

Yale Manual for Psilocybin-Assisted Therapy of Depression

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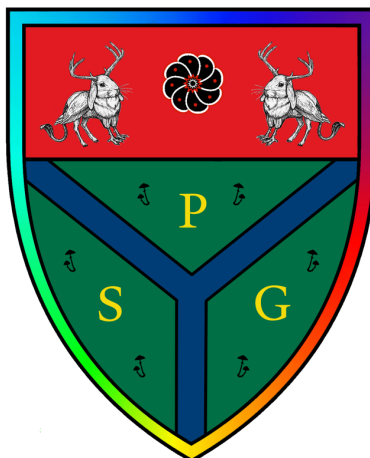
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1.0 INTRODUCTION

Welcome.

The Yale Manual for Psilocybin-Assisted Therapy of Depression is intended to be a resource to help develop the skills, awareness, experiential knowledge and presence of those who serve and support volunteers (“participants” or “subjects”) in the field of research using psilocybin for the treatment of Major Depressive Disorder. This manual provides researchers with methods, structure, and areas to consider regarding the use of psychedelic-assisted therapy in conducting these trials. This manual is intended only for use with participants of an approved clinical trial who have provided their informed consent.

1.1 Goals of this Manual

This manual provides researchers, therapists, and sitters with a method of psychedelic-assisted therapy to be used in the study of psilocybin-assisted therapy for depression. 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 typically involves several experimental sessions with associated **preparatory** and **integrative** therapy sessions. Preparatory psychoeducation sessions are two hours in length while integrative debriefing and follow-up sessions are 1 hour in length. The experimental sessions during which psilocybin is administered are approximately eight hours.

The specific goals of this manual are to:

- 1) Delineate the essential elements of research based psychedelic-assisted therapy, including establishing and maintaining proper set and setting.
- 2) Delineate theoretical and clinical approaches drawn from Acceptance and Commitment Therapy (ACT) and Mindfulness-Based Cognitive Therapy (MBCT) as a model for understanding and treating depression that may be uniquely effective in psilocybin-assisted therapy.
- 3) Provide guidelines to therapists for use of this model in conducting preparation

(psychoeducation), dosing (experimental session) and integration (debriefing and follow-up) sessions.

- 4) Education of therapists regarding self-care practices that support this work.
- 5) Education of therapists regarding inclusion and exclusion criteria, screening procedures and consenting procedures.
- 6) Define basic criteria required to function as a study therapist.

1.2 Essential Elements of the Therapeutic Method

1.2a 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 that begins before the psychedelic dosing session, and continues after it. While most clinical trials of psychedelic therapy have followed the basic preparation, support, and integration model, the content of the preparation and integration sessions has varied considerably between 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, support, and integration. 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 and the therapeutic approach to be used. Additionally, the sessions seek to clarify expectations of the medication session, including logistics of the session (how long it will last, the type of music to be utilized) and to delineate acceptable boundaries of interaction between the participant and the therapist. Support in this context refers to the supportive, largely nondirective stance taken by the therapists while accompanying participants during the experimental drug sessions. In psilocybin trials, therapists generally encourage participants to have an inward directed

experience during dosing sessions and provide emotional support or encouragement to engage with difficult thoughts, sensations, or memories that arise. They also ensure safety and assist the participant in meeting any immediate needs. The integration phase usually begins the day after the dosing session and involves thoroughly reviewing the participant's experience during the dosing session and, in some cases, applying therapeutic techniques to reinforce particular aspects of the experience such that they foster sustained desirable patterns of thought and behavior. In other words, integration can be understood as the continuation of a therapeutic process that began during preparation sessions, and intensified during a psychedelic experience. The role of the therapist is to facilitate the integration process and help consolidate the newly developed mindset.

It is a well-established principle that subjective effects are highly variable and seem to be strongly influenced by psychological and environmental factors, commonly referred to as “set and setting” (Leary, Metzner, & Alpert, 1995). “Set” refers to the mindset and intention of the individual prior to the experience. This includes their beliefs, hopes, fears, traumas, personality and temperament, as well as their expectations and fantasies about psychedelic experiences. In the context of clinical research, the participant's attitude toward the research setting, the medication, and the therapists, as well as expectations for relief also constitute important parts of the participant's set. “Setting” refers to the physical space and environment 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 possibly, to enhance therapeutic response. Guidelines for maximizing safety and minimizing risk in research studies with psychedelic substances have been published (M. Johnson, Richards, & Griffiths, 2008) and 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.

1.2b Theoretical Orientations of Psilocybin-Assisted Therapy for Depression

While most clinical trials of psychedelic therapy have followed the basic preparation, support, and integration model, the content of the preparation and integration sessions has varied considerably between protocols, based on the condition being treated as well as the therapeutic orientation of the researchers writing the protocol. Importantly, some studies have employed non-specific supportive psychotherapeutic models while others have incorporated elements of evidence-based, condition-specific therapies. An example of the

latter is a study of psilocybin-assisted therapy for alcohol use disorder underway at New York University School of Medicine, which integrates elements of Motivational Enhancement Therapy into the familiar structure of preparation and integration sessions (Bogenschutz & Forcehimes, 2017).

In contrast, supportive models are not linked to a particular therapeutic orientation, nor do they target the specific disorder being treated in the study. Instead, they provide containment, safety, and clear guidelines to help participants navigate and make meaning of 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,” akin to the protocol described in Carhart-Harris (2016). This likely reflects research priorities in drug efficacy trials aiming to isolate drug effects from therapy effects. However, it also reflects 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 healing power” that abides within the psyche of the individual person and is unleashed by the psychedelic medicine. The job of the guide, then, is to “hold space” for the natural healing process of the individual to unfold. We do not question the possibility that a self-regulating process with the potential for internally generated self-repair may be a part of psychedelic therapeutics. 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 an explicit therapeutic modality 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. Whatever changes that come from the intense psilocybin experience will inevitably be

countered by deeply ingrained patterns of thinking and behaving that are unlikely to be permanently erased by even the most intense psychedelic experience. Setting the groundwork for the psychedelic experience to occur in a specific way during preparatory sessions and then reinforcing that approach during integration can help direct the psychedelic experience in ways that are theorized to be therapeutic for depression. As we will discuss later, this is our intention in including 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 would 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 therapy procedures presents a problem for controlled research. Without selecting a therapeutic approach, much of what the sitters or guides do or say goes unaccounted for and leaves hidden the role of their therapeutic attitudes. We do not believe the provision of “psychological support” can be done in a completely neutral manner, as this ignores unconscious process, as well as consciously held attitudes, beliefs and emotions that live under the blanket of “support.” The supportive interactions of monitors are likely to amount to more than neutral space holding, especially while working with and bearing witness to the suffering of significantly depressed participants. In this scenario, each study therapist is likely to employ his or her own intuitive therapeutic modalities at different times and in different ways with different participants. Thus, we believe it is more scientifically rigorous to proactively outline a therapeutic approach and structure, acknowledging there will be some reasonable variability in session content, rather than to refrain from delineating these variables at all.

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

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 conceptual overlap with psychedelic therapy. Our goal was to find a therapeutic approach that would target depression and offer a structure for the preparation, support, and integration sessions. We specifically sought a therapeutic approach that would potentially be facilitated by the effects of the psychedelic dosing 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 (ACT) (Zettle, 2007).

Our process involved outlining the following key factors for each modality: the etiology of depression (how the causes of depression are understood), the therapeutic mechanism(s) (how the therapy intends to relieve depression), targeted outcomes (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 values-based action (also, often deficient in depression). Thus, ACT seemed to provide the most conceptual overlap with our notions of how psychedelic therapy may be beneficial in the treatment of depression.

A brief description of MBCT and ACT follows.

Mindfulness Based Cognitive Therapy

Happiness is not ready made. Happiness is created from your own actions.

- The Dalai Lama

Mindfulness Based cognitive therapy (MBCT) was originally created as a relapse prevention treatment for depression (Seligman & Reichenberg, 2007, Linda & Lourie, 2014) and may be particularly effective with major depressive disorder (Piet, & Hougaard, 2011). MBCT utilizes mindfulness and mindfulness meditation, along with education about the

nature of depression. Mindfulness practice teaches uncritical awareness of incoming thoughts and feelings, accepting them, and not attaching or reacting to them. This aids in disengaging from self-criticism, rumination, and dysphoric mood that arise in depressed individuals.

Mindfulness, at the core of MBCT, is an area of intense research and theoretical exploration. Shauna Shapiro, et al (2006) writes that “meditation is the scaffolding in which to develop the state or skill of mindfulness”. This apt metaphor gives a spatial model that separates the behavior (meditation) from the transformed state of consciousness (mindfulness). She describes three components or axioms of mindfulness.

Intention: Why you are meditating? What is your purpose? Some religious meditation is undertaken to find compassion for all beings. More frequently, in our culture, meditation is undertaken for self-regulation, self-exploration and finally, self-liberation. It is vital to include the question, “Why am I meditating? Why am I practicing mindfulness in any program that is recommending it?”

Attention: This refers to the observation of the operations of one’s moment-to-moment internal and external experience which allows a “return to things themselves”, with a suspension of interpretation: pure experience, attending to the contents of consciousness with bare awareness.

