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Article

Ketamine: Catalyst for Paradigm Change in Mental Health

Scott Shannon, M.D. FAACAP

We see signs of a failing mental health care system everywhere we look. Depression is now endemic in the US. Rates of suicide have risen by about 30% in the last twenty years, despite the escalating use of anti-depressants [1] Less than half of patients respond to their first prescribed anti-depressant [2] and over time, treatment-resistant major depression affects 30 to 40% of those prescribed [3]. According to the CDC, deaths of despair—those caused by drugs, alcohol, and suicide—more than doubled from 1999 to 2017 [4]. Furthermore, it is no better for teens: 42% of high schoolers have recently reported feelings of sadness or hopelessness [5], and only half of suffering children find the care they need [6].

The COVID-19 pandemic has made things even worse. The rates of depression had already increased to over 20% prior to COVID [7], and new research from a 2021 Boston University study found that only 12 months into the pandemic, bed past 30% [8]. The pandemic accelerated a pernicious trend of overwhelm and compassion fatigue among nurses and physicians, with 40 to 60% now experiencing burnout and depression [9]. Caregivers have been particularly affected. As canaries in the coal mine for the mental health of our culture, teen visits to the emergency room for suspected suicide attempts escalated by 51% between 2019 and 2021 for girls [10]. These numbers carry jaw-dropping power.

This data points to an ineffective model of mental healthcare, and the pandemic dramatically exposed and worsened the pre-existing flaws of the already broken system. Despite the labors of caring, dedicated, and intelligent providers, we are not making progress. Clearly, we need a new model of care with new treatment options to tackle this growing crisis. Luckily, there are new options for care that may help address it—including ketamine. Ketamine offers both the potential to more effectively treat those suffering and a catalyst for a profound and much-needed shift in our paradigm of mental health care.

With ketamine as a tool, providers can focus on holistic patient care. The problem of the ineffective model of care does not lie with the providers but in fact, with the very foundations of the care they provide. Modern psychiatry is built upon the premise that the symptomatic brain is broken, chemically imbalanced, and the only hope for relief comes from medications to rebalance neurotransmitters. This chemical imbalance theory posits that the typical psychiatrist must deeply understand the nuances of the neurochemical environment of the human brain, the most complex system in the known universe. However, after a brief interview, the psychiatrist selects a pharmaceutical agent to improve the delicately nuanced neurotransmitter soup found within the central nervous system, thereby (or ideally) relieving suffering. Not only does a psychiatrist select this without any biological assessment of the brain or neurochemicals, but they are also making this selection without any psychiatric access to a solid understanding of how anti-depressants actually work. So, while this process is sometimes effective at muffling psychic distress and misery, more often than not, they are merely dulling the inner turmoil and simply enabling individuals to care less about it. As a result, their apathy might even extend past their suffering. Studies have found that individuals treated with anti-depressants often care less about everything else, including their spouse, other relationships, sexual passion, and more. Regardless of these

challenges, the vast majority of people are not cured by these agents [11].

Perhaps, then, building the edifice of modern psychiatry on an unclear, untestable model for treating those suffering is creating the real imbalance in our field. The use of psychiatric medications came on empirically without a proper foundation in science while simultaneously serving as a boon for the pharmaceutical industry. The first anti-psychotic (chlorpromazine) and first anti-depressant (iproniazid) were both discovered through serendipity [12] and soon after, in 1988, Prozac was introduced. Since then, the use of anti-depressant medications has steadily risen to almost 14% of the US population [13], reaching 24% in some demographics such as women over 60 [14]. This consistent increase in use provides pharmaceutical companies with $5.6 billion in US sales alone for these medications [15]. Still, the chemical imbalance of serotonin in depression has never been proven [16], and there is now considerably more evidence disproving its connection to depression [17]. This rebalancing of neurotransmitters stands at the very core of what modern psychiatry does, yet it is never presented as the evidenced-based foundation for how and why we practice. As the evidence for the serious limitations of the existing model grows, so too does the number of dissatisfied psychiatrists and suffering individuals, all in search of a new path. They all share a sense of impotence with our current options and an increasing impatience for something more effective.

Nevertheless, it is not all doom and gloom. The last decade has seen exciting developments in psychedelic medicine (PM). This renewed model of care utilizes a psychedelic framework to create a therapeutic container, encouraging a patient's inner exploration via a range of medicines that act as catalysts for altering consciousness and opening new doorways of awareness, insight, and experience. Medicines such as psilocybin or MDMA—and, of course, ketamine—are given to augment psychotherapy delivered with preparation, integration, and focused attention to set and setting (the container). They open new experiential territory in the psyche and function as catalysts for cognitive shifts—something we have not yet seen with psychopharmacology. We now have research that documents how psilocybin can alter an individual's metaphysical belief system and their existential world [18, 19], which has benefits like decreased fear of death [20] and durable relief of depression [21]. This spiritual belief system frees our motivation, establishes hope, and secures a sense of connection, or it can lock us into despair, isolation, and apathy. PM seems to open our spiritual perspective to inquiry and revision and it may be spiritual medicine.

