March 2020 Volume: 2 Issue: 1
ISSN: 2690-0912

The Journal of *Psychedelic Psychiatry*

- Psilocybin Assisted Psychotherapy Protocol
- Integrating Psychedelic Use: A Cautionary Note for Licensed Health Care Providers
- Positive Response to Ketamine Administration in Treatment Resistant Psychosis: A Case Report
- A Review of the Psychotherapeutic Effects of Ayahuasca

THE JOURNAL OF
PSYCHEDELIC
PSYCHIATRY

Editorial Board

THE JOURNAL OF
PSYCHEDELIC
PSYCHIATRY

New Perceptions Podcast

Expand Your Knowledge by listening to the official podcast of The Journal of Psychedelic Psychiatry. Join us as we discuss the latest trends within the Psychedelics community with Clinicians, Advocates, and Policy Makers. We also explore the latest research in our author interviews and through our roundtable editors' discussions.

Subscribe

Spotify: Apple Podcast Google Play Overcast

Stitcher RadioPublic Breaker Anchor

Follow Us

Twitter Facebook Instagram

THE JOURNAL OF
PSYCHEDELIC
PSYCHIATRY

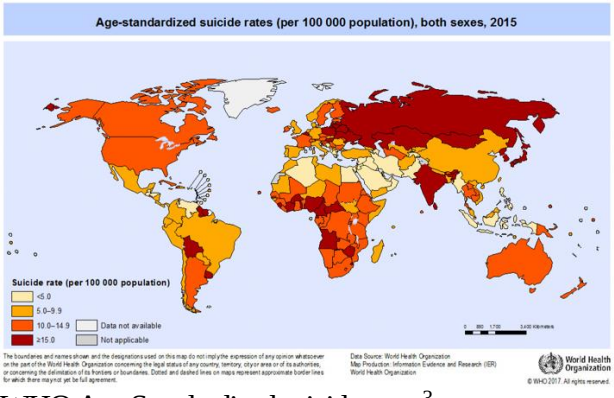
Articles:

Psilocybin Assisted Psychotherapy Protocol

Gershom Hernandez, M.D.

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.

AUTHOR INFORMATION:

Send correspondence to Dr. Gershom Hernandez (ghernandez3@kumc.edu)

Hernandez, G. (2020, March). Psilocybin Protocol. *The Journal of Psychedelic Psychiatry*, *2*(1).

REFERENCES

1. Brody, et al. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. NCHS Data Brief, No. 303, Feb 2018
2. Bachmann, S. Epidemiology of Suicide and the Psychiatric Perspective. *Int. J. Environ. Res. Public Health* **2018**, *15*, 1425.
3. WHO Figure: Age-Standardized Suicide Rates: Male: Female Ratio (Per 100,000). Available online: http: //www.who.int/gho/mental_health/suicide_rates_male_female/en/
4. Neuroscience and Biobehavioral Reviews 84 (2018) 272–288
5. Bergfield, I, Et al. Journal of Affective Disorders, Treatment-resistant depression and suicidality. Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
6. Matthew W. Johnson (2018) Psychiatry might need some psychedelic therapy, International Review of Psychiatry, 30:4, 285-290,
7. Carhart Harris, et al. The entropic brain: a theory of Conscious states informed by neuroimaging research with psychedelic drugs. Neuroscience, 2014
8. Ross et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life threatening cancer: a randomized controlled trial. Journal of Psychopharmacology, Vol 30, issue 12, 2016
9. Griffiths, et al. Psilocybin produces substantia and sustained decreased in depression and anxiety in patients with life threatening cancer: A randomized double-blind trial. Journal of Psychopharmacology, Vol 30, Issue 12, 2016
10. Carhart-Harris, R. L., et al. Psychopharmacology, 235: 399, 2018
11. Lopez-Lopez, J.A, et al. The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. Psychological Medicine, Sep 2019, 49(12): 1937-1947
12. Pradhan, B. Yoga and Mindfulness Based Cognitive Behavioral Therapy, A Clinical Guide. Springer International Publishing, Switzerland 2015
13. MDMA Assisted Psychotherapy Treatment Manual, Version 7: 19, August 2015
14. Blewett, D.B, Chwelos, N., Handbook for the therapeutic Use of Lysergic Acid Diethylmide-25 Individual and group procedures. ORC by MAPS, 1959

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

Integrating Psychedelic Use: A Cautionary Note for Licensed Healthcare Providers

Rose Jade, LCSW [1]

Introduction

As popular media is regularly reporting, psychedelics are making their way "back" into mainstream culture. See, for example, *My adventures with the trip doctors; the researchers and renegades bringing psychedelic drugs into the mental health mainstream*, published by The New York Times Magazine in May of 2018 [1]. Licensed health care providers involve themselves professionally (taking classes, participating in FDA or DEA[2]-approved clinical research, investing in clinics and patents, offering "integration" services), and more personally (trying psychedelic substances themselves). In December of 2019, Psychology Today published *Ten Reasons Psychotherapists Should Learn About Psychedelics* [3] [2]. Companies are publicizing plans for opening clinics or bringing the drugs to market. See, e.g., *Transforming psychedelics into mainstream medicines*, published online at www.statnews.com on January 7, 2020 [3].

This article hopes to prompt licensed clinicians to carefully examine some of the foreseeable consequences of offering psychedelic-assisted therapy (PAT), in particular, "integration" services, at this point and time. Often, most of the clinicians who are enthusiastic about providing PAT minimize the risks to their professional license. Also, many Masters-level therapists (the majority not being trained scientists) often have mis-understandings about the proven efficacy (to date) of PAT. Bringing PAT to market, mainly via unproven cost-saving changes in clinical research protocols, will pose additional ethical dilemmas and risks.

By "licensed," it means any provider who is licensed, regulated, or credentialed. By "PAT," it means activities -- marketed or understood as therapeutic (compared to recreational) -- surrounding the intentional dosing or ingestion of drugs defined as psychedelics (e.g., psilocybin, psilocin, LSD, ayahuasca, and other similar compounds). For this article, this category also includes non-hallucinogens, like MDMA and ketamine, which are currently associated with the resurgence in medicinal uses of psychedelics. The PAT-related activities discussed will include:

Health-care professionals who offer pre-dosing or post-dosing "integration services" to underground or aboveground psychedelic users.

Health-care professionals who offer, witness, and or supervise the actual aboveground dosing or ingestion of psychedelics or psychedelics-associated substance (e.g., ketamine) *outside of* a phase I, II or III FDA or DEA clinical trial (e.g., at an expanded access MDMA clinic, or one offering off-label use of ketamine).

Health-care professionals who encourage, offer, or participate in allegedly aboveground dosing and or "integration services" at a setting outside of the United States (for instance, Jamaica, Costa Rica, or Peru).

Underground situations, e.g., those in which health-care professionals engage in illegal possession or supervise the illegal dosing or ingestion, of psychedelic substances, will not be addressed.

This article is primarily for health care providers licensed in the United States. Importantly, this article is not offered or meant as legal advice – the reader should consult a licensed attorney in their state or district for any matters of concern. At times, to provide an example, the Oregon Revised Statute (ORS) or an Oregon Administrative Rule (OAR), which governs Regulated Social Workers in Oregon, will be cited. Because every career category of health care provider has its credentialing board, readers should review the laws pertaining to their specific practice(s).

Review

The circumstances in which psychedelics use occurs is typically divided into "aboveground" and "underground" settings. *Aboveground* use refers to the legal possession and use of psychedelics. *Underground* use refers to the illegal possession and use of psychedelics.

In the United States, generally speaking, the possession and use of psychedelics is highly illegal except for very limited and strictly controlled circumstances (e.g., FDA or DEA approved clinical trials, or an extremely narrow set of religious ceremonial uses acknowledged by the U.S. Supreme Court and thus tolerated by the US government [4]). Psychedelics (including MDMA) are Schedule I Substances under U.S. federal law (the most stringent prohibition, based on no recognized medicinal value [5]). Only ketamine, which is a uniquely distinct substance, is available by prescription (primarily used as an anesthetic [4]) but with other off label uses; it also has underground popularity [6]. Like MDMA, ketamine, along with some of its analogs are currently being researched and promoted as psychedelic-like substances with possible value for treating psychiatric conditions [5].

In addition to federal laws criminalizing the possession, selling, or use of these substances, states have prohibitions [7]. Furthermore, while there are efforts afoot to locally *de*criminalize these drugs in some U.S. cities or states (including Oregon), local rules do not, and will not, immunize the possessor or user from broader state or federal prosecution and constraints (something marijuana growers and retailers know only too well).

These prohibitions are important because most, if not all, licensed health care providers explicitly agree to comply with federal rules and regulations, and for a variety of reasons. These include requirements for eligibility and inclusion on insurance panels, use of electronic medical record portals, receipt of research or community health grants, or because their employment is contingent on federal tax dollars. Frankly, any local decriminalization is merely irrelevant if health-care providers want to maintain their credentials.

There are some countries outside of the United States, where the possession and use of psychedelic substances are purportedly legal or at least less criminalized. This means that it is (arguably) possible for a licensed health care provider (or anyone else) to have an "aboveground" experience with psychedelics outside the U.S.

FDA or DEA approved clinical trials involving psychedelics.

Researchers are working on PAT around the world. In the United States, permission to work with Schedule I drugs (or any others not yet approved and regulated by the FDA) comes from the FDA and DEA. The Multidisciplinary Association for Psychedelic Studies (MAPS) has been the leader in obtaining U.S. federal approval for research into the medicinal value of psychedelics, with a goal of getting psychedelics rescheduled (moved out of Schedule I).

To obtain FDA and DEA approval for a clinical trial involving psychedelics, a challenging set of applications must be completed and accepted, detailed protocols must be crafted and followed, and all the while the applicants face an ongoing endurance test of vetting and scrutiny by federal and state officials. It takes *years* to get the ball rolling, and it costs a great deal of money to 1) initiate the research and 2) to take it to completion. "Big Pharma" has little interest in funding this foundational line of research because there is little likelihood of profiting from the sale of these substances, let alone recouping any initial research investment, as any patents are expired, unavailable or deemed not lucrative.

While it *is* exciting that psychedelics such as psilocybin (psilocin) and MDMA have shown favorable results in their initial phase I and phase II FDA clinical trials, and have even been "fast-tracked" by the FDA, it is the phase III clinical trials that, arguably, will make or break the approval and entrance of a new therapeutic drug or drug application. Even Big Pharma has promising, fast-tracked drugs, aimed at alleviating symptoms of mental illnesses, that nevertheless encounter difficulties at phase III (e.g., Allergan's rapastinel [8] [6]

and Johnson & Johnson's esketamine [7]). Each "phase" of FDA clinical trials typically has different goals, screening criteria, and protocols, and generates different types and volumes of data. For this article, the MAPS MDMA clinical trials will be the reference, although the points apply to any research into PAT.

The MAPS phase II MDMA trial data is from (only) 105 enrolled "participants" (volunteers who made it past an intense screening process), and 8 dropped out early [8]. In the current phase III MDMA trials, more robust data will be available about the effectiveness -- or the ineffectiveness – of the compound as *administered within the phase III therapy protocol* [8], as well as more information about side effects. It is crucial to remember that *we do not have phase III data yet, and the data collection process is occurring under a protocol distinct from phase II.* And while the FDA has approved expanded access for MDMA, initial enrollment is limited to 50 patients (to be spread across a maximum of 10 clinics) and the proposed protocol includes changes from the phase II and phase III protocols [9].

So, whether a health-care provider is contemplating trying out these drugs themselves or encouraging someone else to, thinking about offering psychedelic "integration" to clients, or possibly considering investing in a prospective commercial application or clinic, it is imperative to remember that we do not have a significant volume of robust clinical data yet.

There is, however, a lot of 1) media buzz about the phase I and phase II trials regarding "therapeutic" applications of psychedelics; 2) anecdotal knowledge from individuals who have taken, and continue to take, some form of these substances with the majority of these being "underground" and typically for recreational purposes; and 3) knowledge regarding the classification of these substances and that it is illegal to possess them in the United States.

The Intersection of Psychedelic-Assisted Therapy and a Professional License.

Predictably, in the face of so much kindling of the market for psychedelic-assisted therapy, an increasing number of licensed health care providers are offering, or seriously considering beginning to offer, "integration services" to psychedelic users. Indeed, the Psychology Today blog cited above offers clinicians a variety of rationales for signing up for an increasing variety of continuing education courses about psychedelics, marketing angles, and even practice tips regarding offering "integration."

While overtly pitched as a new and powerful way to help clients who are suffering from PTSD, depression, and other psychiatric conditions., the unspoken pitch is one of marketing: "here are ways to increase revenue in light of exciting clinical results."