Attitude: How we attend is at question here. The qualities brought to meditation is central: an attitude of curiosity, acceptance, and interest. This type of attitude is difficult to sustain, and we can imagine that with depressed individuals, attitudes of self-criticism, self-hatred, pessimism, and rigid constricted patterns of psychic function will require particular attention to bringing bare attention to consciousness when defensive patterns become triggered.

Reperceiving: Shapiro describes *reperceiving* as an overarching mechanism at work in mindfulness. Reperceiving involves a shift in perspective: rather than being immersed in a personal narrative or drama, one stands back and witnesses. This practice brings the profound awareness that the phenomena contemplated are distinct from the mind contemplating them.

Other proposed mechanisms of mindfulness:

Deautomatization: an undoing of automatic processes that control perception and cognition (Diekman, 1982).

Detachment: adopting a phenomenological attitude, with the resultant expansion of attentional space (Bohart, 1983).

Values clarification: meditative awareness can elicit information regarding values and the questioning of externally imposed values and internally chosen ones. This requires asking what is truly important from what has been reflexively accepted from external sources. This can lead to a clarification of values with subsequent action

informed by those values.

Acceptance and Commitment Therapy (ACT)

ACT was developed in 1982 (Hayes & Zettle, 1985; Hayes, Steven, Strosahl, & Wilson, 2012) through the integration of radical behaviorism with experiential and existential approaches intended to target transdiagnostic drivers of psychological distress. The FEAR acronym describes the common targets that ACT is oriented toward: “fusion, evaluation, avoidance, and reason giving” (Hayes, Strosahl, & Wilson, 2003). The common human experience of over-reliance on thoughts and beliefs over direct experiences (i.e., fusion), the evaluation of our experiences as wanted or unwanted, and attempts to avoid both external and internal (e.g., thoughts, feelings, memories) antecedents of unwanted experiences can all amplify and create the experience of suffering. Within the context of a culture that values the pursuit of positive emotions over a life lived in accordance with one’s values or a sense of deeper meaning (Ryan, Huta, & Deci, 2008), attempts to control or avoid unpleasant internal states become a major source of unhappiness and psychological distress (Hayes, Strosahl, & Wilson, 2011).

Thus, in ACT, problems (including depression) are caused by:

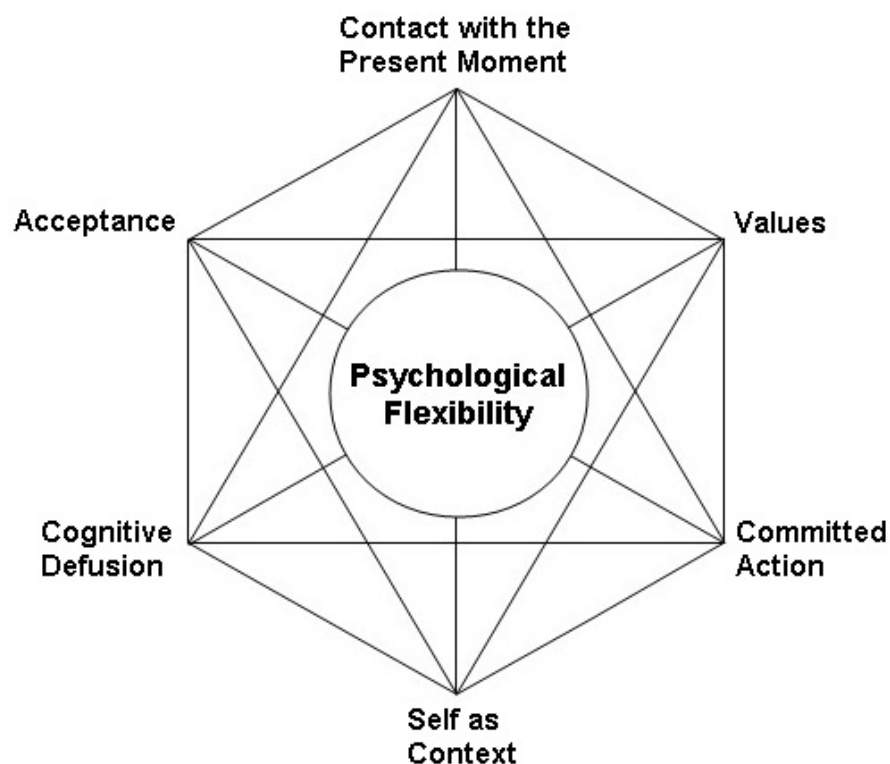
Cognitive fusion: the overvaluation of thoughts, words, or language by experiencing them as if they were true. For example, the thought “I am a worthless person” is experienced as true in an absolute sense. This is based on the phenomenon of bidirectionality of human language in which the memory/thought of an event evokes the emotions of that event and makes it true in the present moment. “I am my thoughts and feelings.” This vulnerability to internally generated pain is defended through:

Experiential avoidance: an attempt to avoid thoughts feelings, memories, physical sensations and other internal experiences through thought suppression, rigid rumination, and behavioral avoidance (social withdrawal). Experiential avoidance is maintained through negative reinforcement - it relieves pain in the short run by removing a negative stimulus - but is associated with persistence or exacerbation of the painful feelings in the long run. This is countered in ACT by conscious acceptance of internal sensations of all kinds.

Reason-giving/rumination: the search for reasons that one is depressed is not linked to recovery, and in fact can lead to persistence or exacerbation of depression. Often the “reasons” discovered are unchangeable, making recovery from depression feel hopeless (which it is, if that paradigm is true). For instance, “my childhood trauma caused this depression,” and nothing can change what has already happened, therefore my situation is hopeless.”

ACT principles for treatment:

The central treatment target of ACT is the development of psychological flexibility, cultivated through six core processes: present-moment awareness, acceptance of one's experiences, defusion from the literal belief in one's thoughts, values clarification, the identification of specific behaviors in the service of those values (committed action), and contact with a flexible experience of the self (self-as-context) (Hayes et al., 2011).



Cognitive defusion: decreasing identification with thoughts; thoughts/feelings are not facts; memories do not constitute the self.

Acceptance: allowing thoughts, emotions, and interoceptive states to come and go without struggling with them.

Awareness of the present moment, experienced with openness, interest and receptiveness; be interested in what is internal; mindfulness.

The Transcendent self: reperceiving the self as distinct from thoughts and feelings: the ground (Self) abides, the “weather” (internal experience, emotions, thoughts) are always changing and do not constitute the Self.

Values clarification: defining which values have the most meaning in the participant's life.

Action: setting goals based on values and taking committed actions to carry them out responsibly.

1.2c Why utilize Acceptance and Commitment Therapy 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 primarily 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 the myriad psychological, social, and spiritual or energetic^[1] conditions that contribute to 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, ACT asks patients 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, ACT targets the more complex construct of psychological flexibility as discussed above. Part of increasing psychological flexibility involves acceptance of internal and external discomfort, which perhaps paradoxically for some patients, involves decreased avoidance of unpleasant thoughts and emotions, and instead, fully experiencing them with openness and acceptance. Doing so in the name of living a values-driven life is thought to lead to a reduction of depressive symptoms indirectly.

Similarly, we conceive of psilocybin-assisted therapy as also requiring the active engagement of participants in their own healing. We question the view of psychedelic medicines as a “magic bullet” intervention, requiring only the safely contained dosing of the

medicine by the depressed participant. Certainly, psychedelic substances may have beneficial pharmacological effects that are independent of set and setting or therapeutic approach. For instance, recent studies suggest that psychedelics can alter functional connectivity in a manner that disrupts stable spatiotemporal patterns of brain activity and increases communication between brain regions that are usually isolated (Carhart-Harris et al., 2014; 2012; 2017). Additionally, the study of which the ACT therapy protocol described here is a part (NCT03554174) is investigating further the hypothesis that psilocybin induces a transient neuroplastic brain state (Ly et al., 2018). While these pharmacological effects may inherently confer some degree of symptom relief or benefit, we suggest that the full potential of psychedelic therapy is more likely to be unlocked when the participant is actively engaged in a multifaceted therapeutic process of interrupting deep-seated pathological patterns of thought and behavior through integrated neurobiological *and* psychosocial intervention. This is especially the case 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 MDD 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 psilocybin experience, 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 all the thoughts, sensations, emotions, and memories that arise. These experiences are generally perceived as occurring beyond conscious control, often as a stream or flood of consciousness.^[2] Participants are instructed during preparatory sessions and encouraged during drug sessions to surrender to the experience, 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 important aspect of psychedelic experience is the way in which self-perception may be profoundly shifted in the direction 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 defined by or 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 not uncommon for psychedelic experiences to assist an individual in gaining clarity of his/her/their values and priorities in life (Swift et al., 2017). The experience of psychedelic therapy 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 principles 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, we may find that multiple psilocybin sessions are optimal for the treatment of Major Depressive Disorder. It also speaks to the important role of preparatory and 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, lacks an operational relationship to the problem being treated. It is often a non-specific mixture of supportive listening and encouragement to engage in introspective practices, such as journaling, meditation, and spending time in nature. In the context of our study, ACT offers a template for use in integration sessions, as well as preparatory sessions with depressed individuals, which we will outline in the following section. We believe that having such a template will allow therapists to meaningfully engage with familiar depressive negativism, pessimism, self-criticism and despair as they may arise during follow-up integration sessions.