The research supporting the enduring value of PM has come on forcefully in the last few years. The FDA has awarded three versions of PM Breakthrough Therapy Status [22, 23]. The published effect sizes of MDMA, for example, humble those found in the suppressive tools of conventional psychopharmacology by a factor of 2x to 3x in effect size [24]. While we wait for the definitive results from the large Phase III studies, expected in May of 2023 [25], a range of other neuroimaging and smaller clinical results support the promise found in this research. However, we cannot and should not make the same mistake we have made with medications like Prozac. Psychedelic medicine, while powerful and much needed, is not a complete mental health care system. Psychedelics are merely a tool, and their efficacy does not eliminate the need for a comprehensive system of care that educates, prevents, and offers other avenues for support.

We must acknowledge that a broad range of presenting complaints in mental health are not appropriate for PM. These include child psychiatry, adjustment issues, self-limiting concerns, family conflict, and all of the

presentations driven by epigenetic and lifestyle issues,. For example, we now appreciate that diet and nutrition play a significant role in the risk for depression, bipolar disorder and anxiety. We know that our inherited genes as expressed by single nucleotide polymorphisms (SNPs) are a factor in less than 30% of major mental illnesses. The balance of the risk is driven by environmental factors such as abuse history (adverse childhood experiences-ACEs), relational support and lifestyle choices that alter the expression of our genes by epigenetic modification. Lifestyle choices include diet, exercise and self-care. These appear to alter our genetic expression by methylation of the histones found on the genes. A focus on PM alone that misses the opportunity to address our risk factors is an incomplete system.

Quite simply, psychedelic medicine should not be mistaken for comprehensive mental health care, and any overly enthusiastic attempt to make it so will ultimately harm patients. Integrative medicine (also known as natural medicine or holistic medicine) can supply this broad foundation for psychedelic medicine, partly because it and PM share the same roots. Integrative medicine builds upon a foundation of body-mind-spirit unity, and both posit that all healing—and health itself—is built upon the innate ability of our being to move towards wholeness when barriers, such as excessive self-referential thinking, are removed. These models are built on the concept that each person we meet has the innate capacity to self-heal. This stands in stark contrast to the chemical imbalance model of conventional psychiatry that does not embrace the concept of healing, just medication maintenance. Integrative psychiatry and psychedelic medicine can represent a complete mental health care system.

This concept of body-mind-spirit unity brings us quickly to spiritual medicine. Spiritual medicine embodies a different perspective and requires a different type of caregiver relationship—one that's built more on personal journeys and emotional insight rather than one centered around enduring and impersonal neurotransmitter manipulation. PM validates this new perspective of wholeness by moving the seat of power from the therapist to the person immersed in the psychedelic experience. The therapist takes on the role of sitter, container, and facilitator. At the same time, the individual immersed in the close encounter with the depths of the psyche plays the role of expert and explorer. Thus, the classic polarity of wise expert and suffering patient or client so central to the psychotherapeutic paradigm becomes reorganized to reflect this new perspective about the primacy of the psyche and its innate spiritual wisdom.

Spiritual medicine is our most potent medicine, and is always personal: it is not scalable, cannot be commodified as a protocol, does not embrace a postmark, and always holds irreconcilable mystery. PM and its spiritual incisiveness carry the power of a surgeon's knife to the psyche not the blunt and often damaging instruments we have grown so frustrated with. It is no surprise that the excitement about psychedelic medicine is palpable. We see it in the professional interest in drastically oversubscribed training programs and the explosion of political action across the country. There is no mistake: our healthcare professionals, our society, and the boundless suffering populace cry out for a spiritual and grounded approach to care.

This shift from the status quo reveals that introducing a new paradigm—one that prescribes medication to speed psychotherapy, not fuel apathy—can deepen our potential to heal and help repair the rift between therapists and prescribers. MDMA and psilocybin have been the main actors, but it is time to introduce a new character: ketamine. Ketamine offers a portal to effective mental health care that engages our spiritual self, lubricates psychotherapy, and relieves depression.

Ketamine is fueling this profound shift in the paradigm of mental health care. It supports the industry in moving away from a suppressive model of care that fears the psyche to an evocative model that honors the psyche.

Ketamine plays this pivotal role in this transition from the old models of mental health (daily mediated suppression of the psyche and the therapist as an external expert) to a new evocative model in a few different ways. First, ketamine typically works better for severe depression than conventional medications. Dr. C. Andrade, a well-known psychiatric researcher, described it in a 2017 review article, "the marked acute antidepressant efficacy of ketamine, even in medication-refractory patients, now seems beyond doubt" [26]. This potency has gathered the attention of modern conventional psychiatry and pharmaceutical companies, as witnessed with the release of Spravato (found as one-half of generic ketamine) by Janssen in 2019 [27]. Second, ketamine works when given in an episodic manner and does not require daily doses to suppress symptoms [28]. Third, ketamine is an agent that decreases the activity of the default mode network just as classic psychedelics do [29]. So, it can trigger profound psychedelic-like insights that can alter someone's life trajectory with just a single dose. Finally, many are finding that ketamine, like MDMA or other classic psychedelics, can enhance psychotherapy by accelerating and deepening the process.