Based on several face-to-face discussions with a wide variety of licensed professionals interested in psychedelic research and therapy, and on internet searches on the topic, a concerning view emerged. There is a prevalent assumption that as long as the health-care professional is not personally providing or ingesting the psychedelic substance, there is nothing wrong with offering "integration services" (however defined) to anyone who is interested and can afford the service.

Putting aside the "rightness" or "wrongness" of this assumption, the point of this article is to inform health-care professionals about the risks of engaging in PAT. The list of risks does not comprise an exhaustive list, but the objective is to give all health-care providers pause and to encourage discussion.

A professional license is a privilege, not a right (and why this distinction matters).

The basic health-care license is issued by a Board, typically comprised of licensed peers and usually a few members of the public. The Board operates by State law and an accompanying set of administrative rules.

Typically, the highest priority of a health profession board – the reason it exists – is to protect the public. Everything a Board does is (theoretically) related to this primary function. The Board requires

that a professional meet a specific educational standard before becoming licensed to practice, and the Board handles complaints about any licensee who behaves (on or off the clock) in a way that reportedly poses a hazard to the public, to clients, or to the profession itself.

Of relevance here, in order to get an initial license, and to continue to keep it, a health-care provider must have a reputation for knowing the rules, obeying the rules, obtaining satisfactory training, and acting with good judgment. In other words, a provider must be of good moral character and be fit to practice [10]. They must not pose a risk to the public or the profession (the exact language differs from state to state, board to board, but the bottom line is public safety).

It is essential to understand the following key points:

1.A license is a privilege, not a constitutional right.

2. A licensing Board has a statutory duty to receive and *investigate* concerns and complaints about health-care providers that (1) allege a violation of state law or rule, or (2) report an impairment. Peers may have a mandatory duty to report their concerns about a health-care provider to the Board [11]. There is no explicit limit on the range of circumstances that is reportable, or a limit on how long ago the worrisome event must have occurred [12]. A provider agrees to this oversight when they apply for and maintain their license. The Board does not have the luxury of ignoring valid concerns and complaints.

3. Licensing Boards had broad investigatory powers that operate before, and distinct from, evidentiary constraints in contested case (administrative) hearings. If a provider requests a formal hearing for a complaint filed against them, the Board typically proceeds and operates under administrative rules (a state's version of the federal Administrative Procedure Act (APA [13]). In many ways a provider is much more vulnerable in front of a licensing Board (pre-hearing), and under the APA protocol (during a contested case hearing), than they are as a litigant in a state or federal court (due to procedural and evidentiary rules).

4. If a licensing board contacts a provider about a concern or complaint (e.g., begins an investigation), they must file an answer or else they will likely end up losing their license [14]. Never ignore a Board.

5. Psychedelics are illegal to possess and ingest in the United States, outside of very narrow circumstances.

6. The off-label use of an FDA-approved drug (e.g., ketamine, or perhaps MDMA soon) may form the basis of a complaint to the board, particularly if the complaint raises issues of competency, client injury, or public safety.

7. If a provider is under investigation regarding an offer of "integration services" (or for any other conduct), it would be extremely foolish to provide *any* type of response without the assistance of an attorney experienced and specializing in defending identically licensed peers before the same Board. Most Boards have an attorney (often an Assistant Attorney General) assisting them in the investigation. Because a provider has so very much to lose, the provider will want an attorney who thoroughly understands the Board's legal process as well as the collateral consequences in state and federal court of any statements made by the provider to the Board. A simple "good faith" explanation about what a provider did, or is doing, can go sideways quickly. Note: these attorneys are very, very expensive (for obvious reasons). They will likely require a hefty

retainer fee upfront (before the attorney will begin work)

8. Under the rules of procedure which the Board operates under, a provider typically does not have the full set of rights given to a criminal defendant or a civil litigant appearing in a court of law. For instance, hearsay may be admissible in the investigatory stage, or during an administrative hearing, meaning the Board can consider the information and the provider may not have a right or opportunity to cross-examine the primary source[15]. Furthermore, while a provider presumably does have a constitutional right to remain silent (under the Fifth Amendment), "silence" can and probably will result in a license suspension or revocation. The Board is charged with protecting the public – not with protecting a provider's license or their livelihood. If there is a complaint relating to a client or public safety that the Board finds credible, and a provider stays silent, they may thereby avoid going to jail (for the moment) but they will likely lose their license.

9. Every time a provider files paperwork to become "credentialed" with a new insurance company or to be hired or given "privileges" by a hospital or other agency, these institutions typically ask whether the provider is currently, or has ever been, disciplined *or investigated* by the licensing board. Answering "yes" triggers more paperwork and more scrutiny and delay: it is a big red flag. If a provider must answer "yes," the asking party will typically want a full record of the matter (which is why an experienced attorney's assistance is so valuable). If the matter concerns illegal drugs, the applicant will likely not be a favored candidate for the job, credential, or insurance policy.

10. Many Boards have a legal responsibility to refer complaints involving criminal behavior to state and/or federal law enforcement [16].

11. Clinicians with the "deepest pockets" (the most robust professional liability coverage), and any type of state-issued credential, are vulnerable to complaints, charges, and civil tor lawsuits regarding actions and omissions committed by lower-level staff, including paid and unpaid interns, working at the clinical site.

Examples of Foreseeable Complaints.

The following scenarios will hopefully give the reader an idea of the kinds of complaints that a board might receive about "integration" services.

- A parent files a complaint against a provider, livid that the provider condones the illegal use of psychedelics by his 19-year old daughter, and that the provider bragged about their own "great" psychedelic experiences to his child. Note: technically, the adult client has not explicitly waived confidentiality.
- A client files a complaint asserting that a provider did not sufficiently warn him about the dangers of off-label use of ketamine, the provider exaggerated its efficacy, and the use has psychologically and physically harmed him, including so-called "integration services." He has incurred tens of thousands of dollars in bills from an in-patient hospital stay beginning one week after his last ketamine therapy.
- An estate of a client has filed a complaint. The client died in a single-car accident, which occurred 30 minutes after an "integration" session ended (after he left your office). The autopsy disclosed psychedelics found in his blood system, and a text on his phone indicates that his provider knew he planned on taking

psychedelics for the appointment. The client's estate has attached to their complaint a copy of their civil tort claims against the provider.

- A U.S. attendee from a group psychedelic dosing session held two years ago in Peru filed a complaint against a provider who provided clinical therapy services to the attendees in Peru. Last month, when both individuals were again in Peru (by coincidence), they engaged in sexual activity. The next day, the provider blocked the patient on the provider's phone. The patient requested (by mail) his Peru-era records from the provider, a request that was ignored. The patient provided the Board with a signed authorization for release of his confidential records, which the Board has attached to their letter to the provider, requesting a response [17]. The "clinic" has since closed, documentation in Peru was purposely minimized, and the provider has no client records from their work there. The provider does have a PayPal record reflecting that they were paid for services rendered in Peru, and phone and internet providers have plenty of email and text records supporting the patient's factual claims.
- The District Attorney has provided the Board with a certified copy of a grand jury indictment accusing a provider of manslaughter. A client died 75 minutes into a "magic mushroom session" at the provider's office. Although the provider did CPR and cooperated with law enforcement at the scene, the medical examiner has listed the psilocybin mushrooms as the cause of death. Unfortunately, the grand jury did not believe the provider's testimony that the provider did not provide the mushrooms. It is currently irrelevant that in two years, when the provider finally goes to trial, their defense attorney will successfully challenge the cause of death [18].
- The spouse of a U.S. attendee at a group psychedelic dosing session in Jamaica filed a complaint that a provider practiced unlicensed psychotherapy with his spouse in Jamaica, and with her later, via Skype (both live within the same state). Although the provider has a "bodywork" credential, they have never applied for credentialing from *this* Board. They do have sufficient education and training in "interpersonal therapy" such that the Board asserts jurisdiction over them (for the practice of counseling/therapy without a license). The provider was invited to "help" with the retreat in Jamaica (and expenses were covered) because of their training. The retreat website offers a full archive of events there. Skype (of course) has archives of the sessions with the spouse.
- Someone who shares a "turn-key" office writes the Board (and copies a provider's professional liability insurance carrier), wanting to know whether the Board approves of psychedelic "integration services" and if not, will they be at risk for discipline (or liability) for sharing an office space with the provider?
- The District Attorney informs the Board that a provider is under investigation for the distribution of psychedelics. The provider's "integration" client got busted and charged with possession of LSD and asserted (falsely) under oath that the provider was the source of the drugs. The fact that the client lied to protect his real source and assumed that the provider would not get in trouble if he named them because they are "credentialed" is currently beside the point.
- A peer files a formal complaint that a colleague is encouraging illegal drug use and going beyond the scope of their license by advertising "integration services" aimed at users of psychedelics. Four teens from the town (including siblings of two of the provider's adult clients) were hospitalized last week for ingesting the "wrong" kind of

little brown mushrooms, and a local radio station is publicizing the complaint.

- Law enforcement provides the Board with a copy of the report following the execution of a valid search warrant for a provider's office and or home, based on a judge finding "probable cause" existed that the provider possessed psychedelics. This followed upon a radio show in which the provider was interviewed about their training and enthusiasm for PAT. Everyone knows the provider just returned from Costa Rica where they were doing ayahuasca – they have been talking it up. The fact that the cops did not find anything is not particularly relevant.
- A client at an expanded access clinic is suing the physician for negligent supervision, emotional distress, and related medical bills suffered after the physician's "intern" broke off a sexual relationship that began the night of the client's first dosing session (1 year ago), after all staff (except the overnight CNA) had left the clinic. The intern had returned at the client's request via text that night, and they engaged in sexual activity and entered into a drama filled relationship. The relationship continued until two months ago, more than a year since the patient's treatment at the clinic had ended. The intern quit six months ago and has left the country. The physician had no direct personal knowledge of this affair but had heard rumors about it yet did not investigate.

The first question is: does a provider have $10,000 - $40,000 in cash, or other assets which they can easily liquidate, to hire an attorney to *begin* to help defend them in the matter before the Board? One should not assume that their agency, employer, or professional liability or malpractice insurance carrier is going to volunteer to assist and defend them. Defendants do not get a "court-appointed" attorney for Board matters (a civil, administrative proceeding), and providers likely are over-income for a court-appointed attorney in any related and pending criminal case. Collateral damage alert: a provider might abruptly receive notice that their professional malpractice insurance has been suspended or canceled (due to the ongoing Board investigation or criminal charges). This is another one of those credentialing questions that no one ever wants to have to answer "yes" to (Q: has your insurance ever been suspended or revoked?).

Next, let us look at files – one or more of which will likely be requested by the Board. This includes any and all informed consent paperwork, disclaimers, chart notes, time of sessions, if, how, and why a provider billed insurance for the session, and all related phone texts and email records. (If the complaint was not made by the client, and if there is no Release of Information signed by the client, a provider will need to carefully figure out what information they may lawfully turn over to the Board in your defense.) What did they charge? How long was the session? Who was billed, and under what diagnosis and which CPT code? How was it paid for? What *are* the overall billing practices? (Note: the argument that a provider did not charge for the session will not reduce the Board's jurisdiction or scrutiny.)

Next, the actual session. What happened? When? What was the length? What was the plan? Moreover, what -- exactly -- is "integration"?

The dictionary definition will be of little help [19]. The term is used, but not defined, in the most recent report on the MAPS MDMA clinical trials (Mithoefer et al. 2019 [8]). The MAPS Training Manual does not define it but does provide a dozen or so pages of suggestions and guidance for therapists who are providing post-dosing integration sessions [20]. (Concerning PAT, many readers would agree that "integration" generally refers to getting the most out of a psychedelic dosing session, in a positive way.)

Assuming that at some point, a provider and the Board can agree on what integration means (or at least the Board comes to an understanding about what the provider means), the next inquiry might be about training. What training does the provider have in providing "integration" for psychedelic dosing? How long have they been doing this? Ethically

(check current administrative rules), a provider is not supposed to offer services that they are not qualified to offer. What is the provider's experience and qualifications with psychedelics? (Bear in mind that for about fifty years, these substances have been highly illegal, and the Board is now asking pointed questions about the provider's private use and knowledge of illegal drugs, *and* the Board is documenting those answers – answers that are given under the penalty of perjury).

One point that is very important to make is that during the MDMA clinical trials, the post-dosing "integration" is not a stand-alone, post-dosing event. It occurs within an ongoing therapeutic relationship that begins with the first pre-dosing therapy session and is strengthened via the therapists' presence during the dosing session[21]. Therefore, arguably, successful "integration" as that term is used in the MDMA Training Manual and the clinical protocols to date is contingent upon the therapists' presence during the pre-dosing therapy *and* dosing sessions and continues until the participant is finished with the trial. One could even argue that "integration" includes the pre-dosing and dosing sessions. This may sound extreme, but it is plausible.