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

the therapists. Lastly, it is worth noting that our mode of linking aspects of psychedelic experience with specific psychotherapeutic processes may help shed light on mediating reasons why “mystical type experiences” have thus far been correlated with therapeutic outcome in recent trials.

2.0 THERAPIST FOUNDATION

Therapists will receive this manual, complementary readings, and specific training in the psilocybin-assisted therapy for depression method described here. Training consists of reviewing relevant source papers and books, reading the treatment manual, and in-person training, including role play. Training may also include other modules such as observing therapy sessions or attending supplemental trainings given by MAPS, California Institute of Integral Studies' psychedelic psychotherapy program or applicable internal or external trainings.

2.1 Essential Therapist Background

Study therapists need to be fully trained psychiatrists, psychologists, master's prepared social workers or psychiatric nurses (Registered Nurses with a BA, BSN or APRN's with a MSN), with a minimum of 5 years clinical work treating psychiatric patients. Experience with the therapeutic use of altered states of consciousness is highly valuable. Credentialing with the West Haven Veteran's Administration Medical Center is required for the present study.

2.2 Specialized Therapist Skills

This training model is designed to teach competency in applying the essential elements of this method of psychedelic-assisted therapy for Major Depressive Disorder. Some of the therapy and experiential trainings that have been influential for the manual authors in developing this model include: yoga and mindfulness practices, holotropic breathwork, flotation tank work, and psychodynamic psychotherapy.

Acceptance and Commitment Therapy: Therapists will read relevant texts on ACT and participate in two in-person, live trainings to become familiar with the treatment model. Consultation with ACT practitioners will be available to therapists.

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 (Stolaroff, 2004, p.30).

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 he/she finds there. A participant’s set refers to their beliefs, hopes, fears, trauma, deadness, aliveness, personality, temperament and wounds. Set also includes the participant’s attitudes and fantasies about psychedelic consciousness, toward the research setting itself, medication, relief and hope and toward providers and therapists. Set is also the particular state of mind the participant is in on the day of taking psilocybin.

We do not know what traits or types of people will have which kinds of experiences, but through this study, we will be asking: what do depressed people bring to psychedelic experience? How do we observe that in our participants? What do we look for? Is this person using cognitive fusion in a way that seems extreme, or are they engaging in multiple self-hatred scenes, or hopelessness loops with rumination? All the things that are depression are part of this person, including their attitude towards psychiatry and psychiatric medicines.

3.2 Setting: The outer world of the participant

As far as the physical setting goes, we will seek to create a warm, inviting, and private, environment in which the participant feels comfortable and safe to both experience and express themselves. Other psychedelic researchers have used such things as an oriental rug, single rose, Buddha books, icons and a couch.

The participant-therapist relationship provides a primary, and primal, setting that contains the participant in his/her encounter with psilocybin. This therapists’ role consists of helping the participant prepare for the dosing session, providing a quiet meditative presence during the dosing session, debriefing the psilocybin experience,

and integrating the experience during follow up sessions.

There is no one particular psychotherapeutic dynamic school among psychedelic therapists, but most have academic training in psychiatric contexts, and a blend of psychodynamic approaches. The approach to be employed here involves a combination of the therapists' existing identity and therapeutic style, with the application of ACT/MBCT principles. In this approach, it is important that the therapists have preparation in treating depression from a modified ACT and MBCT point of view. This is the setting the therapists are consciously, mindfully offering. Of course each therapist brings her or his identity as a therapist, history with depression (or not), with psychedelics (or not), and time spent in relationship with depressed patients. Therapists also carry their own experiences, transferences toward the study, their home institution, transferences between therapists, and between disciplines and the psychedelic world. All these are part of the setting that the therapists bring. It is valuable for therapists to be mindful of how their life experience affects what they bring into the clinical sessions.

3.2 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 an environment that is conducive to the psilocybin therapeutic experience, and which will allow the participant to fully attend to her/his internal experience.

The physical setting should generally be private, free from interruption, with minimal external stimuli. The room itself should be comfortable and, to the extent possible, should avoid an overly clinical feeling. The room can be made more comfortable with the presence of such things as fresh flowers, artwork, warm colors and home like furnishings. The participant should be made aware of all safety measures and equipment in place to respond to the unlikely possibility of a medical complication.

Integral to the physical space is the ability to play music. The physical space, or setting, will be greatly colored for the participant by the deliberate production of music (see section on music below).

Other necessary parts of the physical setting are medical equipment, including means of readily assessing blood pressure and heart rate, 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. Psychedelic-assisted therapy should be done 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 ambulate. They should also ensure adequate but not excessive fluid intake (i.e. not more than 3 L over the course of

the psychedelic-assisted session). They may also wish to provide electrolyte-containing beverages or juices.

3.3 Preparing social support following medication sessions

Following a dosing session, the participant is to be discharged from the treatment setting 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 with this individual during one of the preparatory sessions. During this meeting, the therapists are to 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 both therapists' cell phone numbers or emergency contact numbers.

3.4 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. The role of the music, regardless of the style, is to provide guidance and a sense of motion or movement 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 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 ambiently in the 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 to be used in the present study was created specifically for a phase 1 clinical trial at Imperial College London, using psychedelic therapy to treat depression by Mendel Kaelen, who researches the effects of music in psychedelic-

assisted therapies. In developing this playlist, he writes: “Apart from the music selection and the structuring of this selection into a particular order, the mixing is an important aspect. The ways songs transition into each other, the fade-ins, the fade-outs, and the periods of silence, all together determine an experience of flow and continuity: The way the music *breaths* in and out of silence, and in and out of diverse emotional trajectories, is attuned to the experience.” In order to control variables between placebo and drug conditions, the same playlist will be used in both experimental sessions.

3.5 Relationship with therapists as setting: the therapists’ commitments

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 review each session and make several specific agreements during the preparation sessions:

1. The therapists commit to providing adequate preparation time during preparatory, debriefing and follow-up sessions (minimum 45 minutes per session).
2. Therapists agree to boundaries regarding touch as defined in the first preparatory session. 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 are 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 duration of the psychedelic-assisted sessions except for brief periods for restroom breaks or other such needs.
4. The therapists will assess the participant along with the supervising physician to determine mental status and stability to leave as part of ending the dosing session.
5. The therapists are 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.

4.0 Prior to the first session with therapists

4.1 Screening and consent

The screening and consenting process will be done by the Principal Investigators, other research personnel or those designated by the PI. The study therapists do not participate in these session. It is worth noting that the establishment of a trusting rapport begins with the first phone call and includes every bit of the screening and consenting 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. 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 experience), and 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 complete the necessary forms while still attending to and allowing time for fostering a therapeutic setting and deepening the therapeutic alliance.

4.2 Prerequisites and Contraindications

Prior to enrolling in the study, participants will be provided with written information about the clinical trial. Participants must be provided with ample time to ask questions and discuss the informed consent with study staff prior to signing.

4.3 Commitments from the Participant (part of consenting)

1. The participant agrees to attend all preparatory therapy and follow-up sessions, completing the evaluation instruments, and complying with dietary and drug restrictions.
2. Participants are not required to complete participation in the study and may withdraw consent and leave the study. 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 she/he will remain within the treatment area until completion of each session. It is the responsibility of the therapist to assess the participant's emotional stability and the cessation of the psychedelic effects of the medication before permitting the participant to leave.

4. Participants are requested to commit to safety from self-harm during the study, to communicate suicidal ideation to their therapists or seek emergency room care if self-harm is imminent.
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 wait until after the completion of the study to engage in public/medical discussions of their experience. We encourage each participant to discuss this decision with the therapists, in order to emotionally prepare for the experience and its aftermath.

5.0 PSILOCYBIN ASSISTED THERAPY: OUTLINE of SESSIONS

The therapy consists of a preparatory period with screening and introductory sessions, psychoeducation sessions, followed by experimental sessions, interspersed with integrative sessions (called debriefing sessions) and later follow-up sessions:

- 5.1 Psychoeducation session #1 (2 hours)**
- 5.2 Experimental session #1 (8 hours)**
- 5.3 Debriefing session #1 (1-2 hours)**
- 5.4 Debriefing session #2 (1-2 hours)**
- 5.5 Psychoeducation session #2 (2 hours)**
- 5.6 Experimental session #2 (8 hours)**
- 5.7 Debriefing session #3 (1-2 hours)**
- 5.8 Debriefing session #4 (1-2 hours)**
- 5.9 Follow-up session #1, #2 (1 hour each)**

The overall goal of a psilocybin-assisted therapy is to increase skills for lessening the “depressogenic” patterns of cognition that characterize depression while increasing values-based active engagement in the world. Fostering these two types of change through the interactive effects of the therapy work and the medication sessions is the central mechanism for change and improvement from depressive symptoms. This goal is accomplished through psychoeducation, the experimental sessions, and debriefing/follow up sessions.

The therapist’s responsibility is primarily to establish a well working therapeutic alliance, feel a sense of rapport, and to support the participant’s honest expressiveness. The therapists, during the first sessions, learn which depressive cognitive/behavioral patterns are most prominent for this particular individual, and use these observations to facilitate change by supporting the creation of intentions for the psilocybin sessions. During experimental sessions, these goals may be best accomplished by silent, empathic presence. In other sessions, the therapist will need to provide more active guidance. The therapist works to support the participant’s openness, self-acceptance, willingness to take action, and increased mental flexibility. They attempt to engage with a participant’s depressive way of 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, the type of therapists that they are in other walks of life; each brings his or her own unique way of working with patients.