These facets become quite apparent when you work with ketamine in a clinical setting, as they foster exploration and allow the practitioner to go beyond an infusion routine. As more and more practitioners are drawn to ketamine by one of these angles, more and more begin to embrace the paradigm of PM. It is a slippery ride on an effective slope. Many professionals were drawn to mental health by the promise of working with the human mind, and, finally, after years of ineffective medicines and faulty systems, there is a tool that opens up this realm for exploration: ketamine.

Ketamine can create psychedelic effects while simultaneously being an accepted part of the conventional toolbox, ultimately bridging the old and new models of care. Ketamine is a gentle, safe, and more accessible entry point for explorations of the psyche, providing flexibility and provider confidence. Whether you are a novice psychonaut (explorer of the psyche), an unseasoned practitioner, or a veteran of many decades working in the trenches, ketamine might help all practitioners understand what is available to them and become comfortable in this realm prior to full legalization of psychedelics.

To begin with, let us explore the items that reflect ketamine's ease, comfort, and safety:

Ketamine reduces anxiety. It quiets that part of our central nervous system that worries and frets. Many classical psychedelic medicines can have a significant element of anxiety as part of the journey (found in 20% of participants in one LSD study [30]. If you are new to psychedelics, this tension can be intimidating and overwhelming. Research indicates that ketamine is euphoric and mood-boosting for most people [31]. Unpleasant or frightening trips are possible but much less likely than with psilocybin or LSD as ketamine is well tolerated in a range of ages and indications [32-36].

Ketamine opens the floodgates slowly. Both ketamine and the classical psychedelics decrease the activity of the default mode network [29], which may be our closest brain equivalent to the ego [37]. The classical psychedelics can and will release a tsunami of unconscious material that can be very powerful (and overwhelming)

when these self-created filters are decreased. Ketamine does decrease the filter of the self. However, it simultaneously decreases the power of cortical functioning [38] and thus reduces the unpredictable wave of the unconscious material brought to awareness. Traumatic experiences may be accessed, but the weight of the new insights is typically more limited. Ketamine can work as a gentler introduction to these inner experiences.

It is brief. The half-life of ketamine is short, about 45 minutes [39]. This means that the entire experience lasts less than one hour. Good or bad, the journey is short and manageable. The total time from check-in at the office to walking out the front door is typically about two to three hours. People clear from the effects of ketamine fully in a few hours, and the practitioner can treat multiple people in a workday.

It is safe. Over the last 50 years or so, ketamine has become a well-known and well-utilized medication in operating rooms, emergency departments, and pain centers. The track record is one of safety and predictability at the doses being employed in psychiatry (0.5 to 1.5 mg/kg) [33-36]. A few years ago, at a Kriya conference Steve Levine, then of the Ketamine Treatment Centers, noted that they had delivered over 10,000 psychiatric doses of ketamine without one serious adverse event [40]. With modest caution, ketamine has proven to be a safe medication for psychiatric applications.

It is pharmacologically clean. Unlike MDMA and the classic psychedelics, ketamine has little in the way of contraindications with psychiatric medications. The Phase II and Phase III protocols for MDMA, psilocybin, and LSD include a contraindication for concurrent dosing with most psychiatric medications, especially antidepressants. This means most psychiatric patients must endure a medication taper and washout period that can take weeks to months. This is not trivial. Many patients have been on these medications for years, if not decades. After years of medication management, the body's ability to find neurotransmitter balance begins to weaken and fail. This is the primary unspoken liability of psychiatric prescribing, but ketamine does not challenge levels of the monoamines commonly targeted with psychiatric medications (dopamine, serotonin, and norepinephrine). As such, it does not require a taper of psychiatric medications or a washout. Plainly put: ketamine is more straightforward for the patient and the psychiatrist.

It is cheap. While it may be crass to talk about cost, it is a genuine concern. Over half of Americans limit health care simply due to the cost [41]. As deductibles and co-pays grow, so does treatment avoidance. The cost of ketamine is not a limitation. The cost of the medicine needed for a typical intramuscular injection is less than $5. The vast majority of the price for ketamine-assisted work lies in the cost of the provider's time. Group therapy and trainee involvement offer some potential solutions to this challenge. In a very real way, ketamine frees us from the exorbitant business model of pharmaceutical companies.

Ketamine can also create powerful and psychedelic-like effects, aiding the caregiver in supporting healing. Like classic psychedelics, it diminishes the effects of the default mode network. It also dramatically enhances neuroplasticity [42]. This shift may explain some of the power of ketamine to lift mood, alter insight and enhance motivation; this is a big part of the inherent attractiveness of ketamine. Overall, it possesses a number of other observable effects that make it attractive to providers working in this space:

> ***Ketamine is powerful.*** Never mind that ketamine is not a true psychedelic. This experience may be one of the most profound alterations of consciousness that anyone will ever experience with any agent. As a dissociative agent, ketamine disconnects most of our cortical awareness and creates an experience that will astound patients. Patients and practitioners should not underestimate the power of this experience. This dramatic and abrupt departure from our normal state of consciousness often triggers curiosity and profound respect.
>
> ***Ketamine alters our thinking***. Ketamine modifies the default mode network, disrupts slower thalamocortical relays, and significantly enhances neuroplasticity [29, 43, 42]. It offers a new way of thinking, particularly about one's life and the big picture of our existence. A different vantage point offers a new perspective. People come away with a refreshed look at their life journey and options for change. After a ketamine experience, the brain is more open to change. This enhanced plasticity lasts most acutely for 24 plus hours [43], but with proper integration, the changes could last a lifetime.
>
> ***Ketamine has a clear and varied dose-response curve.*** Individuals can dial in the intensity of experience they would like to have- low dose: verbal, yet quite altered (somewhat like peyote); moderate dose: some verbal capacity, but without most of the personal narrative (more like psilocybin); high dose: non-verbal and disconnected from our body and earthly plane (similar to 5-MeO-DMT). This dose-response curve reflects how our consciousness functions. Different doses open up unique elements of consciousness and thus unique pathways for healing awareness. We must learn this terrain well and enhance our ability to direct specific mental health and psychotherapeutic challenges in a specific direction. We have yet to map this needed but uncharted territory. Ketamine offers guidance on this needed task.

Ketamine offers therapists a pathway to process trauma and can also be applied to the therapeutic encounter in a number of other ways as well. The dissociative mechanism inherent with ketamine reduces the intensity of all emotions, including fear and anxiety, making it a valuable tool for psychotherapy. It helps to limit the excessive emotional pain linked to trauma and interpersonal conflict. Once partially dissociated, someone with a trauma history can access distressing emotions without disorganizing terror or panic. MDMA does this as well, but it maintains complete cognitive clarity. Given this difference, MDMA is a superior tool for processing trauma, but it is not yet available for therapists legally.

Ketamine enhances immediate psychotherapy. The options for ketamine-assisted psychotherapy are twofold: immediate and delayed: The immediate psychotherapeutic benefits are part of the low-dose lozenge method in which the practitioner sits with someone under the influence of low-dose sublingual lozenges (most common) or a slowed IV drip or subcutaneous injection (less common). Low-dose lozenges provide a twilight experience that enhances access to painful material and speeds psychotherapy (called the psycholytic model) [44]. We tolerate the difficult insights better and can process our wounding at a much deeper level. Ego controls are reduced but not gone. This catalyzes psychotherapeutic exploration. Ketamine is an anesthetic agent, but when used in this manner, it opens our access to trauma and repressed pain. Some direct processing is possible after the traveler emerges from a deeper (psychedelic) IV or IM session. The challenge here is that, especially with the IM injection, this time frame between first engagement and full sobriety can be quite brief. However, it allows for some existential processing and anchoring of the major experiential qualities. Immediate psychotherapy can take many forms, and therapists will find that ketamine offers manifold options to guide another toward healing.

Ketamine enhances delayed psychotherapy. The alterations found with dissociation in these brain regions and in these specific brain locations (default mode network, amygdala, and hippocampus) [29, 45, 46], while maximal for the hour's journey, linger for beyond 24 hours. This offers a practical window for enhancing conventional psychotherapy. Our experience indicates that the results are enhanced and synergistic if conventional psychotherapy occurs within 36 hours of the dosing. Psychotherapists unfamiliar with Ketamine Assisted Psychotherapy (KAP) will comment that the gains made in one of these penumbral sessions will often surpass all of the conventional therapy done in the prior months or even years in terms of cognitive flexibility and insight gained. Delayed psychotherapy can simply look like effectively catalyzed conventional care.

Ketamine enhances group psychotherapy. While inherently powerful, group psychotherapy can be challenging to orchestrate well. Participants may come from a wide range of perspectives and vary in comfort with the process. Ketamine facilitates a profound experience that supports a more consistent shared foundation for group exploration. It also reduces the anxiety that may block open sharing and genuine honesty. Providing a normative experience of processing with peers also reduces stigma and shame. The powerful psychedelic experience drives a deeply enhanced sense of connection and bonding that often takes months of regular group sessions to nurture. Ketamine often provides a quality of heart-opening and unconditional positive regard. While this is not as consistent or deep as that found with MDMA, ketamine can foster a sense of group caring and comradery that feels priceless. In toto, ketamine can unleash the power of group work and facilitate gains that may exceed those found in individual work, as humans often feel a sense of

safety in numbers. Group work may be the future of PM.

Ketamine enhances psychotherapeutic training. Ketamine provides psychotherapists an invaluable tool for learning the basics of psychedelic-assisted psychotherapy. Given these dosing and delivery options, a vast range of journey experiences can be arranged for the apprenticing therapist to witness and support. The short time frame of a ketamine journey makes it more practical for psychotherapeutic training. Ketamine is more predictable than the classic psychedelics. This makes it an ideal tool to deliver safe and effective training experiences that do not overwhelm the student seeking to learn from another's powerful inner experience. The fact that these powerful inner and outer experiences can be linked in time also builds empathy and therapeutic wisdom. For therapists in training for work in PM, it is very important to have a personal experience of a powerful state of non-ordinary consciousness. Ketamine provides this and more in a safe and manageable manner. It will allow the emerging profession to train the providers needed to usher in this new paradigm.