Importantly, neither the number of therapists present nor the continuity of their presence during each stage of the protocol (pre-dose, dosing, post-dosing) was a variable during the clinical trials. Therefore, there is no evidence, from these particular trials, as to how effective MDMA-assisted therapy *in toto* will be without the presence of two therapists throughout the entire protocol. Similarly, there is no evidence as to how effective "integration" (however defined) is, when applied to the experience of taking illegal drugs in an underground setting.

The point here is that when people read about these encouraging phase I and phase II clinical trial results and start asking around for "integration" services ("because I have already done the MDMA, I guess I just need to integrate it"), they are vulnerable to being exploited and hurt. Similarly, when a therapist gets excited about these clinical results and starts offering stand-alone post-dosing "integration," relying in good faith on the MAPS clinical data but not understanding how to read and interpret clinical results correctly, the therapist risks exploiting the client for financial gain, and possibly causing iatrogenic harm.

Going back to the Board's investigation, a provider might try explaining (rationalizing?) that their services are in the realm of "harm reduction" (as propounded by the authors of the Psychology Today blog). The Board will then proceed to look at their training in substance use and abuse in general, and in particular, their training in "harm reduction" concerning *psychedelics*. Are they a Certified Alcohol and Drug Counselor? If not, what classes, courses, and supervision have they had or taken, related to *harm reduction for psychedelic use*? Were the classes taught by credentialed educators? Did they obtain continuing education credits? What is the theory exactly? What do they assert are the *recognized harms* to the user of illegal psychedelics? What empirical evidence are they relying on? How did or would their *recommendations r*egarding "set and setting" reduce the risk of harm? And by how much? Furthermore, how do they know? Identify the *harm reduction* language in their advertising, and their client consent form and treatment plan. How much of each session was spent on *harm reduction* versus *integration*? Does their billing reflect the distinction, and if not, why not?

It looks and sounds like they think that the illegal possession and use of nonpharmaceutical grade psychedelics (whatever is offered for sale on the street as a psychedelic) can have a positive effect -- outweighing all harm -- if "integrated" properly. How do they even know what their client will ingest or has ingested? Did they or someone else test it? Did they offer to? Why not? Would this approach ("positive" pre- or post-dosing integration) work for other illegal drugs like heroin and methamphetamine, or troubling criminal behaviors like domestic violence? Is there an "upside" to such experiences? Why or why not?

A provider might offer the explanation that "published research has shown integration to be helpful." Providers should be prepared to answer questions about how closely their "integration services" follow the procedures in the published research they cite (FDA approved trials), how it

differed, and why those differences are unimportant. Explain their understanding of why the FDA requires three phases of clinical trials, pharmaceutical grade drugs, and the current clinical trial status of the drug(s) at issue. Explain how clinical trial outcomes are relevant to their assisting clients in "integrating" illegal acts with illegal drugs in non-clinical settings.

A provider might try offering an explanation involving their own or their client's "freedom of speech" or the right to encourage "cognitive liberty." The Board would likely promptly re-focus the provider on the fact that they are concerned about public safety, which includes first and foremost the provider's fitness to practice: the provider's moral character, and the illegal nature of psychedelics. The Board is not prohibiting or limiting the provider's constitutional rights to free speech or thought. They are free to take – or promote the taking of – illegal drugs. However, they are not free to keep their license while doing those things. The Board will remind the provider that their license is a privilege that can and will be suspended or revoked by them if they decide the provider is morally unfit to keep practicing.

For those readers who have never experienced a grilling by an administrative Board, or read a transcript of one, these questions may sound ridiculous or exaggerated, but they most assuredly are not. If a provider is in doubt, they should find an attorney who defends licensed health care professionals before their Board, and seek their counsel and, at the very least, inquire about the potential outcomes.

Other Ethical Quandaries.

As this goes to press, MAPS is finalizing the protocol to be used in expanded-access clinics for MDMA assisted psychotherapy. Negotiations are underway for how closely these clinics will have to follow the phase II and phase III FDA protocols (an issue that may constrain future off-label use of MDMA [22]). The phase II protocol was very labor-intensive. It was "based upon initial work with classic psychedelics and early reports of MDMA in a therapeutic setting [8]." For the initial round of MDMA-assisted therapy treatment, each of the two therapists were in direct face-to-face contact with the "volunteer" (and each other) for approximately 20 hours, for a minimum of 40 client-hours [23] [8].Add to this the typical overhead expenses of clinic operation and a high cost per treatment is likely.

Importantly, the MAPS trials were and are primarily funded by MAPS -- a 501(c) non-profit (with taxpayers picking up the government agency tabs). The expanded access clinics will need to raise their *own* operating funds or pass those costs onto clients. Another challenging issue is staffing. To date, during the MDMA trials, both therapists must be attending to the client during the dosing sessions – therapists are not allowed to be doing other activities: they must be genuinely present and always attuned to the patient (no computer or phone use). As videotapes of these sessions show, this is not typical or comfortable work for the average health care professional (sitting bedside with a patient, with a 2nd therapist in the room, for 6-10 hours at a stretch, solely focused on the patient). Given the intensity of these sessions, it has been suggested that the therapist teams be limited to one dosing session per week. That is a significant constraint on resource scheduling and income generation.

The cost and staffing of PAT has been at the center of the discussion about 1) whether it is possible to provide effective PAT via a cheaper protocol, 2)if so, how to bring down the delivery cost of PAT (to a price that Medicaid and the Veterans Administration will tolerate) without losing efficacy, 3) how best to handle the recruitment, training, and retention of PAT therapists, and last but not least, 4) how to solve the dilemma of who does or does not get the treatment. Investors and clinicians are negotiating amongst themselves and with the government. See, e.g., *Expanded Access: Creating a Psychedelic Therapy Center in the Pacific Northwest* [9], and the website at www.fieldtriphealth.com. For-profit clinics will be free to make as much profit as they can (and investors typically demand this). It is unclear how far these clinics will be allowed to stray from the phase II and phase III protocols, and what limits (if any) will be put on the prospective "off label" use of FDA-approved MDMA. It is unknown whether a

protocol with much-reduced staffing and or semi-private dosing environments will be affordable and effective.

So, when a client contacts a PAT provider, having relied on media reports generated by the two-therapist, private-room protocol, when and how will any change from this protocol be communicated to the client? What rationale or justification will be offered? What protections will be offered? Assuming there will be pressure to have non-credentialed sitters, replace one or both therapists, at least during the dosing sessions, will there be any meaningful oversight [24]? Given the milieu in which the encouraging data was generated, would a non-credentialed "sitter" working in an expanded access clinic nonetheless be practicing some form of psychotherapy (in the eyes of the patient), yet be doing so without a license? If so, is the credentialed therapist assisting in that unlicensed practice?

Similar ethical considerations confront clinicians who have been or are newly offering off-label ketamine-assisted therapy. It may be "legal," but given the lack of rigorous clinical trials demonstrating the safety and efficacy of these off-label uses, and the long-documented side effects, it is ethical? How are the risks, and the lack of robust evidence communicated to the patient? These clinics are planning to be in place and designed to quickly expand their offerings of PAT, if and when additional drugs become legally available. Assuming there will be a need for a credentialed psychotherapist on-site, what is an ethical caseload and FTE?

A primary goal of many researchers around the work has been to generate sufficient data to convince the U.S. government to move these drugs out of Schedule I (by generating evidence that the drugs *do* have medicinal value). Once that happens, the drugs may be legally manufactured or harvested and prescribed and possessed for medicinal purposes. Unless otherwise restricted, off-label use will likely explode, and manufacturers -- just like the clinicians -- will seek to maximize demand and profits. Specialty clinics will gain a competitive boost if regulators require that psychedelics only be provided at such locales, a requirement that may strike some as grounded more in capitalism than in safety and necessity (especially if credentialed "sitters" are not required for the dosing session, or that the existing protocol is further watered down). Oregon voters will be voting on this issue if enough signatures are gathered to put it on the ballot in 2020[25]. It seems evident that as with all retail level medicine, consumers with the most resources will continue to get the most helpful "set and settings," including as many credentialed therapists and as much privacy as they want. Those who can only afford the economy class protocol will get the "community" set and setting, with maybe one credentialed health care provider for the entire clinic population, popping his or her head in for a few minutes to see how it is going, with interns and minimum wage workers used for everything else.

Concerning traditional psychedelics, a version of this scenario is already playing out at a variety of out-of-country locations currently offering psychedelic-assisted "experiences" marketed as "aboveground." *MycoMeditations* (Jamaica) [10], *Soltara* (Costa Rica [11]), and the *McKenna Academy* (Peru) [12] are just a few examples [26].

Is it ethical for a health care provider to educate a client about these opportunities? Is it ethical to encourage a client to participate in them? Is it ethical to work for one?

It is a given that there are always risks involved in traveling to a foreign country, and one's vulnerability increases exponentially when one is in an altered state of consciousness in a foreign country. The topics of consumer and employee safety, and marketing-versus-the-reality, are hotly debated subjects, as reflected in online reviews and commentaries [27].Typically, the paying customer is required to waive any right to sue the operators for anything that occurs on foreign soil (whether related to the dosing session or not), or related to it upon the customer's return to the U.S [28]. If the customer chooses to indulge in the offered substance, there is no guarantee as to dosage, purity, or effects [29]. Typically, there are few or no credentialed health care providers on-site during the dosing, and no nearby hospital facilities or urgent care clinics [30]. Attendees may be pressured by hosts or other

participants to do additional dosing sessions, and or to increase their dosage during a session [31].

The legality and government oversight of the operation is typically very difficult to ascertain [32]. The screening and acceptance of potential customers (usually strangers to one another) is not transparent, and the group's final "mix" can turn out to be socially awkward or worse. (This could be overcome by organizing a group of sufficient size). Profits are needed and are maximized by having the largest number of customers assembled for each retreat. As in similar quasi-medical, retail operations, there is a weakened (if any) fiduciary duty owed by the retreat operators to the customers.

If the operators and their employees are not credentialed health care providers, there is no mechanism for oversight except for the foreign country's justice system (most of these host countries have much more pressing concerns, so governmental indifference is often at play). If there are credentialed clinicians associated with the retreat (website marketing), that does not mean they will be at *every* retreat and may no longer be associated (marketing is not always accurate [33]). If someone in a dosing group becomes obnoxious or violent, has a "bad trip," becomes ill, or dies, a patient likely will have to witness that (while tripping [34]). Unless the patient brings a friend, no one there will know them, or know how to help them if they feel agitated or scared. Some of the people attracted to and allowed to attend these psychedelic "tours" have serious psychological challenges (PTSD, addictions, personality disorders), and yet are encouraged by the tour companies to "come on down" and "get some help [35]." On the other hand, in a best-case-scenario, these destinations can and do provide an opportunity for someone to experience psychedelics in an ostensibly "aboveground" setting. A clinician making this decision for her or himself is one thing. A provider should avoid lending their credentials and reputation to these retreats, even in a good faith effort to facilitate or influence a client's decision.

Conclusion

Excitement is growing around the world about the potential decriminalization of psychedelics, and their potential to help people through PAT. It is not the intention of this article to diminish this excitement. Nevertheless, health care professionals need to minimize the risk of causing iatrogenic harm or endangering their ability to practice.

Providers, at the very least, should print out a copy of the current statutes and administrative rules governing their profession and *read them carefully*, including the definitions. A phrase such as "good moral character" sounds pretty fuzzy – but it will not necessarily work in their favor if their Board is under political, legal, or media pressure to "take action."

This article does not mean to imply that a licensed health care provider should decline to offer "integration services" or refuse to engage with clinics offering off-label uses of legal drugs. However, the provider needs to have their intention and their story straight. It helps if there is a single-story – the same story that gets told to everyone.

For those providers who have had pleasant or healing psychedelic experiences (whether aboveground or underground): there is no good reason to tell a client about that in detail. Any theoretical benefit of offering a more detailed description can't outweigh the very real risk that the client will minimize the risks they have taken, or are about to undertake, because a provider has "done it" and "it was worth it." As outlined in the thousands of published papers and books on psychedelic use, *there are real risks.* People do die during dosing sessions (as happened in California during an underground magic mushroom session in 2018). The ingestion of psychedelics per se does not immunize the user from cardiac arrest, stroke, seizures, just to name a few, and can, in fact, cause problems. This is the main reason why clinical trial volunteers are so thoroughly screened before being accepted as volunteers, and why participants are so closely monitored during dosing sessions[8].

If a provider is confident that offering integration services for the underground use of psychedelics is valid *and ethically defensible*, start a

workgroup and initiate a conversation with the licensing board and other practice partners. Assuming that clients do and will benefit from such services, what kind of training, precautions, protocols, and chart documentation would they want to see? It will be a friendlier conversation, and a more relaxed opportunity to spread the good news about the encouraging results coming out of psychedelic research.

AUTHOR INFORMATION:

Send correspondence to Rose Jade (rjalate@gmail.com)

Jade, R. (2020, March). Integrating Psychedelic Use: A Cautionary Note for Licensed Health Care Providers. *The Journal of Psychedelic Psychiatry*, *2*(1).