5.1 Psychoeducation session #1 (2 hours)

*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 for the first time. They will have met one or both PIs as part of the consenting process. The following tasks need to be accomplished during the first Psychoeducation session:

1. Building rapport and therapeutic alliance
2. Reviewing the overall structure of today's session
3. Understanding the participant's lived experience of depression
4. Understanding the participant's lived experience of psychopharmacologic treatment
5. Understanding the participant's preconceptions about psychedelic experiences
6. Listening for ACT 'misdemeanors' and formulating the participant in ACT language
7. Education regarding the psilocybin experience
 - i. common experiences with psilocybin
 - ii. difficult experiences
 - iii. therapist interventions
 - iv. rescue medications
 - v. safety agreements/boundary agreements
 - vi. departure requirements
8. Eyeshade and headphone trial
9. Questions and details for arrival for session

1. Building rapport and therapeutic alliance

This aspect will derive from the therapist's own way of welcoming a new patient into treatment, introducing him/herself, and cordially beginning the process of rapport building. It may include questions about experiences in the screening and consenting process, the experience of coming to the sessions, or any way the therapists may choose to make the participant comfortable and welcome.

Ex. of rapport building operationalized:

1. Good (morning/ afternoon), I am “ state name”. It’s good to meet you.
2. Offer hand shake, look into subject’s eyes.
3. Do you want to come in and sit down?
4. Would you like a glass of water or anything before we begin?
5. “How has the process been so far?”

2. Reviewing 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 learn about your depression, then about how treatment for depression has been for you. After that, we’ll go over the Values Clarification Questionnaire that you completed during the consenting process and talk about how this psilocybin-assisted therapy treatment 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 will give you a chance to try out the eyeshades and earphones that you’ll use during the session and review all the sessions that are part of the study overall. Sound good?”

3. Understanding the participant’s lived experience of depression

In this section, the participant is invited to describe how his or her depression expresses itself. Part of the goal here is for the participant to speak freely, without structure, to feel carefully listened to and supported in telling his/her own story. The therapist's role is to offer empathic encouragement for the pain and suffering that the participant is describing, but also carrying out the “*Internal Agenda*” that is described below. The emphasis is not on accurately acquiring a psychiatric history (which presumably has already been done) but in learning the psychological and behavioral patterns that define depression in this individual.

4. Understanding the participant’s lived experience of psychopharmacology treatment

Participants in this study are likely to have had several if not multiple courses of treatment, experiencing numerous medications, medication combinations and practitioners. These experiences may have left an overall transference towards treatment that is likely to be present for each person in the study. The pressure to achieve rapport rapidly and hold an idealizing attitude toward the study medicine may make it challenging for the participant to be genuine with the therapist, therefore it is valuable for therapists to understand the participant’s history with psychiatric treatments. Awareness of the participant's emotional valence toward psychopharmacology as a needed but disappointing presence may be helpful in understanding the relationship with psilocybin.

5. Understanding the participant’s preconceptions about psychedelic experiences

Ask participants about their preconceptions, expectations etc about psychedelic experiences and psilocybin. Elicit their concerns and hopes.

6. Education regarding the psilocybin experience

Some of the following will have been discussed during the consent process with study staff, but it will be important to ensure participants' understanding of this material. It is also valuable for this information to come from the lead study therapist.

i. Common experiences with psilocybin

- Psilocybin is a “classical” hallucinogen that can cause profound changes in sensation, perception, thought processes, emotions, the experience of time, the nature of reality and of the self. The effects may range from very mild to very strong.
- Perception: you may experience visual distortions or illusions, strong visual imagery and rarely true hallucinations. Generally 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 had lived 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.
- It 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.
- We encourage you to take an attitude of curiosity and acceptance toward whatever happens during your session. Whatever comes up has some kind of meaning or innate wisdom that you can learn from. However, this meaning may not be immediately obvious. It is not uncommon to feel as though your thoughts and perceptions are coming more swiftly than you can process them. Fully allowing all your emotions and perceptions, good and bad, is what we hope for, whatever memories, images or body sensations arise. Accepting and feeling this is, strangely, the path toward being able to do something about deep-seated patterns of fear, powerlessness, guilt, and shame.

Ski slope metaphor:

- Thinking over and over again is like skiing down a mountain - once you go down one way you are more likely to go down that way again. In depression, people often ski down well established ruts. Psilocybin is like a new coating of snow on the mountain, so that there is much more freedom to ski anywhere (a greater ability to

think freely and tolerate a broader range of emotions). The psilocybin can be seen as helping you find different paths down the mountain.

ii. Difficult experiences

- This medicine may cause physically or emotionally uncomfortable periods
- Physically, you may experience periods of nausea, chills, anxiety, or panic. Your blood pressure may become somewhat elevated, but we will be monitoring this. Remember that although the psychological effects may be extreme, the physiological risks of this medicine are extremely low.
- You may have bizarre sensations and experiences or there may be very frightening images or thoughts. These may alternate rapidly. This is normal and does not mean anything is wrong. The effects are time-limited and present no major risks to the body. It is best to embrace these experiences as they occur and seek to learn from them.
- It is best 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, especially if your impulse is to run away. Stay with the experience, dive in and explore, allow yourself to be curious about what is emerging in your experience. “Trust, let go, be open”.
- Take a moment to acknowledge that what we are asking the participant to do is difficult, counterintuitive and not our usual pattern of avoiding negative or uncomfortable emotions and experiences. It may be something they will have to remember over and over during the session.
- There are methods for grounding and calming yourself, if you would like to use them. We will teach you several of them before the end of today’s session.
- If you are having difficulty with anxiety, panic, nausea or paranoia, please let us know, and we may be able to help you by providing reassurance, support, redirection or therapeutic touch (if you give permission for that).

iii. Therapist interventions

- During the preparatory and integration sessions, we will have a free exchange of ideas, ample time for conversation and discussion. During the medicine session, you are invited to go on an inward journey, and allow yourself and the medicine to create your experience together. We encourage you to collect experiences and save discussion about them for later review and reflection. We will be in close attendance, may check in with you if you are in distress, but 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 signalling to us, and we will always be present to help you.

Grounding Techniques

Awareness of Body Sensation

- When you are experiencing strong emotion that is causing you to feel you have lost your balance, this mindfulness practice can help you regain a sense of balance.
- As you are lying here, arrange your body in a comfortable position, turning your attention to how it is with your body at this moment.
 - We feel emotions in our body – a heaviness in the heart when we are sad, perhaps, or maybe a tightness across the jaw when we are angry. Where in your body do you feel emotion right now? [*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, as best you can. 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 sensation 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 sensation.
 - This is especially important if you notice yourself lost in thinking about the events or circumstances connected to the emotion. Redirect your attention to what you feel in your body.
 - Purposefully return your attention to bare sensation, as you feel it in your body. [*Pause*]
 - (Wait at least five minutes before giving the following instruction.) Notice if the sensations shift. They may grow weaker or stronger, they may shift in location, they may spread out or shrink. Or they may change in some other way. Whatever happens, whether they change or not, continue resting your

attention on them from moment to moment.

- You can imagine, if you like, that you are sitting on a park bench, gazing at the scenery, observing the changing pattern of the sunlight on the leaves, for example.
- And so, 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.)

Abdominal Breathing

- If you are feeling tense, anxious or overwhelmed during the session abdominal breathing may be helpful.
- Direct your attention to your breathing
- Focus on moving air with your diaphragm rather than your chest muscles
- With each exhalation, let go and feel tension leaving your body

Touch

- It is sometimes helpful to establish physical contact with one of your therapists.
- If you are in agreement, we may offer hand or foot holding or a hand-on-shoulder to make contact with you.
- You may request this at any time during your medication session if you think it would be helpful. We also may offer this to you if it seems like you're having a difficult time. If you can not speak and would like physical contact, raise your hand to communicate this to us. We will only touch you with your advance permission. Do you give us permission to make this kind of contact with you during the session? You may always change your mind and let us know you do not want to be touched at any time.

iv. 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. For the most part, using any of them will be a joint decision, not unilaterally decided upon.
- However, in the case of an unresolvable difference of opinion, the participant

must accept the clinical judgement of the therapists. For example, if the recommendation is for evaluation of hypertension in the emergency department, the participant agrees to comply.