Ketamine can also enhance the study of consciousness, perhaps opening opportunities to recalibrate the mental health field in other ways. For those deeply interested in the power of psychedelics to alter and improve our mental health, ketamine offers some very advanced capabilities that deserve consideration. The dissociative mechanisms of ketamine bring some unique characteristics not shared by classic psychedelics. Much of our cortical self-referential loops are taken offline by the interruptions of these relays [47-50]. This, in turn, creates a much different experience of consciousness. These relays are also progressively altered by the dose of ketamine involved. Classic psychedelics leave these relays less impacted, but instead they create massive shifts in the default mode network with more specificity [51, 52]. Ketamine drives a less specific and more generic separation of awareness from the cortex (and thus the body) [53]. This dose-dependent effect provides psychedelic explorers with useful options for experience and training.

Ketamine offers a sense of pure consciousness. This journey introduces the inner traveler to a non-cognitive open field of awareness that is unique and awe-inspiring. In other words, ketamine decreases our thinking brain enough for us to realize that our awareness exists even without thought. This profound experience often takes years of meditation practice to encounter reliably. This experience of being freed from the limits of severe anxiety or depression can help a client to find hope, let go of outmoded perspectives and open up to more significant change and flexibility. More than that, ketamine often catalyzes profound spiritual insights that alter our worldview.

Gamma power relates to the nature of consciousness. Electroencephalographic (EEG) research documents that gamma wave (30-80 cycles per second) power may be one of the best measures of human consciousness [54-57]. For example, it is dramatically reduced or eliminated by conventional anesthetic agents [58]. Richard Davidson's work at UW with Tibetan monks showed that gamma power is increased by meditative practice in a dose-dependent manner: a monk with

30,000 hours of practice on the mat demonstrates more gamma power than one with 10,000 hours [59]. Very few agents have been documented to increase gamma power. Ketamine is one of them [60, 61]. Interestingly, ketamine increases gamma power through the typical psychiatric dose range of 0.5 to 1.2 mg/kg and then begins to deteriorate, coincident with the loss of recall and awareness in the ketamine session [62, 63]. Gamma power and ketamine may prove to be a portal to a complete understanding of the neural correlates of consciousness.

Dissociation is different. While many will say that ketamine is not a classic psychedelic medicine and thus should play no role in the training of professionals, the opposite is true: a fully dissociated experience is unique and not approximated by classic psychedelics. Ketamine provides a unique experience that teaches us about the underlying nature of consciousness. Psychedelics provide profound disruption of our cortical functions, while ketamine disconnects us from these limitations. Both are useful. There is no priority in these two different road maps. It is merely terrain to be explored and appreciated. Likewise, they also have unique strengths for working with a stuck psyche.

Ketamine can mimic the near-death experience. Near-death experiences (NDE) have been studied for decades. We now know that these close encounters with death provide some individuals with an amazing refresh of their worldview and a spiritual perspective that creates a durable shift in the survivor's perspective on life. This shift results in a movement towards more openness, enhanced love for others, and greater personal optimism, among other positives [64]. In contrast, a small percentage (10 to 20%) of revived people share this specific experience, the essence of it is remarkably consistent and powerful [65]. Recently published research compared the central themes of 15,000 psychedelic journey narratives with 625 NDE reports [66]. The researchers found that the ketamine experience most consistently aligned with the NDE journey compared to other psychedelic agents. Unfortunately, a significant percentage of those facing an NDE do indeed perish. The same is not true of ketamine. As mentioned, ketamine is quite safe, and the death of the physical body is unheard of when employing psychiatric doses. However, the death of the ego and self can be quite common. This may be part of the enormous transformation possible with a ketamine experience. Ironically, death of the ego may be life-giving.

Ketamine, and the larger PM system, are not without challenges. Like most psychoactive tools, it can build dependence and elicit addictive behavior [67]. Frontal lobe disconnection syndrome [68] and erosive cystitis [69] can occur in populations with excessive daily use, even if prescribed. The pandemic forced the federal government in the US to relax restrictions on remote prescribing, allowing for more prescriptions with less oversight. This has unleashed a wave of dangerous profiteering that seems to be an unfortunate echo of the oxycontin disaster that is still unfolding in our society [70]. Daily (and often escalating) use of controlled substances such as ketamine is not part of the psychedelic framework. The psychedelic framework is built upon episodic

transformative excursions into the psyche, not the numbing and avoidance that can be found with the daily use of ketamine. This destructive use of ketamine might ultimately, and counterintuitively, keep us stuck in the old model of managing misery rather than respecting the transformative power of the psyche. If ketamine use is punitively restricted or diminished due to these missteps, it will darken our promising path to a new paradigm in mental health.

What is more, access to this kind of PM treatment is paramount. Since many psychedelic medicines are currently illegal, they are out of reach for many individuals and practitioners. For most practitioners, this legal barrier stands even more foreboding given the career and financial cornerstone their licensure represents. While the barrier on psychedelics does appear to be softening in some places—Oregon and Colorado have now legalized a regulatory pathway for treatment with psilocybin [71]—the emerging paradigm may take a decade or more to reach most patients and caregivers. Nevertheless, Ketamine is legal. Furthermore, ketamine can be a gateway medicine to the new paradigm by opening up both therapeutic access and clinical training.