REFERENCES:

1. Pollan, M. My adventures with the trip doctors; the researchers and renegades bringing psychedelic drugs into the mental health mainstream: The researchers and renegades bringing psychedelic drugs into the mental health mainstream. The New York Times Magazine [Internet] 2018 May 15 [cited 10 Jan 2020]. Available from: https://www.nytimes.com/interactive/2018/05/15/magazine/health-issue-my-adventures-with-hallucinogenic-drugs-medicine.html.
2. Bates, M., Neilson, E.M. Ten Reasons Why Psychotherapists Should Learn About Psychedelics: Here's how therapists can get involved in this groundbreaking field right now. Psychology Today [Internet] 2019 Dec 22 [Cited 10 Jan 2020]. Available from: https://www.psychologytoday.com/us/blog/psychedelics-now/201912/ten-reasons-psychotherapists-should-learn-about-psychedelics?eml
3. Raz, S. Transforming psychedelics into mainstream medicines. STAT [Internet] 7 Jan 2020 [cited 10 Jan 2020]. Boston Globe Media. Available at: https://www.statnews.com/2020/01/07/transforming-psychedelics-into-mainstream-medicines/.
4. Ketamine is a dissociative general anesthetic used in human and veterinary medical procedures: it produces effects very similar to PCP...[It was] first synthesized in 1962...[In 1992 it was] rated as a scheduled substance (depressant - Schedule III)." Inaba D.S., Cohen W.E. Uppers, Downers, All Arounders; Physical and Mental Effects of Psychoactive Drugs. 7th ed. Medford, OR: Paul J. Steinbroner; 2011. 6-19p.
5. Devlin, H. Ketamine-like drug for depression gets UK license; Psychiatrists divided on 'game-changing' esketamine due to potential for addiction. The Guardian [Internet] 2019 Dec 19 [cited 10 Jan 2020] Available at: https://www.theguardian.com/science/2019/dec/19/ketamine-like-drug-depression-uk-licence-esketamine.
6. Idrus, A.A. Allergan's NMDA drug rapastinel flops in phase 3 depression studies. Fierce Biotech (A division of Questex) [Internet] 2019 March 7 [cited 10 Jan 2020]. Available at: https://www.fiercebiotech.com/biotech/allergan-s-nmda-drug-rapastinel-flops-phase-3-depression-studies.
7. Pagliarulo, N. J&J's ketamine-based antidepressant sees mixed results in Phase 3. Big Pharma DIVE [Internet] 7 May 2018 [cited 10 Jan 2020]. Available at https://www.biopharmadive.com/news/johnson-esketamine-antidepressant-mixed-results-phase-3/522942/.
8. Mithoefer, M.C., Feducccia, A.A. et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology. 2019 May 7 [cited 10 Jan 2020] 236:2735-2745, at 2737, 2739. Available from: https://link.springer.com/content/pdf/10.1007%2Fs00213-019-05249-5.pdf https://doi.org/10/1007/s00213-019-05249-5. (hereafter cited as Mithoefer et al)
9. Crespi, T. Expanded Access: Creating a Psychedelic Therapy Center in the Pacific Northwest. MAPS Bulletin [Internet]. 2019 Winter [cited 10 Jan 2020]. 29:3:38-40p. Available at https://maps.org/news/bulletin/articles/438-maps-bulletin-winter-2019-vol-29,-no-3/7950.
10. Accessible at: https://www.mycomeditations.com/.
11. Accessible at: https://soltara.co/.
12. Contact information accessible at: https://mckenna.academy/

FOOTNOTES:

1. Rose Jade has a Certificate in Psychedelic-Assisted Therapies and Research from the California Institute of Integral Studies in San Francisco (2018 cohort). She has a BS in Biology from Massachusetts Institute of Technology, a JD from Northeastern University School of Law, and an MSW from Portland State University. She is a Licensed Clinical Social Worker and a Licensed Massage Therapist in Oregon. She has an inactive license with the Oregon State Bar. This article is not meant as legal advice. Rose Jade welcomes correspondence at rjalate@gmail.com. An earlier version of this article was published in 2018 by SSRN. Jade, R. Integrating Underground Psychedelic Use: A Cautionary Note for Licensed Health Care

Providers [Internet] 2018 Jul 3. Available from SSRN: https://ssrn.com/abstract=3181334

2. Referring to the federal United States government agencies: the Food & Drug Administration (FDA) and the Drug Enforcement Agency (DEA).

3. For a similarly themed article published in 2010, see Jade R. Current Research on the Human Experience of Spirituality Following the Ingestion of 'Magic' Psilocybin Mushrooms: An Annotated Bibliography for Social Workers and Other Health Care Professionals. 2010 Nov 26 (rev 2013 June 6). Available from: https://ssrn.com/abstract=1714051 or http://dx.doi.org/10.2139/ssrn.1714051.

4. See e.g, Gonzales v. O Centro Espírita Beneficente União do Vegetal, 546 U.S. 418 (2006); Employment Division, Department of Human Resources of Oregon v. Smith, 494 U.S. 872 (1990), and the Religious Freedom Restoration Act (RFRA), 42 USC §2000bb, passed by the U.S. Congress in 1993.

5. For example, psilocybin and psilocin are controlled substances under Schedule I (c)(15) and (16), of the federal Controlled Substances Act, 21 U.S.C. 811 to 812.

6. "Ketamine...is known on the streets as "special K," "vitamin K," and "kit kat." *Ibid.*

7. Some 2017-era examples include: ORS 475.005 Definitions for ORS 475.005 to 475.285 and 475.752 to 475.980 *** (6) "Controlled substance": (a) Means a drug or its immediate precursor classified in Schedules I through V under the federal Controlled Substances Act, 21 U.S.C. 811 to 812, as modified under ORS 475.035 (Authority to control schedule). ORS 475.752 (1) Except as authorized by [certain other sections]...it is unlawful for any person to manufacture or deliver a controlled substance. Any person who violates this subsection with respect to: (a) A controlled substance in Schedule I, is guilty of a Class A felony, except as otherwise provided in ORS 475.886***7) Notwithstanding subsection (3)(a) of this section, unlawful possession of a controlled substance in Schedule I is a Class B felony if: (a) The person possesses a usable quantity of the controlled substance and:(A) At the time of the possession, the person has a prior felony conviction; (B) At the time of the possession, the person has two or more prior convictions for unlawful possession of a usable quantity of a controlled substance; or (C) The possession is a commercial drug offense under ORS 475.900 (1)(b); or (b) The person possesses: (A) Forty or more user units of a mixture or substance containing a detectable amount of lysergic acid diethylamide; or (B) Twelve grams or more of a mixture or substance containing a detectable amount of psilocybin or psilocin.

8. Allergan Pic. Allergan Announces Phase 3 Results for Rapastinel as an Adjunctive Treatment of Major Depressive Disorder (MDD) – Three acute pivotal studies did not meet their primary endpoint – – Interim analysis of relapse prevention study suggests the primary endpoint will not be met – ***We are deeply disappointed with these results, and they are a vivid reminder that drug development is extremely challenging, especially in mental health. We are grateful to the patients, their caregivers, and the investigators who supported these clinical studies. We remain committed to the development of new life changing medications to combat the rising global toll of mental illness," said David Nicholson, Chief Research & Development Officer at Allergan***In a previously conducted Phase 2 clinical study rapastinel demonstrated a rapid onset of antidepressant effect within one day, which continued for approximately seven days after a single injection." March 6, 2019. Press release available at: https://www.allergan.com/News/ http://www.prnewswire.com/news-releases/allergan-announces-phase-3-results-for-rapastinel-as-an-adjunctive-treatment-of-major-depressive-disorder-mdd-300808044.html.

9. The Expanded Access protocol differs from MAPS' ongoing Phase 3 clinical trials in that it is limited to treatment-resistant patients with moderate to severe treatment-resistant PTSD. Other differences are that the FDA is requiring at least one therapist of each therapy pair to have a medical or clinical doctorate degree (M.D., Ph.D., or equivalent), there is no control group, and patients are responsible for the costs of their own treatment...[This] protocol must still be approved by the U.S. Drug Enforcement Administration (DEA) and the Institutional Review Board (IRB)." FDA Agrees to Expanded Access Program for MDMA-Assisted Psychotherapy for PTSD, MAPS Press Release 17 Jan 2020 [cited 18 Jan 2020] Available from: https://maps.org/news/media/8008-press-release-fda-agrees-to-expanded-access-program-for-mdma-assisted-psychotherapy-for-ptsd.

10. OAR 877-015-0108 Eligibility Requirements. To be eligible for initial certificate of registration or license, a person must meet the requirements in sections (1) through (6) of this rule. *** (3): To be fit to practice social work in Oregon, the person must have demonstrated and must currently have: (2) (A) Good moral character. For purposes of this rule, lack of "good moral character" may be established by reference to acts or conduct which would cause a reasonable person to have substantial doubts about the individual's honesty, fairness, and respect for the rights of others and for the laws of the state and the nation. The conduct or acts in question should be rationally related to the applicant's fitness to practice social work; and (B) A personal history of conduct that is consistent with the standards contained in division 30 of this chapter of rules. *** (4) The person must be fit to practice social work in Oregon. In making this fitness determination, the board will consider whether the person is subject of an investigation or disciplinary action by a licensing board and the reasons for the action.

11. ORS 675.583 Duty to report evidence of impairment or unprofessional or prohibited conduct; confidentiality of information, limitation of liability. (1) Unless state or federal laws relating to confidentiality or the protection of health information prohibit disclosure, a regulated social worker shall report to the State Board of Licensed Social Workers any information the regulated social worker has that appears to show that a regulated social worker is or may be an impaired professional...or may have engaged in unprofessional conduct according to the guidelines of the code of ethics*** Oregon Laws Chapter 676. Health Professions Generally. *** Reporting Obligations.

*** ORS 676.150 Duty to report prohibited or unprofessional conduct, arrests and convictions; investigation; confidentiality; immunity from liability. ***(2) Unless the state or federal laws relating to confidentiality or the protection of health information prohibit disclosure, a [health profession] licensee who has reasonable cause to believe that another [health profession] licensee has engaged in prohibited or unprofessional conduct shall report the conduct to the board responsible for the licensee who is believed to have engaged in the conduct. The reporting licensee shall report the conduct without undue delay, but in no event later than 10 working days after the reporting licensee learns of the conduct

12. OAR 877-040-0010 Form of Complaints. Any person may file a complaint alleging a violation of ORS 675.510 to 675.600 or of the rules of the board or an impairment. A complaint must identify the complainant and the respondent ORS 675.510 Definitions...(8) "Unprofessional conduct" includes, but is not limited to, any conduct or practice contrary to recognized standards of ethics of the social work profession or any conduct that constitutes or might constitute a danger to the health or safety of a client or the public or in any other manner fails or might fail to adhere to the recognized standards of practice."

13. ORS 675.540 Grounds for disciplinary action; authorized sanctions and penalties; investigations. (10 The State Board of Licensed Social Workers may impose any or all of the sanctions specified in subsection (2) of this section, upon proof, after a hearing pursuant to the provisions of ORS chapter 183 [Administrative Procedures Act] relating to a contested case***

14. OAR 877-030-0090 General Provisions Governing Conduct. (1) A regulated social worker must cooperate with the Board, its investigators, and its committees in investigations made under OAR Chapter 877. (2) A regulated social worker must fully comply with a final order issued to the regulated social worker by the Board.

15. OAR 183.450 Evidence in contested cases. In contested cases: (1) Irrelevant, immaterial or unduly repetitious evidence shall be excluded but erroneous rulings on evidence shall not preclude agency action on the record unless shown to have substantially prejudiced the rights of a party. All other evidence of a type commonly relied upon by reasonably prudent persons in conduct of their serious affairs shall be admissible. Agencies and hearing officers shall give effect to the rules of privilege recognized by law. Objections to evidentiary offers may be made and shall be noted in the record. Any part of the evidence may be received in written form. (2) All evidence shall be offered and made a part of the record in the case, and except for matters stipulated to and except as provided in subsection (4) of this section no other factual information or evidence shall be considered in the determination of the case. Documentary evidence may be received in the form of copies or excerpts, or by incorporation by reference. The burden of presenting evidence to support a fact or position in a contested case rests on the proponent of the fact or position. (3) Every party shall have the right of cross-examination *of witnesses who testify* and shall have the right to submit rebuttal evidence. Persons appearing in a limited party status shall participate in the manner and to the extent prescribed by rule of the agency***. [Emphasis added]

16. OAR 877-040-0016 Reporting Possible Prohibited Conduct to Law Enforcement Agency. (1) If, during the investigation of a complaint, a member of the Consumer Protection Committee or any board member believes a respondent has engaged in prohibited conduct, the committee or member must refer the case as soon as possible to the board for its review. The board will review the case not later than the next regularly scheduled board meeting and will determine whether it has reasonable cause to believe that the respondent has engaged in prohibited conduct. (2) If the board concludes there is reasonable cause to believe that the respondent has engaged in prohibited conduct, the board will present the facts to an appropriate law enforcement agency within 10 working days. (3) In this rule, the term "prohibited conduct" ...means conduct by a licensee that: (a) Constitutes a criminal act against a patient or client; or (b) Constitutes a criminal act that creates a risk of harm to a patient or client. The term "licensee"...includes all regulated social workers.

