set a time daily to meditate, you may light a candle or do another symbolic gesture to initiate and end the sitting. However, music should not be used as it is too easily distracting.
12. This is a practice. You should not expect that it will be easy to do this. It will take time to become better at it. It is something that you will grow into.

If it hasn't already been introduced, the therapist may also guide the participant in the Awareness of Body Sensation exercise described in Psychoeducation Session #1.

9.5 Intention-Setting

Intention is an important aspect of the participant's 'set' going into the experimental session. In this section, we review the concept of intention setting, elicit the participant's intentions for the next dosing session, reflect on how their intentions may or may not have changed from the first session, and encourage the participant to think about their intention between now and the dosing session.

9.6 Ending: Questions, Recap of Details for Arrival for Session

Offer an opportunity to ask questions, confirm details for arrival at dosing session and companion pick up.

NOTE: In this study, Medication Session #2 occurs four weeks after the 1st medication session and can be conducted according to the guidelines described in Section 7.

10. DEBRIEFING SESSION #3

This being human is a guest house.
Every morning a new arrival.
A joy, a depression, a meanness,
some momentary awareness comes
as an unexpected visitor.

Welcome and entertain them all!
Even if they are a crowd of sorrows,
who violently sweep your house
empty of its furniture,
still treat each guest honorably.

He may be clearing you out
for some new delight.
The dark thought, the shame, the malice,
meet them at the door laughing and
invite them in.

Be grateful for whatever comes,
because each has been sent
as a guide from beyond.
~ Rumi

The third debriefing session is one-to-two hours long and occurs the day after the second medication session. As in other debriefing sessions, the primary goal is to support the participant in reflecting on the medicine session. In this session, the therapists also strive to help the participant begin to adopt a more flexible attitude, so they can be less defined by their depressive symptoms, whether they persist or not.

10.1 Open Narrative

The therapist may use the following script verbatim, or simply as a helpful conversation guide:

- "Today our main goal is to talk about your medication session yesterday. We are interested in talking about how the session affected you, what you learned, and most importantly, how it has affected your thinking, feeling, and experience of depression."
- "What happened? What do you remember that surprised you? What did you see? What did you hear or feel? What happened in your body?"
- "What have you been thinking and feeling since the session? What do you notice about your familiar depressive thoughts, beliefs, attitudes, emotions?"
- "What happened that was difficult or challenging for you? Did you have periods of negative emotions, fear, sadness, depression, terror? Did images emerge that were beautiful or confusing or hard to bear? Have any of these persisted; have any of these gotten worse since the session?
- "In the last Psychoeducation session, we talked about many thought patterns that happen when people are in a depressed state, and how the medicine session might change some of those. Did you learn anything about how you experience depression and what perpetuates it? And, what you can do to change it?"
- "How have you been sleeping and eating since yesterday's session? What was it like coming here and seeing us today? How did family and friends feel to you after yesterday's session?"

10.2 Metaphor

If helpful and relevant to the discussion, the therapist may share the poem by Rumi (above) to illustrate the concept of *acceptance*. The following metaphor may also be offered and discussed to help the participant understand the concept of *self-as-context***:**

In the **house and furniture metaphor**, the subject is invited to explore the idea of "self-as-context," vs. "self-as-content". In other words, we encourage the participant to imagine themselves as larger, or more, than their everyday sense of who they are. The house, like their true nature, is permanent and stable; the furniture is more like their thoughts and feelings, which can come and go, and may be in a constant condition of change and flux. We encourage the participant to identify with the house, their larger Self, which we suggest is distinct from

their depressive symptoms. With this concept in mind, they might be able to accept or even welcome a change in the array of furniture or guests (thoughts and feelings).

10.3 Ending

As the debriefing session comes to a close, the therapist performs a mental status exam and safety assessment to evaluate for worsening mood, passive or active suicidal ideation, paranoia or confusion, persistent hallucinations, illusions, or delusions. If acute safety concerns are identified, the therapist should notify one of the study physicians to determine a plan. This may be a phone check in, an additional visit, or an assessment in the hospital ED. If no acute safety concerns are identified, the therapists close the session by confirming the next appointment, and reconfirm their availability by phone.

11. DEBRIEFING SESSION #4

The fourth debriefing session occurs one week after the second medication session and lasts between one and two hours. In it, the therapist continues to help the subject move toward integrating the medication session experience with ACT and taking the values exercise into the action phase.

11.1 Open Narrative

During the first part of this session, the therapist listens to the participant's experiences since the last session in the standard open, empathic way. However, they pay close attention to the places where the participant incorporates the new patterns of thought and behavior that have been taught and, conversely, when the participant engages in thought fusion, internal or external avoidance, reason giving, unrealistic goals, confusion of wanting and willing. The therapist will take a gently didactic approach, pointing out successful changes with praise and encouragement while tactfully correcting ways of thinking/behaving that are part of the depressive condition. The therapist may remind the participant that mindfulness is an ongoing practice.