Years from now, we will likely have MDMA, psilocybin, and many other legal options to provide the much-needed care in the new paradigm of psychedelic medicine. Unfortunately, these agents are years away from approval and ready access. Given the massive load of suffering that we all face, we must speed up the transition to psychedelic medicine and medication-assisted psychotherapy. Ketamine can help us achieve that goal immediately.

Ketamine is a non-specific agent that supports many different functions, all of which can lead to better health and root-cause healing. It can be a chameleon that is cognitively loosening or psychedelically inspiring, predominantly verbal or non-verbal, and it can even simulate a near-death experience. Ketamine can treat severe treatment-resistant depression, provide deep access to consciousness, facilitate psychotherapy, and train psychedelic psychotherapists. Ketamine can also be a path for enhanced self-care and prevention. Dissociation is a powerful tool for therapeutically manipulating consciousness that can be applied in many ways. Ketamine offers a comprehensive and unique range of possible clinical interventions, which we are just beginning to comprehend.

Our society is experiencing pain and distress on epic levels. The mental health care crisis we are currently experiencing is all the more damning as providers and patients alike have lost confidence in conventional tools. Finally, after decades of working at odds with each other, psychotherapy and medication can start to work together towards the same laudable goal: accessing and aiding the psyche. With new, powerful tools at our disposal, like ketamine, we are now moving into a paradigm of care that genuinely respects consciousness and the inner realms of the psyche. This, too, helps mental health professionals in not only embracing the coming psychedelic paradigm but in rejuvenating their passion for caregiving. Ketamine, accessible now, allows us to explore and honor the psyche, not fear it. Ketamine is a much-needed catalyst to open the psyche, transform mental health care, and address this crisis directly.

AUTHOR INFORMATION

Scott Shannon M.D. FAACAP
(scott.shannon@wholeness.com)

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Original Research

Psilocybin Treatment Plan for Major Depressive Disorder: Microdosing vs. Macrodosing

Kevin Enabulele, M.D.

Abstract

Introduction: Psilocybin will soon be an option for treating unipolar depression. Prior to prescribing psilocybin, psychiatrists will need to develop their own treatment plans. This article serves as a guide for those devising their own treatment plan and provides helpful information for psychiatrists to do so, as well as a suggested treatment plan. Currently, no study clearly shows psilocybin outperforming antidepressant medications, but the results are comparable. Evidence supports macrodosing and microdosing, but no studies have compared the efficacy of the two. Microdosing is a popular trend in the populace, prompting some research on the topic. In theory, microdosing would require less time and personnel if it was equally effective as macrodosing. **Methods**: The literature was searched using keywords in the following databases: PubMed, Google Scholar, and connected papers. **Results**: Contrary to the initial hypothesis, there is enough theoretical evidence to advise against microdosing for a long period of time based on permanent changes to brain physiology in rats and 5-HT2B mediated cardiovascular risk. Although many patients microdose for depression, this article advises microdosing only for the purpose of neuropathic pain relief, migraines, and cluster headaches. **Conclusion**: An outline of a potential treatment plan using psilocybin macrodoses involves the following steps: Determine the patient is a candidate, devise a psychotherapy plan, devise a tapering schedule, determine an adequate dose, assess if a second dose is necessary, and maintain patient follow up.

INTRODUCTION

With the recent rescheduling of psilocybin and MDMA (methylenedioxy-methamphetamine) in Australia for the treatment of Unipolar Depression and PTSD (post-traumatic stress disorder), respectively, clinicians planning to prescribe these medications will need to develop their own treatment algorithms prior to obtaining certification. There are currently no widely established guidelines for these therapies. It is imperative that we begin composing standardized treatment plans for the safe use of these substances. This article will focus on compiling information that will be helpful for psychiatrists composing their own treatment plans using psilocybin to treat depression.

In a study comparing psilocybin to escitalopram, a selective serotonin reuptake inhibitor (SSRI), the primary outcomes did not differ significantly, but the results were comparable [1]. Psilocybin has also proven to be an effective treatment for anxiety in end-stage cancer patients [2]. There is enough evidence in research, historical use, and anecdotally to warrant further research [3]. This article will only examine the effectiveness of psilocybin as a therapy in the context of comparing macrodosing and microdosing. More large-scale studies comparing psilocybin to SSRIs are needed before recommendations can be made about which is more effective; current evidence suggests that psilocybin has proven to be competitive.

Templates for treatment algorithms are available in research studies that have used macrodoses but none examine microdosing. One study that surveyed 8703 individuals via a mobile app found that among individuals

reporting mental health concerns, microdosers exhibited lower levels of depression, anxiety, and stress across gender [4]. More research needs to be done comparing both treatment options as macrodosing is time and personnel intensive and requires more infrastructure than microdosing. In addition, some patients may be averse to macrodose therapies due to fear of the experience or difficulties with access. Thus, if a microdosing regimen can achieve similar results to a macrodose, more patients can be treated with fewer resources. Given that there are no articles that expand on psilocybin's use in the clinical literature, this article will attempt to do so by providing helpful information to develop a treatment plan for depression using psilocybin.

