Psilocybin Assisted Psychotherapy Protocol

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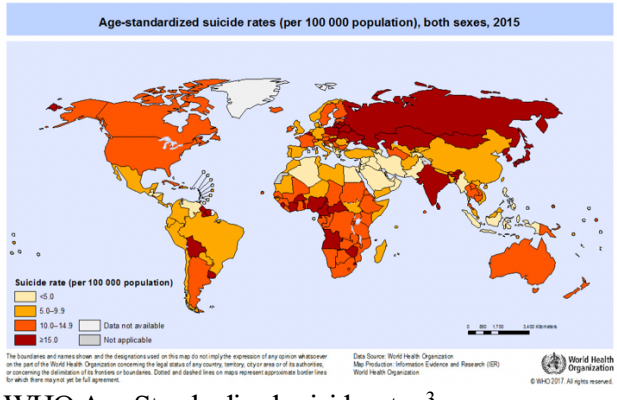
Abstract:
Psychotherapy protocols have been established for psychedelic assisted therapy. No such protocol for psilocybin assisted psychotherapy is currently available. This paper aims to produce a protocol for psilocybin assisted psychotherapy for treatment-resistant depression that is in line with current methods and protocols, and one that includes an evidence-based treatment framework.
Methods: Pub med search for evidence-based therapies for depression and review of currently existing protocols for psychedelic assisted therapies.
Results: A potential protocol for psilocybin assisted therapy to serve as a framework for future studies and to further discussion. More research is required to determine the most efficacious forms of therapy in combination with the potential of psychedelics.

Modern advances in antidepressants are stalling despite no change in the prevalence of depression from 2007-2008 as compared to 2015-2016. From 2013-2016 8.1% of American adults, aged 20 years or older, met the criteria for Major Depressive Disorder (MDD). Women (10.4%) were twice as likely to have suffered from depression than men (5.5%)[1]. The annual United States suicide rate increased by 24% from 1999 to 2014. From 1998 to 2017, suicide was the 10th leading cause of death overall, 2nd leading cause in people aged 10-34, and 4th leading cause of death in those aged 35-54[1]. According to WHO, 8 million people completed suicide, and this is likely the average yearly rate. At this rate, every 40 seconds, someone successfully commits suicide[2]. Suicide attempts were 30 times more common than completed suicides.



WHO Age Standardized suicide rates [3]

Antidepressant treatment for MDD relies heavily on Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Norepinephrine Reuptake Inhibitors (SNRI) pharmaceutical agents developed in the 1980's and 1990's[2]. Depression is the leading cause of disability worldwide, affecting over 300 million people[4]. Fifty percent of people who suffer from depression will have a recurrence of symptoms. Less than half of patients with depression fail to achieve remission after their first treatment modality: antidepressants, therapy, brain stimulation techniques. There are currently 681 separate combinations of symptoms that would meet DSM-V criteria for depression that are distinguished clinically. There are currently no objective biological markers for depression[4]. Treatment resistance occurs in a significant amount of MDD patients with 44% of patients not responding to two trials of antidepressants. 33% do not respond to four trials of antidepressants. Treatment-resistant depression is a life-threatening illness, as 30% of treatment-resistant patients attempt suicide at least once in their lifetime[5].

A 2015 survey study of 190,000 individuals, found that lifetime classic psychedelic use, including psilocybin use, was associated with reduced psychological distress and suicidality in the US adult population[6]. The potential treatment benefit of psychedelics is thought to reduce activity in the default mode network, a biological web of neuronal connectivity that may underlie the sense of self[7].

Evidence of human use of psychedelics dates back to prehistoric times, and use has remained in certain indigenous cultures. Most recently, there has been increased interest in psilocybin, as access to this drug has been more readily available for clinical

trial research. Two studies have been performed with psilocybin that were randomized and double-blind. These are the first studies to rigorously attempt to evaluate the potential for psilocybin and with promising results. New York University in 2016 had 29 patients with cancer-related anxiety and depression in a randomized, double-blind cross over study with placebo control. Niacin was used as a placebo due to autonomic effects that are thought to mimic psilocybin administration. Due to crossover design, patients either received two doses of medication (psilocybin and niacin) at two separate times points and were randomized as to which dose was given first, either psilocybin 1st dose and niacin 2nd dose or niacin 1st dose and psilocybin 2nd dose. All groups were subjected to 9 sessions of psycho-therapy with one psilocybin session and one placebo session. Positive effects on cancer-related depression was seen in 83% of the psilocybin arm, and the effect was within a day. 14% of the placebo arm had an antidepressant effect. Positive effects were sustained after the six months follow up[8].