One important therapist-orientation point to make here: the participant will likely be sharing their material in a way that would evoke an exploratory response from a therapists in a traditional psychotherapy session. In an ACT-based facilitation of psychedelic therapy, the therapists are listening for the change processes defined by ACT and mindfulness-based practice; they privilege this above the content of what is reported, which may reinforce fusion.

For example, a participant may speak in an emotional way about the death of a child, and how this is preventing them from getting out of bed, taking care of other children, and leads them to feel like a bad mother. A typical therapeutic response might be to show empathy for their suffering, to talk about the death, and in doing so, likely deepen the intensity of affect around it. An ACT response might be to listen compassionately, of course, and then use defusion to draw attention to the participant's relationship with this narrative and how it impacts their ability to engage in values-driven behaviors. The therapist might point out that the participant's mind is a relentless machine generating stories and thoughts that can limit freedom to act in the world (not workable). The therapists might clarify values that have become obscured or lost in the relentless story generation and fusion with thoughts.

11.2 Values-Into-Action

This part of the conversation takes up where Debriefing Session #2 ended. By this time, the personal values of the participant have been part of the conversation for at least 3-4 weeks, and through one medication session. That experience itself can have a helpful effect on the discovery or rediscovery of abiding personal values. The therapist and participant devote 20-30 minutes to discuss the topic of values, and any value-driven actions that are underway. The therapist may refer back to the participant's Valued Living Questionnaire or use any other ACT values clarification work sheet. They may offer to assist the participant in planning values-based actions. Some participants may find a small booklet or journal to be helpful in planning. It may also be useful to employ SMART goals (Specific, Measurable, Attainable, Relevant, and Time-Bound). For instance, rather than, "I will start doing some yoga," the therapist should encourage the participant to arrive at a concrete plan, such as, "I will take the vinyasa yoga class this coming up this Wednesday at 10:30 am at the Integral Yoga Institute on Spring Street".

It is very possible, of course, that habitual patterns and processes of psychological inflexibility, as well as strong emotional states, such as fear, doubt, anger, and/or sadness may emerge in the session, especially in response to the encouragement to take action. Thus, this session will be a good opportunity to implement and practice ACT techniques for working with these intense emotional states. The therapist in this session functions somewhat like a coach. Rather than being non-directive, the therapist gently directs the participant to be present with the emotion and to practice: bringing their attention to the present moment, defusing from thoughts, and accepting what is.

It may be helpful to take 3-minute mindfulness breaks during the session to work with activated emotion or experiential avoidance.

11.3 Ending

Confirm safety and stability of the participant. After the session, the participant may go home on their own, provided no worsening depression symptoms have emerged. (If depression symptoms have worsened, a full mental status examination and clinical interview should be done, followed by stabilization of the situation.) Confirm scheduling for the next sessions

12. FOLLOW-UP SESSIONS #1, #2

Follow-up sessions #1 and #2 are designed to keep moving the patient towards psychological flexibility, with an eye towards empowering them to continue making progress after their participation in the study ends. These two sessions reinforce important concepts, encourage successful changes, and facilitate further ownership of lessons and gains drawn from the psilocybin/therapy experience. The sessions provide encouragement of continued practice of mindfulness and ACT skills. The sessions also address study termination issues.

12.1 Follow-Up Session #1

This one-hour session occurs two weeks after the 2nd medication session. If case/therapy supervision is available, the therapists should use this opportunity to discuss the case and consult with the supervisor prior to this session with the explicit goal of establishing an individualized plan for the remaining sessions.

12.1.1 Check-In

This session begins with a brief, cordial check-in and catching up.

12.1.2 Termination Discussion

The therapist speaks to the fact that the participant's time in the study is coming to an end and that there will be one more session after this. The therapist invites the participant to share their feelings, thoughts, and questions about the termination sessions, including disappointment and fears that might be emerging as termination comes closer.

12.1.3 Acceptance and Commitment

This will be the focus of the session. The therapists continue the work of integrating ACT insights and behavioral changes into everyday life. Based on clinical formulation the therapist may focus on specific ACT principles. To facilitate the discussion and review progress made thus far, the therapist may introduce the ACT hexagram and explore how the medicine session and therapy have worked on the points of the ACT hexagram. The discussion focuses on the experiences of acceptance (including mindfulness and self-transcendence) and commitment (values, willingness to act) that are emerging in the participant's life. A brief meditation or period of contemplation may be incorporated into the session.