v. Practical Guidance and Safety instructions

- Think of the experimental session as a multi-day experience: Minimize stress for a few days before the session and especially the day before. Having some time in nature, for instance, is a good idea. You will be in the best position to benefit from the session if you are sober from alcohol and other intoxicants for one week before the session.
- We also suggest not to work the day after the session, or at least have a light schedule. It is good 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, arrive well rested, if possible, but don't be surprised if you have some difficulty sleeping the night before. 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, healthy breakfast either before your arrival or upon arrival to the lab (you will be offered a light breakfast at the lab consisting of cereal and juice). We will have light snacks, such as granola bars and crackers, as well as water and ginger ale available to you throughout the day. 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
- in a change of clothes and feel free to bring photos, small art work, or any objects that you feel will be helpful in focusing your attention during your session.
- On the day of the session, arrive at 8 am to complete final questionnaires, urine toxicology, and urine pregnancy test (if indicated).
- After you take the study medication, you must stay in the clinic for the next 6-8 hours or until you are deemed safe to leave by study staff. Leaving before being cleared by study staff could result in a bad experience or dangerous situations. **We need a firm 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, 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 a few questions on how you're doing; otherwise we will not intrude unless you initiate contact or appear to be in distress.
-
- If you feel emotional, need to laugh or cry or express yourself, please go ahead. This is normal and expected. **However we will work with you to maintain safety for yourself, the study personnel, and the study environment, as you may have an urge to engage in behaviors beyond your volitional control.**
-
- Nausea and stomach ache sometimes happens, vomiting rarely. We will have an emesis basin for you if this occurs.
- After about 6-7 hours, we anticipate that the medication effects will be tapering off. We will check in with you and ask you to complete some more questionnaires.
- **After the session:** After you go home, we ask you to take 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. If you wish to talk about your experience, limit discussions to people who know what you've been doing and are close to you.

vi. Departure requirements

- The participant will have arranged a companion or support person to come at the end of the dosing day and accompany him/her home. That person will be contacted ahead of time by study staff in order to assess competence and appropriateness for their role, and provide psychoeducation. The support person will be educated regarding:
 - Basic structure of the study
 - Range of possible after effects:
 - Headache, common, treated with ibuprofen. 200 mg po
 - Infrequent: changes in mood, confusion, anxiety, insomnia.
 - Rare effects: paranoia, panic, suicidality.
- The support person will be asked to come up to the study area to directly receive the participant upon conclusion of the session. They will be provided an information sheet containing contact information for study staff in case any concerns arise.

Writers gratefully acknowledge the use of work by Bogenschutz & Forcehimes, (2014) in

this section.

7. Intention Setting

Your intentions and relationship with the medicine have a large part in creating the experience that you have. The clearer and stronger your intentions, the more benefit you are likely to derive from the medicine. Remember that the primary purpose of your engagement with the medicine and therapy is to change the ways that you think and act that make up your depression. The goal of the medicine is to help you realize potential positive changes you can make in your life, but it will not make them for you.

The therapist should work with the participant

8. 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 eye shades that will be used in the dosing session, as well as listening to a few minutes of the music playlist. At the same time, the participant will be given an opportunity to recline prone on the sofa or armchair they will use during the actual medication session.

9. 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.

Internal agenda for therapist during Psychoeducation Session #1:

Direct education for 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 be carefully observing which of these are most prominent for this participant, where strengths lie, what particular psychological patterns seem most “depressogenic” and where resilience and creativity may lie.

1. Cognitive fusion: Does the participant have significant experience of thoughts, words, language as if it were true? The thought “I am a worthless person” is experienced as if it were true in an absolute sense. “I am so depressed that I cannot move” is experienced as actually true, “my life is worthless” or “I cannot do anything right” are all 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, that is my core identity” is an example 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) may be defended against through:

2. Experiential avoidance: 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 manner
- 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. “If I don’t get off the couch and go to that party, I don’t feel like a loser when no one wants to dance with me” leads to a reduced negative affect from staying in a safe place, but a more long-term depressogenic isolation and reduced social functioning.

3. Reason-giving/rumination: the search for reasons that one is depressed is not linked to successful change of that condition, and in fact can lead to persistence or exacerbation of the condition. This is especially true with historical events that “caused” the depression that can never be changed, leading to the conclusion that recovery from depression feels hopeless. In other words, “my childhood trauma caused this depression, and nothing can change what happened then, therefore my situation is hopeless.”

4. Self-Discrepancy: cognitive structures that monitor self-concept and goals and find a large discrepancy generate depression. 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 if the assessment is “I am depressed because I am a terrible person, therefore I must become a good person.” In more common language, this reflects unrealistic, grandiose, or even modest self-expectations which generate depressive cognition when not met.

5. 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. This implies that a certain passivity and surrender to the treatment is the primary strategy. The willingness to take action to change one's life is explicitly evoked in ACT (commitment), and the passive wish to feel better solely with the medication is confronted. While this step (confrontation) is not addressed in Psychoeducation Session 1, the therapists are carefully observant of the balance of activity and passivity in the participant’s narrative and behavior in session.

ACT principles for therapist consideration:

Cognitive defusion: decreasing identification with thoughts; thoughts/feelings are not facts, memories do not constitute the self.

Cognitive defusion metaphor

Acceptance: allowing thoughts, emotions, and interoceptive states to come and go without struggling with them.

Acceptance metaphor

Awareness of the present moment, experienced with openness, interest and receptiveness; be interested in what is internal; mindfulness.

Awareness metaphor

The Transcendent self: reperiencing the self as distinct from thoughts and feelings, the ground (Self) abides, the “weather” (internal experience, emotions, thoughts) are always changing and do not constitute the Self.

Self-transcendence metaphor

Values: defining which values have the most meaning in the participant’s life

Action: Setting goals based on values and taking committed actions to carry them out responsibly.

5.2 Experimental Session #1 (8 hours)

Overview

Two study staff will be present for the entire experimental dosing session: the participant’s therapist as well as a second sitter, who may be one of the study PI’s. There will always be a supervising physician available and nursing staff and research assistants will also be present to assist with vital signs collection and completion of scales and assessments. Sessions begin with the arrival of the participant and completion of scales and assessments that are scheduled for the morning of the dosing session. Also, blood pressure and pulse are checked to make certain that they are in an acceptable range for proceeding with the dosing. If the participant is capable of becoming pregnant, a female of childbearing age, a pregnancy test will be done that morning. The room will be devoted to this study participant’s dosing session, exclusively, for that day with no other persons entering the room except in case of emergency. The room will have been prepared previously to create a safe, warm, private atmosphere.

Session preparation Checklist (these are to be gathered and ready the morning of the session)

- Room decor: flowers, fruit etc
- Sheets, blanket, pillow
- 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 medication, PO and IM
- Monitor rating forms and vital sign forms as required

Check In

The participant is greeted by the researchers or their designees and given standard medical/psychiatric assessments: blood pressure and pulse are checked for appropriateness for dosing, the participant is evaluated for suicidality (leading to emergency assessment by therapists and referral as needed), urine toxicology and pregnancy, asking the participant about any changes in their medications.

The participant will be taken to the bathroom before ingestion of the study medication.

Once the study medication has been ingested, the participant will remain under observation for at least the next 6 hours. Maximal effects are expected to occur at approximately between 45 and 90 minutes. At least one member of the study personnel (either the therapist or the supervising physician) will be in the room at all times, the other missing only for visits to the restroom or other brief absences.

Dosing: When cleared to begin the dosing session by the supervising physician, the participant will be offered the study medication and advised to drink an entire cup of water to facilitate the capsule dissolving fully in the stomach. The participant usually will want to speak for a few minutes after swallowing the pill. After 15-30 minutes, the participant is encouraged to lie on the couch wearing eye shades for most of the time throughout the session, unless he/she needs to communicate with the therapists. Interactions with the participants should be supportive and non-intrusive, except for optional brief check-in during vital sign monitoring. Personal items brought by the participant will be available through the session. Vital signs will be monitored at 30 minute intervals for two hours, then hourly. At the time of vital sign assessment, therapists will check in briefly with the participant. 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.

Guidelines for therapist actions/attitudes during session

Principles of non-intrusive presence

The therapist during the session will maintain an attentive but non-intrusive presence. As a rule the therapist will not engage with the subject during the session except in a

supportive manner when sought by the subject.

Responding to invitations to talk

If the subject attempts to engage with the therapist in conversation the therapist will listen and respond in a supportive manner and when reasonable will suggest the subject return to the music and eyeshades.

Responding to intense, painful affect states

The therapist will gently encourage the subject to “lean in” or “go towards” intense or difficult affective states.

Responding to agitation or restlessness

The therapist will encourage breathing exercises if needed to sit up and take off the eye shades briefly while offering reassurance that such states are sometimes to be expected and will likely pass shortly.

Responding to requests for contact

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

Responding to marked agitation

If the subject has significant or marked agitation the therapist will advise the subject to sit up remove the eyeshades attempt relaxation breathing consider changing the music and if all else fails the therapist will consult with the physician to administer benzodiazepine or other medication as needed. Medical intervention will be utilized only when agitation persists and no other means to help relieve the agitation is effective.

Responding to marked, persistent paranoid reactions

If the subject presents with significant persistent paranoia the therapist must remain calm and present. The therapist must be reassuring to the subject that they are safe and that the experience will be time limited and that when the experience ends the concerns they are experiencing will likely resolve.

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 that they had agreed not to undress previous to this additionally the therapist will first ask the subject not to undress and later more firmly if needed tell the subject that they should not undress. If the subject desires to move about the room the therapist will

encourage the subject to limit this as much as possible and will encourage the subject to return to listening to the music and replacing the headphones as quickly as possible.

Therapist's Role/Attitude/Frame of Mind During Psychedelic-Assisted Sessions

A calm, stable attentive self-awareness is of great value during the dosing sessions. An empathic presence during the session will offer the best support to the participant, while at the same time, maintaining clear boundaries of touch and speech. In so doing, the therapists encourage the participant to stay present with her/his own 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 process of re-perceiving 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 offer assistance to the participant for managing difficulty or confusion, while fostering the awareness that the participant's relationship with the medicine is the primary source of healing.