John Hopkins performed a study in 2016 using a similar design to Ross et al., double-blind crossover design randomized, and placebo-controlled. Low dose psilocybin was used for the placebo group, 1-3mg/70kg psilocybin. This low dose of 1mg had no demonstrated mood effect and was reduced during the study from 3 mg due to concern for rates of psychologically challenging experiences being greater at the higher dose. 80% of patients had an improvement in mood, anxiety, and quality of life. Effects were sustained at the six months follow up[9].

The imperial college of London performed an open-label study of psilocybin in 20 patients with treatment-resistant depression. A similar study design to the John Hopkins study published in 2016, which used low dose psilocybin as a placebo. In a small sample size, a 25mg dose of psilocybin demonstrated a significant and substantial reduction in depressive symptoms at one week. Improvement was maintained at 6 months[10].

Over 100 species of mushrooms have been found to contain psilocybin. Psilocybin is a tryptamine based compound that is metabolized to its active constituent, psilocin. The effects of psilocybin appear to be mediated primarily by agonist activity at 5-HT_{2A} receptors. No study has been performed that identifies the biological mechanisms responsible for successful therapeutic outcomes[11]. fMRI studies of brains on psilocybin have shown decreased activity to the default mode network. Entropic brain theory suggests that decreasing activity in an area of the brain that is strongly associated with internal focus could challenge persistent beliefs and chronic patterns of thought, such as those seen with depression and anxiety[7]. The use of psychedelics may foster a plastic state of brain network activity that may be beneficial to establishing longer-term changes in the brain, but further research needs to be performed to support this hypothesis.

Psychotherapy protocols have been established for 3,4-Methylenedioxymethamepheta-mine (MDMA) assisted trauma-focused psychotherapy and are available to view on the website for The Multidisciplinary Association for Psychedelic Studies (MAPS). No such protocol for psilocybin assisted psychotherapy is currently available. This paper aims to produce a protocol for psilocybin assisted psychotherapy for treatment-resistant depression that is in line with current methods and protocols, and one that includes an evidence-based treatment framework. This paper does not endorse or promote the use of psilocybin (or any psychedelic substance) outside of a supervised and FDA approved clinical trial. This paper is meant to serve as a potential protocol for psilocybin assisted psychotherapy and is subject to modification based on any real-world impediments that might arise during implementation.

Psilocybin Assisted Psychotherapy Protocol for Treatment-Resistant Depression

This protocol aims to establish guidelines for therapy as would potentially be conducted under the purview of a scientific study. Therapists are referred to as "Investigators," and patients are referred to as "participants." The therapy utilized will include preparatory sessions, psychedelic sessions, and integrative sessions or post-psychedelic sessions.

This protocol aims to be consistent with similar protocols currently being used for clinical trial research with psychedelics to standardize the treatment. Therapy and treatment may differ slightly due to the varying experiential difference in the psychedelic used. However, an attempt at standardization will help to reduce confounding factors that may be present in a study and allow for a much more straightforward comparison of results between similar studies.

The goals of this manual are

- Establish the essential framework of Psilocybin assisted psychotherapy methods with the potential to be utilized in clinical trials
- Provide guidance to Investigators concerning the process of psilocybin assisted psychotherapy for treatment-resistant depression, while allowing for Investigators to utilize therapeutic interventions that are based on their own training, level of experience, judgment, and intuition

Outline of therapy methods

- Participant safety and well-being are prioritized over any scientific aims of the study
- Investigators shall be qualified therapists with sufficient training and experience relevant to the methods as outlined
- Creating an appropriate set and setting
- Each intervention should be aimed at establishing a therapeutic alliance with the participant
- Inner healing intelligence
- Mindfulness and CBT
- Empathetic presence and listening
- Supportive guidance
- Self-healing model

Before each session, the patient will take the Patient Health Questionnaire-9 (PHQ-9), administered by separate health professionals other than Investigators. Follow up assessments will take place 1, 3, and 6 months post-psychedelic session.