12.1.4 Begin Reviewing After-Care Plan

Begin discussing the participant's plans for ongoing treatment and self-development endeavors beyond the study. If available, give the participant a prepared list of referrals that are suitable for after-care, taking into account their financial, geographical, and clinical needs. Some examples include psychotherapy, psychopharmacologic treatment, group or individual psychedelic integration, ketamine therapy, mindfulness-based stress reduction, meditation groups, yoga studios, and exercise programs.

The discussion regarding ongoing psychotherapy may be complicated as participants may have certain feelings about returning to their prior therapist after having undergone psilocybin treatment. Participants may inquire about continuing therapy with the study therapist and so the therapist and study investigators should develop a plan and position on this ahead of time. In most clinical studies, there is either an indefinite or time-limited prohibition against clinical work together after the study. Therapists or investigators should offer to contact the participant's prior therapist to discuss progress made in the study and how this progress can be continued.

12.2 Follow-Up Session #2

This one-hour session occurs four weeks after the 2nd medication session. After briefly checking in about any significant experiences the participant had in the weeks since last session, the therapist will devote the bulk of this session to reviewing the participant's experience in the study and termination from it. The therapists and participant will reminisce, narrate, and share observations of themselves and each other during the study period. By this time in the study, there may be much improvement to celebrate.

This unique triad will have shared a distinctive experience, nothing ever to be repeated in quite the same fashion. The three will have formed a group, a container, a type of family. The therapist may reinforce practices of mindfulness and acceptance to help the participant navigate the rather abrupt termination of their short-term therapy. They will also review and confirm plans to transition back to the treating psychiatrist and therapist. They may need to restate parameters for contact after the end of the study and discuss norms around phone calls, email, texting, etcetera. The therapists may also need to review the participants ongoing responsibility to the study for assessments.

As the therapists wrap up the last session, they may express gratitude to and receive appreciation from the participant. The therapists may wish to acknowledge the participant's hard work. If it seems appropriate, the therapists may exchange hugs with the participant. If further follow up data collection is necessary, this can be reconfirmed. Finally, therapists and study staff offer goodbyes and well wishes.

13. LIMITATIONS

While our limited experience using this treatment protocol with research participants suggests it holds promise, there are a number of important limitations to the approach outlined in this manual. First, there have not been any trials comparing our approach to psilocybin treatment with non-specific 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 this therapy protocol are effective or helpful to participants. 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 for each participant. For reasons related to feasibility, the number of therapy sessions was constrained; we suspect that more preparatory and follow-up sessions would be optimal. 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.

13.1 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 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. The more neutral term, "Committed action" could be used to identify small steps the participant can take to live a fuller or more meaningful life in line with their stated values. This eliminates any implied link with a lack of commitment and retains 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).

APPENDIX A: THERAPIST SELF-CARE

Compassion and love are necessities; they are not luxuries.

Without them we cannot survive.

- Dalai Lama

Therapists are wise to engage in regular self-care in order to avoid vicarious traumatization and compassion fatigue resulting from interacting with participants' suffering. It is important that therapists continue doing their own inner work and take time for regular debriefing conversations with their co-therapist or study team. This may include an opportunity to process their own emotional responses to participants as well as peer supervision and discussion about the optimal application of the therapeutic method in specific situations. It is also an opportunity for developing and maintaining their skills as a therapeutic team by reviewing their interactions during study sessions.

What is Compassion Fatigue?

Sabo (2006) described compassion fatigue as a severe malaise resulting from the process of giving care to patients who are experiencing any type of pain (i.e., physical, emotional, social). "Compassion fatigue refers to the strain and weariness that evolves over time from offering care to suffering people."

Therapists will spend close, attuned time with participants, being fully present as they describe their life story, concerns, anxieties, and dreams during preparatory, dosing and integration sessions. This close work, especially as a new activity added to existing clinical responsibilities, may lead to compassion fatigue. The following are some simple suggestions for self-care:

a. Listen to your body and pay attention to what it is telling you. It is the best guide to staying healthy.
b. Use your body to inform your own process; are you holding your breath, is your body tense or numb, are you cold or hot?

c. Use either diaphragmatic breathing or simple breathing that expands your ribs front to back and side to side. Do a "body scan" meditation and send breath to the areas of your body that feel tight or numb.
d. Give yourself enough time before you start a session to gather your thoughts, ground yourself, and shift roles. Take enough time to feel "inner stillness."
e. Listen to your expectations and be realistic about your goals.
f. Know who you can ask for support.
g. Take time after the session to release emotions that have come up for you in the session.
h. Have a good nutritious meal after a session and do something grounding and enjoyable.
i. Taking a bath, shower, or hot tub following a session may be relaxing and calming.
j. Consider having your own ongoing psychotherapy and/or supervision with another therapist.