The therapists keep in mind any intentions for the session that the participant has identified during introductory sessions, while also allowing for additional, perhaps unexpected, psychic material to emerge. They also consider individual psychological factors, such as attachment style, that may impact the therapeutic relationship (transference and countertransference) and influence the degree and specific nature of therapeutic intervention that will be best suited to that individual.

First Narrative Telling (15-30 minutes)

Toward the end of the session the participant will be invited to tell the story of the experience that they have had. The therapist will focus on eliciting phenomenology, rather than interpreting. Notes will be taken as the participant relays their story.

Departure:

About 6-7 hours after ingestion of the study medication, the majority of psilocybin effects should have abated and the participant should be capable of sitting up, conversing, and eating some food. He/she is to complete any questionnaires that are part of the study and may share with the therapists some of his/her experiences during the day. It can be very helpful if one of the therapists takes verbatim notes and gives these to the participant to take home. After all assessments, narratives and eating has been done, 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 6 hours minimum. In other words, if ingestion occurs at 9 am, the discharge

will be 3 pm or later. Assessment of readiness to leave the treatment setting entails assessing mental status, physical safety (vital sign stability, coordination, steadiness of gait and assessment for 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 his/her companion for accompaniment home to a quiet, supportive, low stimulation environment. The next days' debriefing session, which has already been set up, is confirmed and the therapist makes certain both the participant and the support companion have both therapist and study staff telephone numbers.

The authors wish to acknowledge the excellent standard of care delineated by Bogenschutz and Forcehimes (2014).

5.3 and 5.4 Debriefing session #1 and #2 (1 hour each)

General guidelines for debriefing sessions: The primary goal for debriefing is to support the participant's reflection on the medicine session. This will be accomplished with open-ended questions about the session, intending to elicit the introspective, interpersonal, spiritual and/or noetic insights that occurred during the session and may otherwise be forgotten or difficult to verbalize. Eliciting such insights may provide important clues to changes in behavior, thought, or relationships that may help alleviate the participant's depression. Therapists will be largely supportive of narrative expression of the participant's experience. A related goal for debriefing will be to listen for (debriefing #1) and explore (debriefing #2) aspects of the participant's narrative that are consistent with the core ACT principles of **Cognitive Defusion, Acceptance, Awareness, Transcendent Self, Values and Action**.

The therapist's challenge during debriefing is to hold an open, affirming narrative style of listening to the psilocybin experience, while exploring aspects of the participant's narrative that can be understood in terms of the core ACT principles.

5.3 Debriefing Session #1 (1 hour; 1 day following Medication session 1)

This session is approximately one hour long and occurs the day after the first medication session. Begin with an opening statement:

- Today the main goal is to talk about your medication session. We are interested in talking about how the session affected you, what you learned, and most importantly, how it has affected your thinking and ideas about your depression.
- Can you tell us everything that you can about your session? From beginning to end: what happened? What do you remember? What did you see? What did you hear or feel? What happened in your body?

- What happened that was difficult or challenging for you? Were there periods of negative emotion, fear, sadness, depression, terror? Were there images that emerged 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? What do you notice about your familiar depressive thoughts, beliefs, attitudes, 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?
- What are you thinking and feeling about your depression today?

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 whether the participant needs to be treated in a hospital ED. If no acute safety concerns are identified, the therapists close the session by confirming the next appointment, and restate their availability by phone.

The authors wish to gratefully acknowledge the work of Bogenschutz and Forcehimes in establishing these guidelines for the preparatory, dosing and integration sessions (2014).

5.4 Debriefing session #2 (1 hour)

The goals of the second debriefing session are similar to the first but will also include an exploration of the role of **personal values** in recovering from depression. The first half of the session (approximately) will be devoted to discussing the previous medication session. The latter half will be reserved for engaging in values clarification, through the use of the Valued Living Questionnaire (VLQ) and values clarification list. The session may conclude with a metaphor to highlight important topics if appropriate.

Debriefing of Medicine Session:

- 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:

- A couple of weeks ago, 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.

Therapists bring out the Valued Living Questionnaire results and give a copy to the participant. Time is allotted to review the results, and then the participant is asked to respond to the feedback.

The therapist tries to help the participant clarify:

- Which values are most important.
- Which he/she is most attached.
- Which values used to be expressed in day to life but were lost to depression.
- Values that were imposed but not chosen, and need to be retired.
- Values from childhood or early adulthood the participant has lost touch with.
- Which values used to be important, but now are unimportant.
- Which values have their expression impeded by depression and how living with depression has led to important values being neglected or discarded.
- As we go through this exercise, what does it make you feel? What memories does it trigger? Are you surprised at what came up for you in the questionnaire?
- Did these values (family, creativity, loyalty, recognition) show up during your medicine experience? Does today's conversation make you think about how you might express these values in your life as you move forward? How do you see your depression affecting you as far as living with these values?

Ending

- Confirm safety and stability of the participant
 - The participant may be sent home after the session on his own, provided there has been no emergence of worsening depression symptoms. If so, a full mental status examination and clinical interview should be done, followed by stabilization of the situation.
- Confirm scheduling for the next sessions: Psychoeducation #2, Dosing #2, Debrief #3 and #4

5.5 Psychoeducation #2 (2 hours)

The second psychoeducation session is designed to teach the participant that the thoughts and behaviors (cognitive processes, actions) that are problematic in depression can be changed through an interactive process between the principles of ACT and

psilocybin.

This session is divided into 4 parts:

- Checking In
- Differentiating traditional psychopharmacology model of depression treatment from the psychedelic therapy model.
- Psychological Processes in Depression
- Mindfulness Practices

5.5.1 Checking In

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

5.5.2 Differentiating the traditional psychopharmacology model of depression treatment from psychedelic-assisted therapy model

1. In traditional psychopharmacology model for depression, depression is seen as a medical illness, that exists in the brain.
2. The doctor (or other MH practitioner) diagnoses the condition, explains it as such to the patient, and prescribes medication.
3. The patient's role is to report symptoms honestly, accept the doctor's diagnosis and treatment recommendation.
4. The medicine, then, is the active agent, which works to change the brain chemistry, and hopefully, improved mood, altered thought patterns, behavioral activation follow over the coming weeks. Ex SSRI or antibiotic as an example.
5. In psilocybin-assisted therapy for depression, the participant is invited to be a more active agent in changing his/her patterns of thinking and behaving.
6. The experience of the medicine and the relationship with the therapists is used to facilitate these changes in thinking and behaving.
7. The medicine may have a profound effect in facilitating these changes, but it will not accomplish it for you.
8. The therapists communicate that active utilization of the medicine experience and the therapy is what will bring about change.

5.5.3 Psychological Processes in Depression

The purpose of this section is to induce Creative Hopelessness: that the participant's normal, instinctive ways of fighting depression are, in fact, sustaining it. This section is didactic, explaining to the participant how we believe our therapy approach works.

Suggested language: "We are going to teach you what the field of psychology has learned about depression, namely, how the mind of people with depression commonly works. It's not about understanding WHY you're depressed, but about understanding HOW the

depressed mind works. 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 wrong 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 your depression. We anticipate that the medicine sessions will help these new ideas to be felt on a deep emotional level."

The following are aspects of depressive thinking that often are part of depression:

a. Cognitive fusion:

The therapist explains what cognitive fusion is and provides some examples of it. Fusion is when thoughts are experienced as true without being able to reflect on their actual truth because they feel so true. You may want to give some examples of cognitive fusion in the abstract, or take some clinical moment from your previous sessions and point out an example of cognitive fusion.

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 bring in the ACT concept of **Acceptance** of that feeling (rather than trying to change so the feeling goes away). The bottom line in this section is to introduce the idea: I am not my thoughts; my thoughts arise and pass away, arise and pass away, and I can observe that happening.

Or the concept of **workability**: The issue is not whether thoughts are true or not but how much they get in the way of someone living out their life in a meaningful way.

b. Experiential avoidance:

Painful thoughts and feelings, even when being observed can be extremely uncomfortable. This can lead to "experiential avoidance." Explain to the participant what experiential avoidance is, though you may want to avoid using the word "experiential". There are two forms of experiential avoidance:

Internal avoidance is trying to avoid or stop painful emotions or thoughts, trying to make these go away either by avoiding thinking about them or trying to fix them through understanding them. Here, give some examples of internal experiential avoidance that you've seen in the weeks of working with this participant. In doing this, you are invoking "Creative Helplessness": what the person has been doing, and doing for a long time, doesn't work in alleviating their depression. This may or may not be easy for them to hear, so there may be distress as familiar strategies for blunting pain are challenged. This is

where radical Acceptance of emotion can be put forward as a healing process.

External avoidance refers to not doing something anxiety provoking leading to a reduction in painful emotion, thus a reinforcement for not taking action in the world. Teach the participant what we mean by external avoidance and if available, give some examples of places where the participant has demonstrated external experiential avoidance.

It might be valuable to explain why giving up experiential avoidance is so difficult: it works, in the short run. But studies show that prolonged experiential avoidance is associated with persistence or even worsening depression in the long run because it reinforces isolation and hopelessness.