METHODS

Using resources within UMass Chan Medical School's Lamar Soutter Library, search strings were developed consisting of keywords and the boolean command "AND" to search titles and/or abstracts using PubMed, Google Scholar, and Connected Papers databases. Keywords included depressive disorder, microdosing, psilocybin, dosing, tapering, SSRI (selective serotonin reuptake inhibitor), SNRI (selective serotonin and norepinephrine reuptake inhibitor), MAOI (monoamine oxidase inhibitor), TCAs (tricyclic antidepressant), lithium, bupropion, serotonin syndrome, mania, psychosis, set and setting, personality, and hallucinogenic persisting perception disorder. Studies included involved administration of psilocybin to human participants, randomized controlled trials, population-based epidemiologic studies, self-reported surveys, case studies, and literature reviews. One animal study was cited in the section "Chronicity of Microdosing" because there were no human studies involving chronic (daily use or every other day use for several months) microdose administration.

CONSIDERATIONS WHEN DOSING

This section will expand on several items to consider when deciding what dose to treat a patient with. These items include the actual dose, how often to dose (chronicity), the absorptive personality type, other antidepressant medications, and potential safety concerns.

Chronicity of Microdosing

Due to the fact that there are no published studies examining chronic microdosing of psilocybin, there is no widely accepted definition of how to microdose. The closest approximation was a survey (primarily from Reddit) of a population of 909 individuals reported using psilocybin (n=235, Mdose= 0.3 g of dried psilocybin mushrooms) on a one-day-on, two-days-off schedule [8]. Unfortunately, this study did not answer the question of how long one should maintain this schedule of one-day-on, two-days-off. Respondents were not a differentiated population and were not necessarily diagnosed with depression. The optimal schedule for a microdoser trying to enhance their performance at work may be different from a patient trying to alleviate depressive symptoms. Regardless, a question that remains to be answered in the form of a clinical trial is how long or how often one needs to microdose to alleviate depressive symptoms and whether or not this is a safe practice.

Regarding its safety for chronic use, psilocybin binds to the 5-HT2B receptor, which is located in endovascular cells and cardiac myocytes. Its activation promotes thickening and hardening of these cells and heart valves. Chronic use of serotonergic agents, in theory, has the potential to increase cardiovascular disease risk [9-12]. This is also supported by acute increases in blood pressure while using classical psychedelics [12]. Given this data, a

schedule that is too long could have negative cardiovascular effects; however, the literature on psychedelics and cardiovascular disease is conflicting.

What is a Macrodose? What is a Microdose? Dosing Recommendations

Route of Administration	Recreational Dose	Intoxication Threshold	Subthreshold
Psilocybe cubensis dried mushroom: PO	3–5g	0.5–1.5g	0.1–0.5g
Psilocybin synthetic: PO	17–30 mg	3–8mg	0.8–5mg
Psilocybin synthetic: IV	2mg/70kg	1mg	0.5mg

Figure 1. Dosing of Psilocybin [5]

Some studies evaluating lifetime users show decreased rates of obesity and hypertension [13, 14]. This effect has been attributed to secondary improvements in mental health disorders. There is also data suggesting anti-inflammatory and immunomodulatory effects of classical psychedelics (Lysergic Acid Diethylamide(LSD), Psilocybin, Mescaline, and N,N-Dimethyltryptamine (DMT)) [12]. To understand the effect of chronic microdosing, a controlled study would need to be done evaluating valvular disease and other negative cardiovascular outcomes.

The closest approximation of chronic psilocybin administration is a study in which rats were given LSD at .16mcg/kg/day every other day for 3-months. Permanent changes in neurochemistry and behavior were observed 24hrs, 2 weeks, and 4 weeks after the 3-month period. Subjects had increased locomotor activity (alleviated with Haldol and Olanzapine). At 1-month, rats had altered social behavior, with reduced sniffing, grooming, and following. They also showed markedly enhanced aggressive behavior (boxing, kicking, wrestling) and exploratory behaviors (sniffing, rearing, hole poking). They found more RNA for dopamine D1 and D2 receptors, brain-derived neurotrophic factor (BDNF), receptor tyrosine-protein kinase erbB-4 (ERBB4), and various NMDA and GABA receptor subunits [15]. This suggests that chronic microdosing is not a safe practice as it increases the risk for schizophrenic changes in this animal model.

Given the increase in dopamine receptors, neurobehavioral changes after 3-months of LSD administration in rats, and 5-HT2b mediated cardiovascular risk, minimizing the length of a microdosing schedule would be wise. This is especially true in those with a family history of schizophrenia. Unfortunately, not many studies evaluate the safety and efficacy of various microdosing regimens.

Although microdosing may not have a role in treating depression, it may be useful in treating chronic neuropathic pain. In a case study examining three individuals with chronic nerve pain, all found relief by microdosing psilocybin. One patient with quadriplegia achieved 90-95% pain relief for 6-8 hours via daily 250mg of ground mushrooms daily and has been doing so for 6-months. A second patient with complex regional pain syndrome achieved 80% pain relief for 3-4 hours via 500mg of ground mushroom. A third patient with degenerative disk disease and lumbar radiculopathy achieved nearly complete pain relief for 2-4 weeks via 1000mg mushroom chocolate bar in combination with physical therapy [16]. Of note, these patients were self-selected, their reports could not be validated as they were outside of

the research facility's health network, and the effect of a placebo could not be determined.