17. OAR 877-040-0015 Notification to Respondent. (1) The Consumer Protection Committee may send a letter to the respondent stating that nature of the investigation and, if appropriate, an authorization to release confidential records. The committee will ask the respondent to provide a written reply within 30 days together with documents the respondent considers relevant. (2) If the respondent replies to the request of the board, the reply is reviewed by the Consumer Protection Committee. The committee may ask for additional or more specific information.

18. Not every coroner or doctor is conversant with how psychedelics are metabolized, and easily debatable conclusions can be erroneously reached, some with serious legal and/or psychological consequences for third parties. Doctors, scientists or local District Attorneys who have specialized knowledge about the metabolism of psychedelics are obviously the best "messengers" for requesting reconsideration of a cause of death determination involving psychedelics. It saves enormous time and resources if this can happen *before* the Certificate is finalized, but that's not always how it goes. A helpful reference is Timmermans S. Postmortem: How Medical Examiners Explain Suspicious Deaths. Paperback ed. Chicago: The University of Chicago Press (2007).

19. According to the online Oxford Dictionary, to "integrate" means to "[c]ombine (one thing) with another so that they become a whole." With respect to psychology, "integration" is defined as "[t]he coordination of processes in the nervous system, including diverse sensory information and motor impulses." With regard to psychoanalysis, it is "[t]he process by which a well-balanced psyche becomes whole as the developing ego organizes the id, and the state that results or that treatment seeks to create or restore by countering the fragmenting effect of defense mechanisms."[Cited 10 Jan 2020] Available at: https://www.lexico.com/en/definition/integrate.

20. "Integration is viewed as an essential and ongoing process as the inner experiences catalyzed by MDMA-assisted sessions

continue to unfold. Follow-up contact with the therapists by phone and during scheduled integration visits is necessary to support successful integration. During these visits the therapists aim to address any difficulties that may have arisen following MDMA-assisted sessions and to anchor the lessons gained in a non-ordinary state of consciousness so they can be integrated into daily life." Mithoefer, M. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. [Internet] 2017 May 22: Version 8.1 [Cited 10 Jan 2020]. MAPS, U.S. p8 (see also pp50-58). Available at: https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/TreatmentManual_MDMAAssistedPsychotherapyVersion+8.1_22+Aug2017.pdf

21. "The successful use of MDMA in therapy depends on the sensitivity and talent of the therapist who employs it. The therapists work with the participant to establish a sense of safety, trust, and openness, as well as to emphasize the value of trusting the wisdom of the participant's innate capacity to heal the wounds of trauma. Greer and Tolbert suggest that 'the relationship should be oriented toward a general healing for the client, who should feel safe enough in the therapists' presence to open fully to new and challenging experiences.' Establishing these conditions requires that the therapists carefully set the parameters of treatment and prepare the participant before each MDMA-assisted session, and then provide appropriate support following the session so that the experience can be successfully integrated." - Mithoefer, MDMA Manual, pg 6 (citations omitted).

22. MDMA-assisted psychotherapy uses MDMA to improve the effectiveness of psychotherapy for PTSD. The treatment involves up to three administrations of MDMA, in conjunction with psychotherapy in a controlled clinical setting as part of a course of psychotherapy. Once approved, patients will not be able to take the MDMA home – patients won't be filling their prescriptions at their local pharmacy. Instead, MDMA-assisted psychotherapy treatment will only be available through a doctor and only in supervised therapeutic settings from certified clinicians." MAPS press release, 17 Jan 2020.

23. "Two to three non-drug 90-min therapy sessions prior to the first experimental session...[an] 8-h psychotherapy session...after [which] participants remained at the study site overnight with a supportive attendant. On the following day, they met with the therapists in a 90-min integration session ...[and] two to three more integration sessions occurred during the month after each experimental session. For 7 days following each experimental session, the therapy team checked in with the participants in brief telephone calls to assess wellbeing and safety....The same male/female therapy team was present for all therapy sessions for a given participant."Mithoefer et al, ibid., pgs 2737-2738.

24. For the expanded access MDMA clinics, the FDA agreed to one therapist being a not-yet-credentialed intern, but newly required at least one of the therapists be a doctorate-level clinician. MAPS press release, 17 Jan 2020. As stated in the MAPS Therapy Training Program Application Requirements: "If one of the practitioners on a therapy pair is not fully licensed, they may alternatively be enrolled in a mental health training program gaining supervised hours of experience (i.e. Marriage Family Therapist Practicum, Social Work Internship, and RN in supervised clinical practice to obtain Psychiatric/Mental Health certification, Psychiatry Residency), AND plan to pair only with a full licensed clinician to conduct psychotherapy who also meets the qualifications of the MDMA Therapy Training Program. *** MAPS Therapy Training Program Application Requirements [cited 22 Jan 2020]. Available from https://mapspublicbenefit.com/therapy-training/program-application-requirements/.

25. For more information, access https://psi-2020.org/the-measure/. This is distinct from a separate Oregon ballot measure effort that seeks to decriminalize drugs. For more information, access https://www.marijuanamoment.net/oregon-activists-begin-signature-gathering-for-2020-drug-decriminalization-initiative/.

26. I have attended one retreat put on by MycoMeditations in Jamaica, and one put on by the McKenna Academy in Peru.

27. Compare, for example reviews posted at https://www.tripadvisor.com/Attraction_Review-g635963-d15695234-Reviews-MycoMeditations_Psilocybin_Assisted_Retreats-Treasure_Beach_Saint_Elizabeth_Pari.html vs. comments posted on Psychedelics Today, explaining why they withdrew support for MycoMeditations as of October, 2018. [cited 22/Jan 2020] Available at https://psychedelicstoday.com/2018/10/24/statement-on-mycomeditations/. Katherine MacLean, PhD, formerly associated with psychedelic research at Johns Hopkins and MycoMeditations, posted on the Psychedelics Today website: *"...[I was] happy to endorse and help Mycomeds at different points, but we've all slowly come to similar conclusions. I have previously endorsed Mycomeds through video, podcasts, my newsletter/website/, social media etc. without any compensation beyond being paid at a reasonable rate for working directly with guests during and after retreats. If someone hears my endorsement, and then gets hurt or worse, I can't live with that pain and responsibility. I still worry about people's safety but I've done what I can. I love many of the people working with Mycomeds and I hope that this public discussion can encourage some very easy and needed adjustments so that they can continue helping people safely and effectively...I think that some of us who have been trained to respect confidentiality and clinical ethics are torn between reporting the safety concerns and protecting the retreat guests rights to privacy. I can say very generally that I witnessed 1-2 (potential) medical emergencies on each of two retreats I helped facilitate, and at least 1 person on each retreat who had multiple incidents of extreme physical reaction to the mushrooms (several hours of vomiting and diarrhea). The other guests who were trained medical professionals were the ones who attended these situations, as there are no medical professionals on Mycomeds staff (no one with clinical psych training either), and the closest health facility is 45 minutes away on bad roads. Mycomeds also accepts applicants who are at extreme risk of harm, including people with physical and psychological conditions that would almost always be excluded from other remote psychedelic or meditation retreats,*

and certainly screened out of clinical trials. I believe they are doing this to try to "save" people who are really suffering, but it endangers the guest and everyone else. I became uncomfortable offering prep and integration support for people with extreme depression, anxiety, suicidality, substance dependence ... and voiced my concerns about taking on such serious and vulnerable cases. But they continued to accept such folks and were not interested in incorporating my safety feedback...I believe there was (is?) so much potential for Mycomeds to be a truly great community resource. I recorded the [initial] interview [for Psychedelics Today] with [hosts] Kyle and Joe when I returned from the first retreat last December [?2017?]. A lot of amazing stuff happened that retreat and really, only that 1 person had a really tough time (medically). I learned a lot in preparing for and leading the women's retreat a few months later [?April 2018?], but it was definitely a more serious and vulnerable cohort. I hoped everything could change and improve after that, because those women were fierce and gave important feedback." This and additional comments are available at: https://www.facebook.com/Psychedelicstoday/posts/620955214967939?__tn__=-R.

28. This was my experience in Jamaica and Peru.
29. *Ibid.* To my knowledge, there was no external testing or measuring of the potency of any substance offered at Jamaica or Peru. Everyone in Peru became nauseous (as expected). Some people in Jamaica became nauseous. At least one person at each locale did not experience any significant "effects."
30. To my knowledge, there were no credentialed health care providers on site or nearby during the retreats I attended in Jamaica and Peru
31. This was my experience in Jamaica and Peru.
32. This was my experience in Jamaica and Peru.
33. This was my experience in Jamaica.
34. This was my experience in Jamaica and Peru.
35. This was my experience in Jamaica and Peru.

Positive Response to Ketamine Administration in Treatment Resistant Psychosis: A Case Report

Joseph Pullara, M.D.

Abstract:
The pathophysiology underlying the schizophrenia spectrum of disorders has been a topic of research for decades. Ketamine has been used as a model for psychosis for over 20 years [1]. Treatment of refractory cases of schizophrenia and similar disorders remains a challenging aspect of psychiatry. This case report describes the case of a 45-year-old woman with treatment refractory schizoaffective disorder who was transitioned off of clozapine due to neutropenia. This resulted in psychotic destabilization and a complicated clinical course, ultimately resulting in a re-trial of clozapine after the failure of alternative psychotropic treatment. During this trial, an MRI brain was obtained, which required a sedating dose of intravenous ketamine due to patient agitation. After just a single dose of ketamine, resolution of behavioral activation and agitation was noted for a short period, something which had not been seen in over a month of hospitalization.

Introduction

Schizoaffective disorder is a psychiatric illness that results in both psychotic and affective symptomatology, initially described as a subtype of schizophrenia that became a standalone diagnosis in later editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Treatment commonly consists of multiple psychotropic medications to treat symptoms of psychosis, depression, mania, or a combination of symptoms [2]. When psychosis persists despite trials of multiple antipsychotic medications, clinicians start to have discussions with patients and their families about the use of clozapine. If clozapine fails to resolve symptoms or if patients are required to discontinue treatment due to harmful adverse reactions (i.e. neutropenia, clozapine-induced myocarditis, or bowel obstruction due to constipation), clinicians face the difficult decision of which treatment direction to proceed next.

Case Report

Mrs. K was a 45-year-old Asian female with a history of schizoaffective disorder, bipolar type who was involuntarily admitted to a state psychiatric facility after displaying delusional religiosity and agitation during a mental health screening at a community mental health center. The patient was an Asian immigrant who had moved to the United States at age 5. She had struggled with schizoaffective disorder for the majority of her adult life but had previously been psychiatrically stable on clozapine. Unfortunately, one month before admission, the patient's absolute neutrophil count (ANC) decreased to 820mm^3. Given this, the decision was made to taper off of Clozapine and onto olanzapine due to its psychopharmacologic similarities.

On admission, it was unclear whether she had been taking any oral medications at all. During the intake process, she was threatening both peers and staff and attempting to elope. The patient believed that her mother lied to her about her father's death in the Vietnam war and that he was still alive and had visited her. Providers attempted to treat this mood lability and psychosis with various mood stabilizers & antipsychotics, but the patient continued to refuse oral medications. Due to concerns for her safety and the safety of other patients, the decision was made to institute a medication over rejection order, and she was given intramuscular (IM) psychotropic medication each time she refused the oral formulations of medications. Despite receiving numerous doses of IM fluphenazine, chlorpromazine, olanzapine, diphenhydramine, and

lorazepam throughout the first week of admission, the patient's condition did not improve. The patient remained aggressive towards staff & other patients, displayed self-harming behaviors, refused most oral nutritional intake, and slept less than 3 hours each night of this hospitalization. On one occasion, the patient was seen banging her head on a wall aggressively, despite one-to-one monitors attempting to prevent her from doing so. Given signs of volume depletion and concern for a head injury, the patient was transferred to a local emergency room for imaging and medical workup.