Creative hopelessness: and you've been trying to avoid painful thoughts and feelings for a while, but unfortunately that hasn't worked so well. We will try to teach you some skills in order to take a different approach.

d. Reason-giving/explaining why/workability: Explain that narratives about the past and what "caused" the depression are not part of this therapy. Not that those narratives are false, but they are not as relevant to solving your depression as they were for causing it. Reviewing these narratives over and over are not helpful as they can limit us from having a more rich, full, meaningful life.

Workability: The issue is not whether the reasons for your depression are true or not but how much they get in the way of you living out their life in a meaningful way.

e. Willingness to act (in valued directions):

Teach the participant the difference between willing and wanting; introduce the idea that how the participant feels about doing something doesn't have to determine whether they actually do it. i.e. they may not want to do something, but can still be *willing* to do it. In contrast, saying "I'm willing to do it only *if I feel like it*" is very problematic and perpetuates depression, rather than addressing it.

See if you can help the participant recognize that while there is one voice in their head that believes "I cannot go to the gym because I am immobilized by my depression," that they are also capable of getting up (they are not truly paralyzed).

I can go to the gym even though I feel tired and depressed. I can feel depressed AND go to the gym.

5.5.4 Mindfulness Metaphor and Practice:

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

There may be some mention about The Transcendent Self, if appropriate.

Introduce mindfulness practices using a metaphor if that seems helpful, such as clouds passing through sky (p. 175)

Examples of such mindfulness practices that may be used are:

1. Breath awareness practices (counting breaths, following breaths, ratio breathing)
2. Mantra meditation
3. Touch points: awareness of the points of your body that contact the environment or themselves
4. Awareness of sounds

A selection of these meditation instructions are available in a PDF in the virtual study library.

5.5.5 Intention Setting

“What constitutes, for indigenous peoples, the self, the person, categories of person-in-time (ancestors and their descendants)? The person consists of several “souls,” modes of consciousness, mental and physical faculties, intentionalities, sentiments, bodies, along with ongoing relatedness to different kinds of beings. The religious beliefs and practices of indigenous peoples are characterized by a conviction that spirit moves through all things, animate and inanimate, subjects and objects, and that the living are intimately connected with the souls of their deceased ancestors.” (Wright, p. 50)

Your intentions and relationship with the medicine have a large part in creating the experience that you have. The clearer and stronger your intentions, the more benefit you are likely to derive from the medicine. The goal of the medicine is to help you realize potential positive changes you can make in your life, but it will not make them for you.

5.5.6 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.

5.6 Experimental session #2 (8 hours)

See 5.2 above

5.7 Debriefing session #3 (1 hour, one day following medication session #2)

The Guest House

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 smiling and invite them in.
 Be grateful for whatever comes.
 because each has been sent
 as a guide from beyond.

— Jellaludin Rumi,
 adapted from the translation by Coleman Barks

This session is one hour long and occurs the day after the second medication session.
 Begin with an opening statement:

- Today our main goal is to talk about your medication sessions. We want to hear about yesterday's session, and also how it compared to the one four weeks ago. We are interested in talking about how the session affected you, what you learned, and most importantly, how it has affected your thinking and ideas about your depression.
- From beginning to end: 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? Were there periods of negative emotions, fear, sadness, depression, terror? Were there images that emerged that were 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 in depression for many people, and how the medicine session might change some of those--or didn't.. Do you feel like you learned anything about your depression and what maintains 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 (the therapists) today? How did family contacts feel since yesterday's session?
- What do you think and feel about your depression today?

Optional metaphor (for transcendent experiences): House and furniture metaphor

where the subject uses the metaphor to see themselves as self as context / larger than their everyday sense of self. The house, like their true nature is permanent and stable, while the furniture, like their thoughts and feelings can come and go or be changed. Ultimately, we would like the participant to adopt a more flexible attitude and be less defined by their symptoms. We encourage the participant to identify with the house, larger, and distinct from depressive symptoms.

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 whether the participant needs to be treated in a hospital ED. If no acute safety concerns are identified, the therapists close the session by confirming the next appointment, and restate their availability by phone.

5.8 Debriefing session #4 (1 hour)

This session continues the move toward integrating the medication session experience with ACT and taking the values exercise into the action phase.

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 to and willing to. The therapist will take a gently didactic approach, pointing out successful changes with praise and encouragement while delicately 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 his/her material in a real life way that would evoke an exploratory response from the therapists in a traditional psychotherapy. In an ACT based way of facilitating psychedelic therapy, the therapists are listening for the change processes defined by ACT and mindfulness-based practice, and 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 their 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 her suffering, to about the death, and likely deepen the intensity of affect around it. An ACT response might be to listen compassionately, but use defusion to draw attention to the participants attachment to 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.

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 (re)discovery of values or reprioritization of values. In this session, the therapist and participant devote 20-30 minutes to discuss any changes in values, and any actions that are underway. The therapist may follow up on values identified as important previously and engage the participant in the 'values four square matrix exercise'. Then the therapist may offer help in planning values-based actions. Some may find a small booklet/journal to be helpful in planning.

Values four square matrix exercise:

It is likely, of course, that fear, doubt, anger, and/or sadness may emerge, so it is a good time to practice ACT techniques for working with these emotional states. The model for the therapist in this session has some similarity to a coach. Rather than non-directive, you are gently directive. You help define exactly what the participant will do, when and where. It is not "take some yoga" but "take a vinyasa class on Wed at 10:30 at Integral Yoga Institute on Spring Street". Pressing like this is likely to evoke depressogenic processes that can be explored and acted on with ACT interventions/ mindfulness. Take 3 minute

mindfulness breaks during the session.

Ending:

- Confirm safety and stability of the participant
 - The participant may be sent home after the session on his own, provided there has been no emergence of worsening depression symptoms. If so, a full mental status examination and clinical interview should be done, followed by stabilization of the situation.
- Confirm scheduling for the next sessions

5.9 Follow-up session #1, #2 (1 hour each)

Follow-up sessions 1 and 2 are designed to address the process of ongoing self-focus on depression recovery, plus issues of termination. These two sessions reinforce important concepts, encourage successful changes, and improvements, facilitate further meaning making for the participant regarding the psilocybin experience, and for continued practice of mindfulness and ACT skills.

Follow Up Session #1 (1 hour)

Preferably there will be the opportunity for case discussion and consultation prior to this session to establish an individualized plan for the remaining sessions.

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

Termination: 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. Feelings, thoughts, and questions about the termination sessions should be invited.

Acceptance and Commitment. This is to be the major part of the session. The therapists continue the work of integrating ACT incites into everyday life. They can introduce the ACT hexagram and explore how the medicine session and therapy have brought each of the points of the the ACT hexagram to light with the opportunity to elicit practices, teach patterns, reinforce successes in defusion, values based action, refocusing, mindfulness practices. The discussion focuses on the experiences of acceptance (mindfulness, self-transcendence) and commitment (values, willingness to act) that are emerging in the participant's life. Then, discuss how these relate to the medicine experience. A brief meditation or period of contemplation may be incorporated into the session at some point.

Teach informal Mindfulness exercises

Review worksheet with participant and identify everyday mindfulness practices they will do.

Begin reviewing after care plan

Begin discussing the participant's plans for continuing therapy, integration and self-development. You may refer to our list of aftercare resources. Some examples include psychotherapy, group psychedelic integration in NYC, ketamine therapy, MBSR, mindfulness practices/groups.

Follow Up Session # 2: The last session. Goodbyes. Future.

Check in. Events of the weeks since last session.

Termination exploration. This session is devoted to review the experience of the study and terminating. The therapists and participant will remember, narrate, and share observations of themselves and each other during the study period. We hope by this time in the study that there will be much improvement to celebrate. The three in the triad have had a unique experience, nothing ever to be repeated in quite the same fashion. The three will have formed a group, a family, a container. They need to face the rather abrupt termination, with mindfulness, acceptance.

Saying Goodbye: The therapists should have clarified the prohibition against clinical work together after the study between therapists and participants. Plans for transition back to the treating psychiatrist and therapist will be discussed. The parameters for contact after the end of the study may need to be restated. Norms around phone calls, email, text, etc should be discussed. Ongoing responsibility to the study for assessments may need to be reviewed. Finally, goodbyes, well wishes, thanks, etc.

6.0 APPENDIX A: THERAPIST SELF-CARE

Compassion and love are necessities, they are not luxuries. Without them we cannot survive. - Dalai Lama

Therapists should engage in some form of 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 that they take time for regular debriefing with the co-therapist. This should include an opportunity to process their own emotional responses to working with 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?

Boyle (2011) writes, "In its simplest form, compassion fatigue implies a state of psychic exhaustion. Sabo (2006) described it as a severe malaise resulting from caring for patients experiencing varying aspects of pain (i.e., physical, emotional, social). Compassion fatigue is associated with the 'cost of caring' and refers to the resultant strain and weariness that evolves over time." Therapists will spend close, interpersonal time with participants, being fully present as they describe their life story, concerns, anxieties, and dreams during preparatory, doing and integration sessions. This close proximity may lead to compassion fatigue. The following are some simple methods of self-care to keep in mind:

- a. Listen to your body- 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 simple breathing that expands your ribs front to back and side to side. Do a "body scan" 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 the people are that have the ability to support you if and when you need it.
- g. Take time after the session to release your role. Shaking your arms and body is a good way to get rid of any energy that has gotten stuck.
- h. Have a good nutritious meal after a session and do something grounding and enjoyable.
- i. Using water in the bath, shower or hot tub and reflecting on the archetypal qualities of water to dissolve and cleanse on many levels.

j. Consider having your own ongoing psychotherapy and/or supervision with another therapist.