Initial introduction: Will include an introduction to the concepts of CBT and Mindfulness, discussion of the goals of therapy, and evaluation of the participant's motivation to engage in psychedelic therapy.

Second session: Supportive therapy will be used to encourage and foster a therapeutic alliance and atmosphere. Questions concerning CBT or mindfulness will be addressed and answered. CBT or mindfulness exercises will not be required, but if the participant engages in CBT or Mindfulness, the participant and investigators are to document and report the use of the specific techniques.

Third session: Discussion of goals, supportive therapy, establish a therapeutic alliance. The participant starts the first writing assignment (Attachment 2)

Fourth session: Discuss the first writing assignment (Attachment 2)

Fifth session: Continue supportive therapy. Discuss the preparation process for psychedelic-assisted therapy. Discuss any remaining questions the participant may have concerning psychedelic therapy.

Sixth session: Continue supportive therapy and practicing mindfulness skills, particularly the ability to manage acute stress through breathing exercises

Seventh session: Second writing assignment (Attachment 3)

Eighth session: Discussion of the second writing assignment (Attachment 3)

Ninth session: Introduction to the eyeshade and preparation for the psychedelic session

Tenth session: Review the goals, motivations, and progress made in the previous therapy sessions. Review the plan for the psychedelic-assisted session and discuss any concerns, emotions, thoughts, or anxieties the patient may have.

Psychedelic assisted session

Eleventh session: Follow up on psychedelic-assisted session, introduce Attachment 4

Twelfth session: Follow up on psychedelic-assisted session, discuss Attachment 4

Set and Setting

Set and setting have been described in earlier literature as paramount to the safe and beneficial use of psychedelics. "Set" denotes the mindset of the person prior to the introduction of a psychedelic. This mindset includes the patient's perceptions, thoughts, emotional state, and expectations. "Setting" is the physical environment. Both can contribute meaningfully to any experience negatively or positively. Set and setting are essential in maximizing and ensuring a comfortable environment and making sure the person taking a psychedelic is mentally prepared. Several studies have noted the importance of a quiet, safe environment, comfortably lit, with access to restroom facilities, music, and art. Participants should be fasting since midnight before the psychedelic-assisted session.

Environmental Setting

- Private, with freedom from interruption
- Quiet, with minimal external stimuli
- Comfortable, with a couch and similar furniture for the participant to rest, recline, or sit on with support from pillows and blankets. Room for a chair for the Investigators to sit comfortably in during the session
- Good ambient temperature control
- Aesthetically pleasing with fresh flowers and artwork. Images with powerful or potentially negative connotations should be avoided
- Well furnished with sleeping arrangements to accommodate the participant
- Eating space and area with the participant's preferred snacks that are easily digestible. Food type and drink preferences of the participant should be readily available.
- Immediate and easy access to restroom facilities
- Art supplies to assist with nonverbal expressions
- Ease of access to the participant's preferred music
- Medical equipment should be easily accessible at all times, including but not limited to a defibrillator, blood pressure cuff, stethoscope, and an oxygen monitor.
- Locked area for personal belongings
- The patient should not have access to their phone or internet during the session

Maintaining physical safety and well-being includes providing ease of access to medical facilities should any issue arise that requires immediate medical attention either prior, during, or immediately following the therapeutic session. During the assisted session, Investigators should remind the participant to rise slowly from a sitting position and help to protect the participant when standing or walking, should these activities become difficult.

Cognitive-Behavioral Model

Cognitive Behavioral Therapy (CBT) has demonstrated efficacy in the treatment of depression. A model for psychedelic-assisted psychotherapy should be started prior to the initiation of a psychedelic, with an introduction to evidence-based treatment and the standards of care. Participant should be introduced to these concepts with the understanding that comprehensive CBT could be pursued after the study, and the therapy utilized during this study is mainly supportive, which issued to help guide the patient through the initiation of a psychedelic to change or accept some behavior, thought, or emotion.