Three weeks later, the patient was deemed medically stable and was transported back to the state psychiatric facility. The patient had been treated for volume depletion and completed a course of antibiotics for a urinary tract infection. Providers had tried to rechallenge the patient with clozapine during her three-week admission at their facility, but the patient again refused most oral medications. When the patient arrived back at the state psychiatric facility for this second admission, she believed that she was God and had been communicating with the devil. The patient was again refusing oral medications and most attempts at oral nutritional intake. The patient's behaviors resulted in many hours of seclusion and physical restraints over the majority of her hospitalization. Even with continuous one-to-one monitoring by staff, the patient remained labile, aggressive towards other patients, sexually inappropriate with staff and other patients, and displayed various forms of self-harming behaviors ranging from slamming her hands onto doors to hitting her head on walls.

Providers tried to reinforce the importance of oral medications continually, but the patient was unable to display any insight into her condition. Throughout what would eventually lead to a three-month admission, she was trialed on combinations of scheduled intramuscular fluphenazine, chlorpromazine, ziprasidone, olanzapine, and haloperidol. Electroconvulsive therapy was considered but providers did not feel the patient was a candidate for this treatment modality, nor would she have been able to give informed consent to treatment. Almost a month into the patient's admission, providers began another trial of clozapine but the patient continued to refuse oral medications intermittently.

One morning, after an overnight incident in which the patient purposefully hit her head on a wall forcefully, the decision was made to transfer the patient to a nearby medical facility for head imaging. At that facility, emergency room physicians decided to perform magnetic resonance imaging (MRI) of her brain. Before the procedure, the patient displayed continued agitation and aggression, so the decision was made to provide adequate sedation in the form of intravenous ketamine. Results of the MRI were unremarkable for acute or chronic pathology, but the patient's mental status and affect were notably different.

Upon awakening from the procedure, the patient was transferred back to the state psychiatric facility. When the patient arrived, she began apologizing to staff for her behavior over the previous few months. The patient expressed interest in seeing her husband again, something she had not mentioned during her entire admission. She was agreeable to taking oral medications; in particular, the patient recalled how important clozapine had been in her life before admission. The patient's sleep patterns remained irregular but had overall improved significantly. The patient remained agitated at times, but much less than previous and could be adequately monitored with 15-minute checks for safety instead of continuous one-to-one monitoring. One week after returning from MRI, the patient was discharged to home care with her husband and mother-in-law. The family considered her recovery to be a "miracle." Ultimately, she was discharged on a combination of clozapine 900mg daily (in divided doses), quetiapine 400mg nightly, and ziprasidone 120mg twice daily.

Before discharge, providers attempted to establish the patient with outpatient services at local ketamine clinics, both with intravenous ketamine and intranasal Spravato (esketamine) but were unable to do so because of financial concerns and lack of insurance coverage. After coordinating care with outpatient providers, the plan was to continue oral antipsychotics and eventually try to taper down to two antipsychotic medications instead of three,

due to the well-known dangers of combining multiple antipsychotic medications. Unfortunately, the patient decompensated and was readmitted involuntarily to the state hospital for a third time just three months after her second admission. She presented with similar agitation and delusional religiosity. She believed that she was pregnant with the son of Jesus, that she was a famous movie star, and that President Jimmy Carter was the leader of the entire world. This admission was similar to previous admissions with much time spent in the seclusion room and requiring physical restraints. After three weeks, she was found to be stable enough to transfer from the acute psychiatric unit to a long-term state psychiatric facility, where she currently resides at the time of publication. Providers were not able to get the state hospital to approve the use of intranasal esketamine or intravenous ketamine.

Discussion:

Ketamine is a widely used pharmacologic agent first synthesized in 1962 as an analog of the anesthetic phencyclidine [4]. It was first used in psychiatry as a drug model for psychosis but later found to be therapeutic for patients with refractory depression [1]. Its use in the intravascular formulation has never been approved by the Food and Drug Administration (FDA) to treat depression, but its use in private practice ketamine clinics is not uncommon across the United States. When used in a sub-anesthetic context, its effects on depression and suicidality have shown positive results in some clinical trials. In March of 2019, the FDA approved the use of intranasal Spravato (esketamine), the S(+) enantiomer of ketamine, for use in adult patients with treatment-resistant depression without psychotic features [5]. While studying esketamine in clinical trials, a critical exclusionary criterion is having a history of a psychotic disorder (including major depressive disorder with psychotic symptoms) or a history of bipolar disorder as researchers have known for almost 20 years that subanesthetic doses of ketamine can induce psychosis similar to that seen in schizophrenia[1,3].

While reviewing the case described above, one would naturally question why ketamine was chosen for sedation in this patient's case given her long history of psychosis. Unfortunately, this was not documented in the records available for review. One hypothesis for why ketamine was helpful in this case without exacerbating psychosis is that this patient had been taking oral clozapine at the time of IV ketamine administration. Granted, the patient had been skipping doses intermittently in the weeks leading up to the MRI, but there is literature to suggest that clozapine has a unique NMDA receptor effect and can blunt the psychotic effects of ketamine in patients with schizophrenia and schizoaffective disorder [6]. How this patient would have responded to intranasal esketamine or repeat infusions of subanesthetic doses of IV ketamine will never be known but may reveal itself as an area for further study in the future.

AUTHOR INFORMATION:

Send correspondence to Dr. Joseph Pullara (jpullara@kumc.edu)

Pullara, J (2020, March). Positive Response to Ketamine Administration in Treatment Resistant Psychosis: A Case Report. *The Journal of Psychedelic Psychiatry*, *2*(1).

REFERENCES:

1. Lahti, A. "Subanesthetic Doses of Ketamine Stimulate Psychosis in Schizophrenia." *Neuropsychopharmacology*, vol. 13, no. 1, 1995, pp. 9–19.
2. Wy, Tom Joshua P. "Schizoaffective Disorder." *StatPearls [Internet]*., U.S. National Library of Medicine, 30 June 2019.
3. Canuso, Carla M., et al. "Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study." *American Journal of Psychiatry*, 16 Apr. 2018.
4. Lanning. "Ketamine Anesthesia." *Annual Reviews*, Annual Review of Medicine 1975 26:1, 137-141.
5. Jauhar, Sameer, and Paul Morrison. "Esketamine for Treatment Resistant Depression." *The BMJ*, British Medical Journal Publishing Group, 23 Sept. 2019.
6. Malhotra, Anil K, et al. "Clozapine Blunts N-Methyl-d-Aspartate Antagonist-Induced Psychosis: A Study with Ketamine." *Biological Psychiatry*, Elsevier, 19 Jan. 1998.

Selective Use of Ketamine in Patients with Psychotic Disorders

Tyler Kjorvestad, M.D.

In this article, Pullara[1] discusses the case of a patient with an underlying psychotic disorder who improved after the administration of ketamine. This dramatic improvement was noted after the failure of numerous trials of both typical and atypical antipsychotic medications. Of particular interest is the effect of the antipsychotic clozapine on ketamine's receptor activity, and its potential implications for the use of ketamine as a treatment for psychiatric conditions in patients with psychotic disorders.

Ketamine was originally discovered in 1962 and used as an aesthetic from the 1970s onward [2]. In addition to anesthesia, ketamine has been used in the treatment of asthma [3], super-refractory status epilepticus [4], and pain management [5]. In the early 2000s, research into its antidepressant effects was undertaken with small scale studies showing positive results [6]. While intravenous ketamine has not been approved for the treatment of depression, it is commonly used off-label, and its enantiomer esketamine, a nasal spray formulation, was approved for treatment-resistant depression in March 2019 [6,7]. During the same period as the antidepressant investigations, additional research was conducted looking at the use of ketamine as a primary agent for the treatment of suicidality [8,9,10] and substance use disorders [11].

Ketamine exerts its effects by binding to multiple different receptors in the brain including, but not limited to: opioid receptors [12], alpha receptors [13], the D2 receptor [14], 5HT-2A [14] and 5HT3 [15] receptors, AMPA receptors [16], and the PCP site 2 receptor [17]. The primary binding of ketamine occurs at the NMDA receptor, where ketamine acts as an ionotropic glutamate uncompetitive antagonist [18,19]. While the precise mechanism of action has not yet been elucidated, it is likely to be multifactorial, given the molecule's receptor heterogeneity. Regarding Pullara's case report patient, it can be hypothesized that the NMDA receptor antagonism and D2 Receptor partial agonism played an outsized role in the resolution of the patient's symptoms.

It has been known since shortly after its development, that ketamine can exacerbate underlying symptoms of psychosis [20]. Given this knowledge, ketamine is not routinely administered to patients with schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders. Additionally, it is known that clozapine, with its high receptor heterogeneity, can counteract the psychotic effects caused by ketamine via D2 receptor antagonism [20]. However, this does not explain why a previously psychotic patient would have near spontaneous resolution of psychosis after a single injection of ketamine. Numerous hypothetical reasons could account for this anecdotal response, but at least a few should be further investigated.

Patients who have schizophrenia develop major depressive disorder (MDD) at elevated rates. With an estimated prevalence around, 40% on average [21]. MDD rates can increase to 60% during an acute episode and have been reported as high as 20% in chronic schizophrenia [22]. In total, up to 80% of patients with schizophrenia will have a major depressive episode at some point in their disease course [23]. The relatively frequent occurrence of MDD in patients with schizophrenia has also proven difficult to treat. Limited evidence exists for the use of antidepressants and psychotherapy in the treatment of depressive symptoms in patients with schizophrenia [23,24]. While antipsychotics have some antidepressant effects, it is unclear if these effects are substantial enough to treat MDD or other depressive disorders in patients with psychotic illness. Depression in patients with psychosis is possibly due to the potentially unique pathway that depressive symptoms emerge from in psychotic patients. It has been theorized that depression may be intrinsic to psychotic disorders. Depressive symptoms may be caused, influenced, or exacerbated by psychosocial factors such as being diagnosed with a psychotic disorder, childhood trauma, or significant

psychosocial stressors. Based on the currently available evidence, the structural brain changes and neuroinflammatory modulation seen in schizophrenia patients correlates strongly with similar changes noted in unipolar depression patients [23]. It is, therefore, not unreasonable to hypothesize that if Pullara's patient was experiencing a severe major depressive episode with potentially psychotic features on top of her known schizophrenia that the use of the novel antidepressant agent ketamine could potentially alleviate the depressive symptoms without any risk of exacerbating the psychotic features given the concurrent use of clozapine. This would also explain why the psychotic symptoms returned so quickly as the antidepressant effects of ketamine are relatively short-lived [25].

A less likely theory is that the combination of ketamine and clozapine exerts a synergistic and heretofore unknown effect that is beneficial in patients with psychotic disorders. Alternatively, the dissociative and euphoric effects that ketamine induces may cause the patient to appear calmer and more subdued. Lastly, this may be simply an anecdotal case that cannot be replicated, and the dramatic effect of the ketamine on the patient was nothing more than a placebo response. In any event, further research should be conducted to elucidate further the efficacy of ketamine in patients with psychotic disorders.

The future therapeutic implications for ketamine are vast and include treatment-resistant depression, treatment of acute suicidality, and substance use disorders. The potential use of ketamine to treat refractory depression in patients with schizophrenia or another psychotic disorder who are on antipsychotics that block the psychosis-inducing symptoms of ketamine is a novel area of study that psychiatry should pursue even if it produces negative results.

AUTHOR INFORMATION:

Send correspondence to Dr. Tyler Kjorvestad (tkjorvestad@kumc.edu)

Kjorvestad, T (2020, March). Selective Ketamine Use in Patients with Psychotic Disorders. *The Journal of Psychedelic Psychiatry*, *2*(1).