APPENDIX B: PSILOCYBIN

"When we look within ourselves with psilocybin, we discover that we do not have to look outward toward the futile promise of life that circles distant stars in order to still our cosmic loneliness. We should look within; the paths of the heart lead to nearby universes full of life and affection for humanity."

~ Terence McKenna

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a tryptamine compound that naturally occurs in species of mushrooms (*Psilocybe* sp.), such as *P. cubensis* and *P. mexicanus*. Psilocybin was first isolated and identified from *Psilocybe mexicana* by Albert Hoffman in 1957 (Passie, Seifert, Schneider, & Emrich, 2002). Once ingested, psilocybin is converted by the liver into four metabolites, of which psilocin (4-hydroxy-N,N-dimethyltryptamine) is the main psychoactive compound (Passie et al., 2002). For the sake of simplicity and consistency with prior studies, the term psilocybin will be used in this protocol to indicate both the ingested and active substances.

Acutely, psilocybin causes profound dose-related alterations in perceptions, emotion and thought in humans, leading to its classification as a hallucinogen or psychedelic drug (Passie et al., 2002). The psychedelic effects of oral psilocybin begin about 30 minutes after ingestion, peak after another 1-2 hours, and last another 1-2 hours more (Nichols, 2004; Passie et al., 2002). The oral bioavailability in humans is 50%, with about 20% variability (Hasler, Bourquin, Brenneisen, Bär, & Vollenweider, 1997; Hopf & Eckert, 1974). It can be administered intravenously with a much shorter half-life and duration of subjective effects, 20 and 15-30 minutes, respectively. Once in the bloodstream, psilocybin and its metabolites are renally cleared (Passie et al., 2002).

Psilocybin acts primarily as an agonist of serotonergic receptors, particularly presynaptic 5-HT_{2A} and 5-HT_{1A} receptors (Nichols, 2004; Passie et al., 2002; Vollenweider & Kometer, 2010). Activation of 5-HT_{2A} receptors is believed to be the source of hallucinogenesis, as ketanserin, a selective 5-HT_{2A} receptor antagonist, blocks the psychotomimetic effects of psilocybin (Nichols, 2004; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998). Other serotonergic hallucinogens, such as LSD, mescaline, and dimethyltryptamine (DMT), also directly bind 5-HT_{2A} receptors (Nichols, 2004). However, unlike LSD, psilocybin has no affinity for dopamine D2 receptors though a D2 blocker, such as haloperidol, has been

shown to reduce the acute effects of psilocybin, indicating known overlap between the serotonergic and dopaminergic circuits in the brain. (Passie et al., 2002; Vollenweider, Vontobel, Hell, & Leenders, 1999).

Safety of Psilocybin

Psilocybin mushrooms have been used ritually by native peoples in Mexico in religious ceremonies and for healing from as early as 3000 years ago up until the 16th century, after which the Spanish prohibited their use (Schultes, Hofmann, & Rätsch, 2001). Historical accounts of psilocybin-associated fatalities involve situations that are clearly compounded by other factors: accidental over-ingestion by a child, concomitant heroin overdose, and psychological disturbance (e.g. jumping from a window with the belief one could fly) (Nichols, 2004; van Amsterdam, Opperhuizen, & van den Brink, 2011). The effective oral hallucinogenic dose of psilocybin ranges from 4 to 20 mg (0.06 to 0.3 mg/kg), whereas the LD_{50} for oral psilocybin ranges from 12.5 mg/kg in rabbits to 285 mg/kg in rats and mice (Nichols, 2004; Passie et al., 2002; Usdin & Efron, 1972; van Amsterdam et al., 2011). Therefore, the LD50 in humans is likely on the order of grams (Passie et al., 2002). There are no human cases describing birth defects or complications of pregnancy associated with the use of psilocybin. In a report of one woman who took psilocybin every two weeks during pregnancy, there were no detrimental effects to herself or her baby (Leary, Litwin, & Metzner, 1963). Furthermore, as with other hallucinogens (e.g. LSD), psilocybin is non-addicting (Nichols, 2004; van Amsterdam et al., 2011).

A recent summary of 227 experimental psilocybin sessions in 110 healthy subjects demonstrated safety and tolerability of psilocybin with no evidence of increasing risk of subsequent drug abuse, persisting disorders of perception, prolonged psychosis or other long-term impairments of functioning (Studerus, Kometer, Hasler, & Vollenweider, 2011). The study reported that fatigue, headaches or head pain, lack of energy, difficulty concentrating, a "gone" feeling, lack of appetite, and heavy or tired legs were the most frequent adverse events experienced in the 24 hours following a session with oral psilocybin (Studerus et al., 2011). Other unpleasant somatic effects include dizziness, nausea, flushing, increased heart rate, and elevated blood pressure (M. Johnson et al., 2008).

APPENDIX C: REFERENCES

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