Initial Session:
Introduction of therapy and explanation of Cognitive Behavioral Model and Mindfulness

Cognitive Behavioral Therapy (CBT) was established with early behaviorist theories in the early

1900s. CBT is part of a large group of interventions aimed at challenging inaccurate beliefs and maladaptive information processing. Maladaptive information processing forms the basis for depression with chronic repetitive negative thoughts. The cognitive model states that participants should be able to change their repetitive thoughts through practice. Due to the variable nature of CBT across varying institutions, it would not be recommended to implement a complete CBT course in order to avoid the confounding result in any study that would occur secondary to CBT. However, an introduction to the cognitive model should be established.

The cognitive-behavioral model describes how thoughts and situations influence emotions and behavior. Perceptions during a time of distress can be distorted or pathologically dysfunctional. Identifying and evaluating thoughts as objectively and non-judgmentally as possible is something that takes practice and time. By identifying and evaluating thoughts, one can change recurring negative thoughts that lead to negative feelings and undesirable behaviors[11].

Mindfulness has recently been incorporated into most forms of therapy. Mindfulness has a long history, dating back to pre-yogic traditions concerning the unification of mind, body, and soul[12] centering of the conscious of mind, and focusing the mind single-pointedly on a physical or mental object. Patients are encouraged to use their breath as a physical and mental object of attention and focus. The breath can be followed in its natural rhythm or consciously controlled, by exercising a slow inhale and slow exhale, at a rhythm that is both engaging and comfortable for the participant[12]. Participants may start with five to ten-minute sessions of focus and concentration on their breath. Participants should aim to view thoughts and feeling as they arise without judgment. If distracted by a thought or emotion, the participant is to acknowledge said emotion or thought without judgment and let the thought or emotion pass naturally. Introduction to this basic understanding of mindfulness and the cognitive process aims to assist in the therapeutic alliance and have the participant develop basic distress tolerance skills that could be relied on during the psychedelic-assisted session.

Strictly behavioral or cognitive approaches are likely to be self-limiting if followed rigorously and if not balanced by other approaches in the context of psychedelic-assisted therapy[13].

Inner healing Intelligence

A concept utilized in the MAPS manual for MDMA assisted trauma-focused therapy is a concept that aims to put the participant in touch with their own body's innate ability to heal and grow. The following analogies are paraphrased from this MAP manual:

- The body knows how to heal itself. If someone goes to the emergency room with a laceration, a doctor can remove obstacles to healing (e.g., remove foreign bodies or infection) and can help create favorable conditions for healing (e.g., sew the edges of the wound close together), but the doctor does not direct or cause the healing that ensues. The body initiates a remarkably complex and sophisticated healing process and always spontaneously attempts to move toward healing. The psyche also exhibits an innate healing intelligence and capacity.
- Seeds want to become a plant; it is the natural way.
- A tree always grows toward the sun; it is the tree's natural inclination[13].

The goal of having the patient adopt a mindset of healing helps prepare the participant for potential difficulties during the psychedelic administration. Early introduction and adoption of CBT, mindfulness, and Inner healing intelligence can be relied on during psychological difficulties during the psychedelic experience.

Empathic Presence

Empathic presence is best achieved through a non-judgmental environment. This environment allows for the mindset of the participant to speak openly and

honestly. Therapy is not effective unless the participant is open and honest with the therapist in order to achieve goals and establish long term change. Empathic listening is a skill that requires the Investigator to listen beneath and beyond the surface value of spoken words for deeper meanings. Empathic presence is acknowledging the participants suffering and validating their individual experiences. This involves the encouragement of progress and validation of feelings, while demonstrating a genuine appreciation and sincerity toward the participant. Empathic presence reduces the feelings of the participant concerning abandonment and or isolation and fosters the therapeutic alliance[13]. The following is a descriptive list of components as paraphrased from the MAPS MDMA assisted psychotherapy Treatment Manual:

Essential components of empathetic listening and active listening:

• Minimal encouragement both verbal and non-verbal
• Invitation rather than direction
• Paraphrasing
• Reflecting
• Emotional labeling
• Validating
• Reassurance and waiting
• Allowing participants to come to conclusions themselves[13]