REFERENCES

1. Pullara, J (2020, March). Positive Response to Ketamine Administration in Treatment Resistant Psychosis: A Case Report. *The Journal of Psychedelic Psychiatry*, *2*(1).
2. Ketamine. (n.d.). Retrieved from http://www.cesar.umd.edu/cesar/drugs/ketamine.asp#5
3. Agrawal, A., & Goyal, S. (2013). Ketamine in status asthmaticus: A review. *Indian Journal of Critical Care Medicine, 17*(3), 154-161. doi:10.4103/0972-5229.117048
4. Gomes, D., Pimentel, J., Bentes, C., Sousa, D. A., Antunes, A. P., Alvarez, A., & Silva, Z. C. (2018). Consensus Protocol for the Treatment of Super-Refractory Status Epilepticus. *Acta Médica Portuguesa, 31*(10), 598. doi:10.20344/amp.9679
5. Karlow, Nicholas, et al. "A Systematic Review and Meta-Analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department." *Academic Emergency Medicine*, vol. 25, no. 10, 2018, pp. 1086–1097., doi:10.1111/acem.13502.
6. Molero, P., Ramos-Quiroga, J. A., Martin-Santos, R., Calvo-Sánchez, E., Gutiérrez-Rojas, L., & Meana, J. J. (2018). Antidepressant Efficacy and Tolerability of Ketamine and Esketamine: A Critical Review. *CNS Drugs, 32*(5), 411-420. doi:10.1007/s40263-018-0519-3
7. Hashimoto, K. (2019). Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. *Psychiatry and Clinical Neurosciences, 73*(10), 613-627. doi:10.1111/pcn.12902
8. Bartoli, F., Riboldi, I., Crocamo, C., Brita, C. D., Clerici, M., & Carrà, G. (2017). Ketamine as a rapid-acting agent for suicidal ideation: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 77*, 232-236. doi:10.1016/j.neubiorev.2017.03.010
9. Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., … Sanacora, G. (2018). The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. *American Journal of Psychiatry, 175*(2), 150-158. doi:10.1176/appi.ajp.2017.17040472
10. Andrade, C., & Rao, T. S. (2017). A possible role for ketamine in suicide prevention in emergency and mainstream psychiatry. *Indian Journal of Psychiatry, 59*(3), 259. doi:10.4103/psychiatry.indianjpsychiatry_345_17
11. Jones, J. L., Mateus, C. F., Malcolm, R. J., Brady, K. T., & Back, S. E. (2018). Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review. *Frontiers in Psychiatry, 9*. doi:10.3389/fpsyt.2018.00277
12. Kohrs, R., & Durieux, M. E. (1998). Ketamine. *Anesthesia & Analgesia, 87*(5), 1186-1193. doi:10.1213/00000539-199811000-00039
13. Robson, M. J., Elliott, M., Seminerio, M. J., & Matsumoto, R. R. (2012). Evaluation of sigma (σ) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. *European Neuropsychopharmacology, 22*(4), 308-317. doi:10.1016/j.euroneuro.2011.08.002
14. Kapur, S., & Seeman, P. (2002). NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D2 and serotonin 5-HT2 receptors—implications for

models of schizophrenia. *Molecular Psychiatry, 7*(8), 837-844. doi:10.1038/sj.mp.4001093
15. Appadu, B. L., & Lambert, D. G. (1996). Interaction of i.v. anaesthetic agents with 5-HT3 receptors. *British Journal of Anaesthesia, 76*(2), 271-273. doi:10.1093/bja/76.2.271
16. Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., . . . Gould, T. D. (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature, 533*(7604), 481-486. doi:10.1038/nature17998
17. Rothman, R. (1994). PCP site 2: A high affinity MK-801-insensitive phencyclidine binding site. *Neurotoxicology and Teratology, 16*(4), 343-353. doi:10.1016/0892-0362(94)90022-1
18. Tyler, M. W., Yourish, H. B., Ionescu, D. F., & Haggarty, S. J. (2017). Classics in Chemical Neuroscience: Ketamine. *ACS Chemical Neuroscience, 8*(6), 1122-1134. doi:10.1021/acschemneuro.7b00074
19. Roth, B. L., Gibbons, S., Arunotayanun, W., Huang, X., Setola, V., Treble, R., & Iversen, L. (2013). The Ketamine Analogue Methoxetamine and 3- and 4-Methoxy Analogues of Phencyclidine Are High Affinity and Selective Ligands for the Glutamate NMDA Receptor. *PLoS ONE, 8*(3). doi:10.1371/journal.pone.0059334
20. Rame, M., Caudal, D., Schenker, E., Svenningsson, P., Spedding, M., Jay, T. M., & Godsil, B. P. (2017, May 04). Clozapine counteracts a ketamine-induced depression of hippocampal-prefrontal neuroplasticity and alters signaling pathway phosphorylation. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5417651/
21. Conley, R., Aschersvanum, H., Zhu, B., Faries, D., & Kinon, B. (2007). The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophrenia Research, 90*(1-3), 186-197. doi:10.1016/j.schres.2006.09.027
22. Upthegrove, R., Birchwood, M., Ross, K., Brunett, K., Mccollum, R., & Jones, L. (2009). The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatrica Scandinavica, 122*(3), 211-218. doi:10.1111/j.1600-0447.2009.01506.x
23. Upthegrove, R., Marwaha, S., & Birchwood, M. (2016). Depression and Schizophrenia: Cause, Consequence or Trans-diagnostic Issue? *Schizophrenia Bulletin*. doi:10.1093/schbul/sbw097
24. Helfer, B., Samara, M. T., Huhn, M., Klupp, E., Leucht, C., Zhu, Y., . . . Leucht, S. (2016). Efficacy and Safety of Antidepressants Added to Antipsychotics for Schizophrenia: A Systematic Review and Meta-Analysis. *American Journal of Psychiatry, 173*(9), 876-886. doi:10.1176/appi.ajp.2016.15081035
25. Zhang, K., & Hashimoto, K. (2018). An update on ketamine and its two enantiomers as rapid-acting antidepressants. *Expert Review of Neurotherapeutics, 19*(1), 83-92. doi:10.1080/14737175.2019.1554434

A Review of the Psychotherapeutic Effects of Ayahuasca

Adam Bertroche, D.O.

Objective: This paper aims to outline the background, pharmacology, subjective effects, and tolerability of the South American hallucinogenic tea, ayahuasca.
Methods: Literature Review
Discussion: Ayahuasca is a South American hallucinogenic tea that has been used in shamanistic practices for centuries and has become popularized globally through use by Brazilian churches and has potential implications for the treatment of psychiatric conditions due to its serotonergic activity. It relies on monoamine oxidase inhibition to prevent degradation of its psychoactive ingredient, DMT, allowing it to be absorbed into the systemic circulation and act centrally. Subjective effects acutely include perceptual, cognitive, affective, and somatic changes and is generally well tolerated with mild increased in cardiovascular parameters, possible gastrointestinal symptoms such as vomiting, and rarely prolonged psychosis

Introduction

The Amazonian tea, ayahuasca, prepared from a combination of botanical ingredients, has been used in religious ceremonies and for medicinal treatment in South America for centuries. Its use has also spread to the United States and Europe through religious groups, including Santo Daime and the União do Vegetal [2]. It is prepared from the vine *Banisteriopsis caapi* in combination with other Amazonian plant species which contain psychoactive molecules, thus leading to its classification as a hallucinogen [5]. Generally, hallucinogens fall into three different structural groups; tryptamines (including psilocybin and DMT), lysergamides (including LSD), and phenethylamines (including mescaline) [3]. Ayahuasca exerts its hallucinogenic effects through monoamine oxidase inhibition (MAOI) properties caused by *B. caapi* in combination with effects derived from plants containing N, N-dimethyltryptamine (DMT).[1] *Psychotria viridis* and *Diplopterys cabrerana* (used in Ecuador and Columbia) are plant species commonly responsible for providing the hallucinogen, DMT, found in Ayahuasca [2]. Historically in the United States, the recreational use of hallucinogens was met with backlash, which led to stigmatization and legislative restrictions stifling research into other potential treatments [4]. However, the church, União do Vegetal, victoriously asserted at the Supreme Court of the United States that their religious use of ayahuasca is protected under the First Amendment's free exercise of religion clause. This ruling may open the door for potential research into other psychiatric uses of ayahuasca [4].

Hallucinogens such as DMT exert their effect through the serotonergic system, and as a result, have implications for the treatment of psychiatric disorders. Ayahuasca may offer an alternative effect on the serotonin system through an entirely separate neurotransmitter pathway, which may be beneficial to individuals afflicted by psychopathology who have not responded to conventional therapies [1,3]. There may be a potential benefit in the treatment of substance use, anxiety, and depressive disorders [1]. In a recent longitudinal and cross-sectional study on participants naïve to ayahuasca use, there was a significant reduction in participants meeting diagnostic criteria for psychiatric illness at both 1 and 6 months following ayahuasca use. They used a battery of questionnaires at baseline and found that 45% of participants in the study met the criteria for psychiatric illness prior to ayahuasca administration. Of the 45% that had met criteria, 61% no longer met criteria for psychiatric illness at follow-up, and 22.2% had a reduction in the number of current psychiatric conditions. The psychiatric conditions of the participants at baseline were primarily anxiety, substance use, and mood disorders [11]. In a separate study on six volunteers with varying severity of major depressive disorder, there was a statistically significant reduction in MADRS and HAM-D scores following ayahuasca use on

days 1, 7, and 21 after administration [12]. Panic-like symptoms and hopelessness were found to be reduced in a study of Santo Daime members after the acute ingestion of ayahuasca as well.[14] In another study of 12 subjects participating in 4 days of counseling in addition to two ayahuasca ceremonies, there was a statistically significant reduction in cocaine use in the participants following the intervention [13].

The increasing use of ayahuasca world-wide, as well as being a potential therapy for psychiatric pathology, warrants a further investigation into its pharmacology as well as effects on users. This paper will discuss the historical use of ayahuasca, the absorption of DMT, pharmacology, subjective effects, and tolerability of ayahuasca.

Background

Ayahuasca use is common in several South American countries, including Peru, Columbia, Brazil, and Ecuador. According to the book, "Sacred Vine of Spirits: Ayahuasca," the name ayahuasca is derived from the language, Quecha. "Huasca" meaning "vine" in Quecha and "aya," meaning "souls," "dead people," or "spirit." The ceremonial brew is believed to have up to 70 different names [2] including caapi, natema, mihi, and yage [7]. One of the botanical components is the vine of the plant, *Banisteriopsis caapi*, which has MAO-inhibitor properties. It is used in combination with a plant species containing N,N-dimethyltryptamine (DMT), commonly *Psychotria viridis*. However, other plant species containing DMT may be used, such as *Diplopterys cabrerana*, which is frequently found in brews in Ecuador and Columbia. There are complex variations of ayahuasca containing up to 90 different plants [2]. The brew is often used in shamanistic societies. Shamanism, which is any practice of healing and divination that involves the purposive induction of an altered state of consciousness according to "Sacred Vine of Spirits: Ayahuasca." In shamanistic ceremonies, fast-paced, rhythmic drumming is utilized to keep visions moving, which prevents stagnation on potentially terrifying images. Brazilian churches such as Santo Daime or União do Vegetal use priests or officiants (rather than shamans or healers) to administer ayahuasca as a sacrament in group worship and celebration. Generally, the ceremonies take place in dim light or darkness to be more conducive to visions derived from the experience. Guided tours to areas of South America involving Ayahuasca sessions performed by a shaman have increased as interest and awareness has grown. Ayahuasca administrators have made trips to the United States and Europe to perform ceremonies [7].

In addition to the previously mentioned Brazilian churches use of ayahuasca, other groups such as The North American Peyote church using peyote and the African bwiti cult using iboga also use "entheogens" in their rituals. The term "entheogen" has been used to describe substances such as LSD, DMT, mescaline, and psilocybin that promote an altered sense of consciousness for religious or spiritual reasons [7].

DMT Absorption

The effects of ayahuasca rely on the interplay between compounds derived from multiple plant species that allow for N,N-dimethyltryptamine (DMT) to be absorbed into the systemic circulation [3]. The vines from *B. caapi* are ground up and provide compounds such as harmine, harmaline, and tetrahydroharmine (THH). These are alkaloids with beta-carboline structure and have monoamine oxidase inhibitor properties, which prevent degradation of DMT in the gastrointestinal tract [2]. As mentioned previously, DMT is derived from other plant species such as *P. viridi* [5]. After degradation of DMT is prevented by beta-carbolines (harmine, harmaline, and THH), DMT is able to enter the systemic circulation. DMT is structurally similar to serotonin and is, therefore, able to bind to serotonin receptors centrally [2].

In a double-blind, placebo-controlled, crossover trial measuring ayahuasca's pharmacokinetic properties following consumption, blood levels of DMT, harmine, harmaline, and THH were obtained. Harmine levels were undetectable during the study, but its degradation product, harmol, was

present, suggesting that it is rapidly degraded after consumption. In this study, urinary metabolites from MAOI activity were also measured. With extensive MAOI activity, a reduction in metabolites of serotonin, norepinephrine, and dopamine would be expected, but this was not found in this study. The lack of a reduction in these metabolites suggest that the MAOI activity of ayahuasca is in the periphery, enough to prevent metabolism of DMT, but not enough activity to have significant effects on these other neurotransmitters centrally [2].

Pharmacology

Ayahuasca's subjective effects generally begin 30 minutes after its consumption,[1, 6] with peak effects occurring at ~1.5-2 hours[2] and ending 4-6 hours after ingestion[1, 6]. The peak effects from ayahuasca are similar to DMT's [1]. Maximum visual analog scale scores following consumption of ayahuasca were achieved around 1.5-2 hours in one study, with initial scores at 30 minutes and a significant increase at around 60 minutes. Return to baseline occurs within 6 hours [2]. This is compared to psilocybin which is active for 4-6 hours and LSD which can be active for 12 hours [3]. When the DMT levels are measured in plasma following the consumption of ayahuasca, they correlate with the subjective reports of its effects [2]. Measurable levels of harmaline and THH seem to peak after the psychedelic effects of ayahuasca have resolved [1]. Subjective effects from Ayahuasca seem to occur in the absence of measurable plasma levels of harmine after administration [2].