7.0 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,

Effects of Psilocybin Total Time for Oral Synthesized=approximately 4-7 hours (effects may vary with each individual; physical and mental effects do not necessarily correlate with each other)

Onset: 15-40 minutes Coming Up: 15-30 min. Gliding Down: 1-3 hours (Effects generally last for 6 hours, stay in Session Room for 8 hours)
Next day fatigue, or “hangover” After Effects: 0-6 hours Plateau: 1-4 hrs.

Chemical structure of psilocybin and psilocin similar to the neurotransmitter serotonin. Involved in: appetite, sleep, memory, learning, temperature, mood, behavior, muscle contraction, depression, CV function, endocrine and aging regulation, bone metabolism, wound healing, possibly migraine headache.

Psilocin is the active agent after psilocybin has been ingested (phosphorus removed). Primary effect of psilocin is on the receptors for serotonin.

From the PK Study Protocol: “Psilocybin(4-phosphoroyloxy-N,N-dimethyltryptamine) is a hallucinogenic tryptamine that was first isolated from Psilocybe mushrooms in 1957, followed by de novo synthesis the following year. Psilocybin was marketed internationally in the 1960s as Indocybin (SANDOZ), and although it was well tolerated and demonstrated potentially useful effects, it and the other classic serotonergically mediated hallucinogenic drugs were placed in Schedule I in 1970 and removed from research use When mention is made of psilocybin’s effects, it is understood that the active constituent is psilocin. Like lysergic acid diethylamide (LSD), the psychoactive effects of psilocybin are thought to act primarily through its agonism at the 5-HT_{2A} serotonin receptor: unlike LSD, psilocybin is not thought to have any effect upon the dopamine receptor. Three structural groups of psychedelics/entheogens are: tryptamines, phenethylamines (mescaline), and ergolines. Tryptamines includes psilocybin, psilocin and N, N-dimethyltryptamine (DMT) and they bear close structural similarity to serotonin (LSD has tryptamine as a core framework but is

an ergoline.)

As a tryptamine-class effect of hallucinogens, psilocybin causes both psychic and somatic (physical) effects. Physical symptoms are typically mild and usually are not noticed by the subject. Despite common, mild elevations of blood pressure and heart rate, recent clinical studies do not indicate a need for the administration of medications to lower blood pressure during a treatment procedure, and controlled hypertension is not an indication for exclusion (Johnson, 2012). Although active at the 5-HT_{2A} serotonin receptor, there are no cases of serotonin syndrome toxicities with psilocybin or with LSD (Gillman, 2009). Ergolines and phenethylamines do not resemble serotonin in structure, but all 3 classes seem to exert their effects on human consciousness by interacting with similar targets in the brain. The 5-HT_{2a} serotonin receptor is a key site for action of entheogens.

Brain imaging studies need to be done to support a variety of hypotheses as to where in the brain psilocybin has an effect/ attributed effects." For more detailed chemistry and pharmacology see:

Hasler, F., Grimberg, U., Benz, M.A., Huber, H., & Vollenweider, F.X. (2003).

8.0 APPENDIX C: The Entropic State and Psilocybin Therapy

Carhart-Harris et al. (2014) argued for a novel theory of consciousness developed from research using psychedelics and contemporary brain imaging techniques. It is based on the concept of system entropy, which is a lack of order or predictability, and criticality, which is the point at which an organized system is on the verge of losing its organizing structure. In this model, evolution led to increased order (decreased entropy/a move away from criticality) as life evolved. More order led to more complex systems, including the human brain. Early humans were able to organize their experience through reality testing and planning, ultimately allowing for mastery over the surrounding world (which is less ordered). In depression, it is hypothesized that this process reaches a point where it is counterproductive, where individuals become 'stuck' in an inflexible pattern of reality testing, which while initially adaptive, becomes maladaptive by countering happiness or contentment (so-called depressive realism). In other words, depression is understood as one example of a low entropic brain state where cognitive processes and related brain networks are unusually rigid. Psychedelic medicines move brain networks toward greater entropy, that is, lower levels of organization, more randomness and greater flexibility (towards criticality). This state of greater entropy is often described at the personal, subjective level as a greater sense of freedom of thought and decreased rigid patterns of cognition.

The entropic brain hypothesis

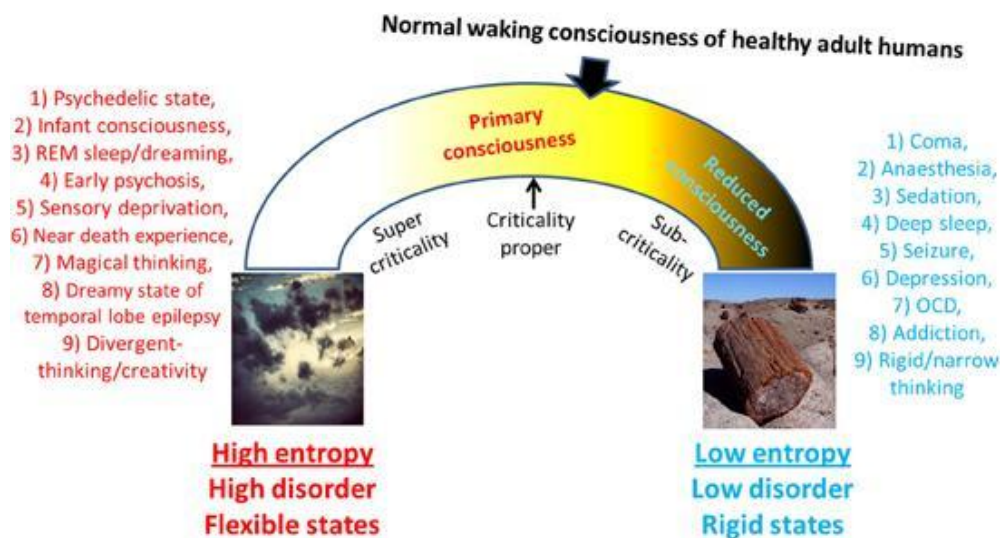


Figure 7. Spectrum of cognitive states. This schematic is intended to summarize much of what this paper has tried to communicate. It shows an “inverted u” relationship between entropy and cognition such that too high a value implies high flexibility but high disorder, whereas too low a value implies ordered but inflexible cognition. It is proposed that normal waking consciousness inhabits a position that is close to criticality but slightly sub-critical and primary states move brain activity and associated cognition toward a state of increased system entropy i.e., brain activity becomes more random and cognition becomes more flexible. It is proposed that primary states may actually be closer to criticality proper than secondary consciousness/normal waking consciousness.

Carhart-Harris, et al. (2014)

This model suggests that psilocybin affects the brain by creating a non-specific high entropy state that is intensely active, short lived, more unformed and unpredictable than ordinary consciousness. We can differentiate this from depressive patterns of cognition, which are rigid and repetitive, that is, low entropy. The hypothesis is that the heightened entropic state of psilocybin intoxication is a nonspecific state of arousal that can be shaped by priming, prior to the medication session, and active meaning-making during integration sessions. This model is distinct from the neuroscience paradigm of a chemical imbalance, from the need to evoke an “inner healer” model, or from the notion that the mystical state itself is therapeutic (from religious tradition). The latter two dislocate the curative/therapeutic action into discourses that are outside the realm of psychiatry and psychology. While we do not wish to denigrate any of these three models, it is our belief that the discourse of empirically tested psychological therapies for depression holds special

utility in creating the most useful platform for psilocybin-assisted therapy for depression.

The purpose of this therapy platform is to shape the ways that participants anticipate, experience and utilize psilocybin-induced openness and flexibility. The preparatory sessions are used to identify and educate the participant on the problematic cognitive patterns that perpetuate and deepen depression symptoms. Follow-up sessions then attempt to teach coping strategies that are consistent with ACT and mindfulness-based therapy. The participant, then, brings this awareness into the psilocybin medicine session, and finally, the changes in cognition and behavior are reinforced in integration sessions. The therapy's role is to use the position of openness (during and after the medicine session) to reinforce behaviors, thought forms, skills and practices that are useful to countering the maladaptive thought patterns/ruminations/etc. previously fortified by the rigid, low-entropy brain. In this model, the participant is expected to be an active participant in the recovery process, rather than awaiting the emergence of an inner healer or an outside agency (higher power) to bring about change. While spiritual awakening and the emergence of an inner healer certainly have heuristic value as models for psychedelic action, the passivity, pessimism, inactivity, and rigidity of depression might be better treated by using psychological models derived in the development of ACT and MBCT.

This program of psilocybin-assisted therapy will employ core components of Acceptance and Commitment Therapy and Mindfulness Based Cognitive Therapy to help participants learn how to prepare for and use the psychedelic experience in a way that is carefully tailored to their particular problem, rather than using a non-specific supportive approach. Additionally, the therapist may instruct participants on meditation, exercise, creative endeavors or relational problem solving that are known to be useful in recovery from depression (Salmon, 2001).

9.0 APPENDIX D: REFERENCES

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