Two concepts should be taken into consideration: the process from the participant's perspective and the process from the investigator's perspective. The investigator should be cautious in forcing the experience of the participant to fit into a theoretical framework. Which may limit the ability of the Investigator to accurately and naturally guide the participant. Three traits the Investigator should rely on include:

1. Openness
2. Compassion
3. Curiosity

During the psychedelic session, it will be equally important not to judge the experience of the participant or provide ontological or teleological explanations for their experience. The Investigator's goal is to guide the participant through difficult emotions and thoughts as guided by the participant's experience as it unfolds. Any philosophical, ontological, or teleological epiphanies should be regarded without judgment by the Investigator while nurturing the space for the participant to explore those feelings, thoughts, emotions, and or epiphanies. Any epiphany or strong feeling should be explored during the session. However, the Investigator should not attempt to make concrete sense of the experience, as the incorporation of the experience and following therapy will be more important as the experience is integrated as an impetus for change.

Writing

Participants will compile a written account of the motivations, behaviors, thoughts, and emotions that are personally unsatisfying. (Attachment 1) Participants will also complete a total of three writing exercises. The first will be a written account of significant events that have shaped them in the past. The second will be a written account of their present thoughts, emotions, behaviors, and significant events occurring presently. The third will be written post-psychedelic experience towards the end of therapy and will be aimed at thoughts, feelings, and emotions about the past and present, and what direction the participant would like to move in in the future. All writing exercises will be shared with the Investigator.

The goal of the writing exercises will be to compare the patient's thoughts, emotions, and goals before and after psychedelic administration to ease the integration of the experience.

Integration

The integration of a psychedelic experience is to be understood as an ongoing process, and one that is essential to therapy. Investigators will address any difficulties during non-psychedelic therapy sessions.

The therapy before the psychedelic and during the psychedelic-assisted therapy will aim to provide a non-judgmental environment for the institution of change.

Music

Participants may choose a selection of music that they find comforting or that they enjoy. Music can be played during the session or with eyeshades present while encouraging the participant to "look inward."

Therapeutic Foundation

Investigators will receive specific training as it pertains to this protocol, which will include individual reading of this protocol and a one-on-one meeting with a psychedelic-assisted therapeutic supervisor. Investigators must have experience with the treatment of depression using CBT. Each investigator should be able to teach a method of stress reduction, such as diaphragmatic breathing.

The background of investigators would ideally include experience with Mindfulness, supportive psychotherapy, Jungian psychology, Buddhist psychology, or psychodynamic psychotherapy. Work involving holotropic breathwork, Internal family systems, Sensorimotor Psychotherapy may be beneficial to working with participants during altered states of consciousness. Though potentially beneficial, this background is not inclusive and is not meant to be prescriptive during the study.

Therapeutic Adherence

Adherence to the therapeutic approach will be monitored by independent review against the above-listed protocol. Therapeutic treatment, in general, involves a high degree of individualization, and this protocol is meant to serve as a guideline. Any deviation from the order or structure should be reported and included in the data gathered as part of any research study.

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SUPPLEMENT:

Attachment 1:

"The participant must realize that present methods of behaving are inadequate and personally unsatisfying. This may be a difficult and painful process of coming to understand and accept yourself. On the basis of this self-understanding, the participant must learn how to alter behavior to satisfy the new pattern of motivation which has developed out of self-understanding."[14]

Please write your following motivations for change, your current behaviors you desire to change, current thoughts you desire to change, and current feelings you find difficult to experience or accept. You may use an additional sheet of paper if you desire.

Motivations:

Behaviors:

Emotions:

Thoughts:

Attachment 2:

Write about your life from birth until the recent past. You may write as much or as little as you feel would be helpful to you. You may start with "I was born in _____, and I grew up _____ with _____...." or you may start any way you wish.

Attachment 3:

Write your daily life, as it is presently. Focus on thoughts, emotions, behaviors, and situations that you would like to change or find challenging to accept. Write as little or as much as you find is helpful. You may start with "Today I felt ____, and my thoughts were _____..." or you may start in any way you wish.

Attachment 4:

Write your future: plans, goals, and motivations following the session.

Write current thoughts, behaviors, emotions, and motivations