Mechanism of Action

Hallucinogens exert their effects primarily through agonism on the serotonergic receptor 5-HT2A. This hypothesis finds support in research demonstrating that partial agonists and antagonists at the 5-HT2A receptor block the effects of the hallucinogen psilocybin. Other serotonergic receptors are likely implicated in the psychedelic effects of hallucinogens as well. The agonist lisuride, having a high affinity for the 5-HT2A site, produces no hallucinogenic effect, while LSD being a comparatively weak partial agonist at the 5-HT2A site has significantly more hallucinogenic effects than lisuride, supporting the theory of other receptor sites contributing to the effects seen with psychedelic substances. Additionally, hallucinogens have potent effects at other serotonergic receptors, such as 5-HT2C and 5-HT1A. These receptors have been implicated in psychiatric disorders [3].

As mentioned previously, N, N-dimethyltryptamine (DMT) is present in the plant species *P. viridis* and other plant species found in ayahuasca brews. DMT is made available for absorption due to MAOI effects from compounds found in *B. caapi* that prevent the first-pass metabolism in the liver and GI tract. Similar to LSD and mescaline, DMT binds as an agonist at the 5-HT2A receptor in the central nervous system.[2] Its structural similarity to serotonin allows it to have an affinity for the 5-HT2A receptor, making it a possible therapeutic modality with potential benefits for the treatment of depression and anxiety disorders among other psychiatric conditions [1].

Subjective Effects

Ayahuasca has been found to produce perceptual, affective, cognitive, and somatic changes in users [6]. Perceptual changes from DMT include changes in visual imagery, such as visualizing geometric patterns, brighter or more intense colors, and auditory effects such as high-pitched noises or hyper-awareness of room sounds. Somaesthesia effects include sensations of hot and cold temperatures with alterations between the two. Some patients experience a detachment or dissociation from their body, described as a lack of awareness of their physical body. Changes in affect include anxiety at the start that evolves into a feeling of euphoria. Some users also note alterations in emotion from euphoria to anxiety to a sense of calm. Cognitive changes involve speeding up thought processes, having a new perspective on their life, or describing the experience of being in a dream-state. Alterations in volition are also noted with DMT use. Users of DMT note a loss of control and have a feeling of helplessness [8].

In a study of 12 volunteers receiving IV DMT at various doses, the Hallucinogen Rating Scale was used to measure the subjective effects of DMT with subscales to measure effects on somaesthesia, affect, volition, cognition, perception, and intensity. Subjective effects correlated with blood levels of DMT. At the lowest dose of 0.05 mg/kg of IV DMT, some physical effects were elicited but difficult to differentiate from placebo at times. At the 0.1 mg/kg dose, somaesthetic properties were predominant. Increasing to the 0.2 mg/kg dose and above, hallucinogenic effects became present, and all subjects reported visual perceptual disturbances such as brightly colored, shifting visual images. At the 0.4 mg/kg dose, subjects of the study were overwhelmed with the intensity and rapid onset of effects [8].

In a study of 6 volunteers that consumed freeze-dried ayahuasca tea, changes in perceptual, cognitive, affective, and somatic domains were found. Compared to IV DMT, ayahuasca's effects were of longer duration and less intense overall, which is thought to be due to the oral route of administration as opposed to IV DMT. A significant effect was found in all subscales of the Hallucinogen Rating Scale previously discussed, except for volition. Like IV DMT, lower doses of ayahuasca produced somatic effects rather than significant perceptual effects. The highest dose of ayahuasca resembles a moderate dose of IV DMT for all of the statistically significant subscales except for cognition. This indicates possible milder effects of ayahuasca when compared to IV DMT. Other scales were also used to measure subjective effects during ayahuasca use, such as the Visual Analog Scale and the Addiction Research Center Inventory. Significant increases were also found in all Visual Analog Scale items, which include "any effect," "good effects," "liking," "drunken," "stimulated," and "high" categories. Within the Addiction Research Center Inventory, the Amphetamine, LSD, and Morphine-Benzedrine groups were significantly elevated, which indicates a degree of activation, somatic-dysphoric effects, and euphoria or feeling of well-being, respectively [6].

Tolerability

Hallucinogens generally appear to be well tolerated [3]. Risks of hallucinogen use generally appear to be psychological rather than physiologic in nature, and without significant risk for organ damage or neurotoxicity. Classic hallucinogens increase heart rate and blood pressure, however, as well as a rare risk of prolonged psychosis or persistent perceptual disturbances following use [4].

Studies of effects from ayahuasca ingestion have suggested an increase in both blood pressure and heart rate as well [6]. In a study of subjective effects and tolerability of ayahuasca, systolic blood pressure and diastolic blood pressure trended upward without meeting statistical significance. The peak difference in systolic blood pressure between placebo and high dose ayahuasca (1mg DMT/kg) was 13.8 mmHg. The peak difference was 8.8 mmHg between placebo and low dose ayahuasca (0.5mg DMT/kg). There was a trend of an increase in diastolic blood pressure as well, with a peak difference of 10.4 mmHg between high dose and placebo. The peak difference was 8.6 mmHg between low dose and placebo. Heart rate was modestly affected as well, with an increase of 9.2 beats per minute between the high dose and placebo, and 6.2 bpm for low dose vs. placebo [6]. In a study conducted with 17 participants administered ayahuasca in two consecutive doses given 4 hours apart, tolerance in regard to increases in systolic blood pressure and heart rate following the second dose was noted. Overall, the second dose of ayahuasca was not tolerated as well due to gastrointestinal side effects, which correlated with increases in DMT plasma concentrations [5].

It was hypothesized that nausea associated with Ayahuasca was possibly due to beta-carbolines present in the tea, that would not be present with IV DMT [6]. Serotonin is present in the gastrointestinal tract, and the MAOI activity of these beta-carbolines may be responsible for the gastrointestinal symptoms following ingestion. Mestizo healers, despite being unaware of the specific pharmacologic properties of the plants, understood that the vine with harmine compound was responsible for the gastrointestinal symptoms. They even referred to the

reaction from these plants as "la purge." They adjusted the proportions of each plant in the brew according to the reaction they wanted. For example, they would increase the number of vines containing harmine in the brew if they wanted to purge toxins from their system [7].

The potential risk of a prolonged psychotic episode following acute hallucinogen use has been reported. However, these cases have considered being rare [4]. A 1960 study on LSD; a questionnaire was sent out to LSD and mescaline investigators to determine the subjective effects of these substances. It was found that the rate of prolonged psychosis (psychosis lasting >48 hours after use) was 0.8 per 1000 in experimental participants and 1.8 per 1000 in patients undergoing psychotherapy [10]. In a relatively recent systematic review of ayahuasca and DMT risk of psychotic episodes, it was found that prolonged psychosis is relatively rare across multiple settings. Cases of psychosis following DMT and ayahuasca use was often in subjects that had other factors possibly contributing to their psychosis, such as history of psychosis, family history of psychosis, or concurrent drug use. Therefore, it was suggested that the rare cases of psychosis following DMT or ayahuasca could be reduced by adequate screening of personal history of psychotic disorder, bipolar disorder, or substance use prior to administration [9].

Conclusion

Ayahuasca has been used historically for spiritual and religious reasons for centuries in South America [5]. Use of ayahuasca has become more common in the United States and Europe in part by the use of religious groups, including Santo Daime and Uniao do Vegetal as well [2]. Its effect on the serotonin system may make it a research candidate for the treatment of psychiatric conditions in the future [1,3]. Subjective effects and potential benefits rely on DMT that is provided by various plant species, and *B. caapi* that has monoamine oxidase inhibitor activity, which prevents degradation of DMT in the periphery leading to successful absorption [2,3]. Once consumed, the tea produces subjective effects including, perceptual, somatic, affective, and cognitive changes[6]. At lower doses, the effects of DMT are more somaesthetic and physical, and perceptual disturbances predominated at higher doses [6,8]. Compared to IV DMT, actions of ayahuasca are slower in onset, milder, and longer lasting Generally, hallucinogens appear to be fairly well tolerated. Ayahuasca, like other hallucinogens, has the potential to increase blood pressure and heart rate [6]. In addition to increases in these cardiovascular parameters, ayahuasca has the potential for unpleasant gastrointestinal symptoms believed to be from MAOI activity in the gastrointestinal tract [7]. In conclusion, ayahuasca is a psychoactive, South American tea with potential therapeutic benefit in psychiatric illness. It has acute somatic, affective, perceptual, cognitive, and volitional effects and is generally adequately tolerated with acute gastrointestinal side effects, modest increase in cardiovascular parameters, and rare complication of prolonged psychosis.

AUTHOR INFORMATION:

Send correspondence to Dr. Adam Bertroche (abertroche@kumc.edu)

Bertroche, A. (2020, March). A Review of the Psychotherapeutic Effects of Ayahuasca. *The Journal of Psychedelic Psychiatry*, *2*(1).

REFERENCES

1. Domínguez-Clavé, Elisabet, et al. "Ayahuasca: Pharmacology, Neuroscience and Therapeutic Potential." *Brain Research Bulletin*, vol. 126, 2016, pp. 89–101., doi:10.1016/j.brainresbull.2016.03.002.
2. Riba, Jordi, et al. "Human Pharmacology of Ayahuasca: Subjective and Cardiovascular Effects, Monoamine Metabolite Excretion, and Pharmacokinetics." *Journal of Pharmacology and Experimental Therapeutics*, vol. 306, no. 1, 2003, pp. 73–83., doi:10.1124/jpet.103.049882.
3. Baumeister, David, et al. "Classical Hallucinogens as Antidepressants? A Review of Pharmacodynamics and Putative Clinical Roles." *Therapeutic Advances in Psychopharmacology*, vol. 4, no. 4, 2014, pp. 156–169., doi:10.1177/2045125314527985.
4. Johnson, Mw, et al. "Human Hallucinogen Research: Guidelines for Safety." *Journal of Psychopharmacology*, vol. 22, no. 6, 2008, pp. 603–620., doi:10.1177/0269881108093587.
5. Santos, Rafael G. Dos, et al. "Pharmacology of Ayahuasca Administered in Two Repeated Doses."

Psychopharmacology, vol. 219, no. 4, 2011, pp. 1039–1053., doi:10.1007/s00213-011-2434-x.

6. Riba, Jordi, et al. "Subjective Effects and Tolerability of the South American Psychoactive Beverage Ayahuasca in Healthy Volunteers." *Psychopharmacology*, vol. 154, no. 1, 2001, pp. 85–95., doi:10.1007/s002130000606.
7. Metzner, Ralph. *Sacred Vine of Spirits: Ayahuasca*. Park Street Press, 2006.
8. Strassman, Rick J. "Dose-Response Study of N,N-Dimethyltryptamine in Humans." *Archives of General Psychiatry*, vol. 51, no. 2, 1994, p. 85., doi:10.1001/archpsyc.1994.03950020009001.
9. Santos, Rafael G. Dos, et al. "Ayahuasca, Dimethyltryptamine, and Psychosis: a Systematic Review of Human Studies." *Therapeutic Advances in Psychopharmacology*, vol. 7, no. 4, 2017, pp. 141–157., doi:10.1177/2045125316689030.
10. Cohen, Sidney. "Lysergic Acid Diethylamide." *The Journal of Nervous and Mental Disease*, vol. 130, no. 1, 1960, pp. 30–40., doi:10.1097/00005053-196001000-00005.
11. Jiménez-Garrido, Daniel F., et al. "Effects of Ayahuasca on Mental Health and Quality of Life in Naïve Users: A Longitudinal and Cross-Sectional Study Combination." *Scientific Reports*, vol. 10, no. 1, 2020, doi:10.1038/s41598-020-61169-x.
12. Osório, Flávia De L., et al. "Antidepressant Effects of a Single Dose of Ayahuasca in Patients with Recurrent Depression: a Preliminary Report."Revista Brasileira De Psiquiatria, vol. 37, no. 1, 2015, pp. 13–20., doi:10.1590/1516-4446-2014-1496.
13. Thomas, Gerald, et al. "Ayahuasca-Assisted Therapy for Addiction: Results from a Preliminary Observational Study in Canada." *Current Drug Abuse Reviews*, vol. 6, no. 1, 2013, pp. 30–42., doi:10.2174/15733998113099990003.
14. Santos, R.g., et al. "Effects of Ayahuasca on Psychometric Measures of Anxiety, Panic-like and Hopelessness in Santo Daime Members." *Journal of Ethnopharmacology*, vol. 112, no. 3, 2007, pp. 507–513., doi:10.1016/j.jep.2007.04.012

Business Information

The Journal of Psychedelic Psychiatry ISSN 2690-0912 is published quarterly. The views expressed in this journal are those of the authors and the editorial board that accepted them. This is an open access journal and no permission is required for the copying of isolated articles.

Contact:
journalofpsychedelicpsychiatry@gmail.com

Article Submissions:
https://www.journalofpsychedelicpsychiatry.org/contact-1