CHRONICITY OF MACRODOSING

Most studies have used 1-2 large doses, supplemented with psychotherapy before and after sessions. The timing of macrodoses is less debated than microdosing. One study of 59 subjects evaluated psilocybin in comparison to escitalopram. They used two separate doses of 25 mg of psilocybin 3 weeks apart[7]. Patients received psychological support prior to and between sessions. There appeared to be a dose-dependent effect of psilocybin dose and reduction in depression scores. There was also evidence for the effectiveness of a single dose of psilocybin in combination with psychotherapy [17]. One study claimed that two doses of psilocybin was superior, although a benefit was still seen with a single dose [18]. There was a dose-dependent reduction in symptoms, with the greatest reduction at .8mg/kg, with most studies having a treatment interval of 1 week. In summary, two doses may not be necessary if the quality of the first session is satisfactory and the probability of a successful session increases with the dose, adequate and informed preparation, and a quality setting.

Absorptive Personality

Psychedelic substances are unique because personality type plays a role in the individual's response to the substance. Of note is the personality trait of absorption, defined as the predisposition to get deeply immersed in sensory (e.g., smells, sounds, images, memories) or mystical experiences. People with this personality trait are prone to experiencing overall consciousness alteration, dissociation, mystical-type experiences, and visual effects induced by psilocybin [6]. This personality trait is important to assess prior to the administration of large doses as the subjective experience is of greater magnitude. The Tellegen Absorption Scale (TAS) may be helpful when assessing this personality trait [7]. This trait can briefly be assessed by assessing a patient on a 5-point scale (1-never/2-rarely/3-sometimes/4-most of the time/5-all the time) using the following characteristics of an absorptive personality.

Absorptive Characteristic	Sample Screening Sentence
Responsiveness to Stimuli	I can be deeply moved by a sunset.
Synesthesia	Some music reminds me of pictures or changing colors.
Enhanced Cognition	I can often sense the presence of another person before I see or hear them.
Dissociative Involvement	While watching a film I may become so involved that I forget about my surroundings and experience the film as if I was in it.
Vivid Reminiscence	Sometimes I feel and experience things as I did when I was a child.
Enhanced Awareness	Things that seem meaningless to others often make sense to me.

Figure 2. Sample sentences to screen for an absorptive personality

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ANTIDEPRESSANT MEDICATIONS AND PSILOCYBIN

Most medications have unfavorable interactions with psilocybin. Bupropion (Wellbutrin) does not require discontinuation, but all other psychiatric medications will likely need to be tapered prior to psilocybin administration. Due to the fact that chronic use of SSRIs and SNRIs blunt the effects of classical psychedelics via downregulation of 5HT2AR (SSRIs/SNRIs) [19], patients currently taking an SSRI or SNRI will need to refrain from using such medications for at least five half-

lives before psilocybin sessions. MAO (monoamine oxidase) is the enzyme responsible for breaking down psilocin (active molecule). MAOIs should be discontinued to avoid excessive intoxication. Mirtazapine also blunts the effects of psilocybin due to 5HT2AR blockade and will also need to be discontinued. Chronic administration of tricyclic antidepressants, lithium, acute administration of serotonin reuptake inhibitors, and use of haloperidol has been shown to potentiate hallucinogen effects [20]. One study conducted an online survey and found that 47% of 62 cases in which lithium was combined with a psychedelic resulted in a seizure. None of the subjects using lamotrigine experienced seizures [21]. Patients taking the supplements 5-Hydroxytryptophan and St. John's Wart are at risk of serotonin intoxication and should discontinue use prior to psilocybin administration.

When tapering off antidepressants, it is important to be aware of withdrawal symptoms, which are a sign that the tapering schedule needs to be delayed. The acronym FINISH may be helpful: flu-like symptoms/ insomnia/ nausea/ imbalance/ sensory disturbances/ hyperarousal [22]. When tapering off antidepressants, it is important to maintain communication with patients and encourage psychotherapy, physical activity, a healthy diet, and consistent sleep schedules. Figure 2 showcases a time frame for the tapering process, but a 2-week schedule should be employed for the safest results. Fluoxetine will need a schedule on the order of two months as it has a long half-life. Lastly, it is important to note that drugs with shorter half-lives have a higher incidence and severity of withdrawal symptoms [23].

Drug	Half Life	99% out of body
Paroxetine (Paxil)	24 hours	4.4 days
Sertraline (Zoloft)	26 hours	5.4 days
Escitalopram (Lexapro)	27 -32 hours	6.1 days
Citalopram (Celexa)	36 hours	7.3 days
Fluoxetine (Prozac)	4-6 days	25 days
Venlafaxine (Effexor)	5 hours	1 day
Duloxetine (Cymbalta)	12 hours	2.5 days
Desvenlafaxine (Pristiq)	12 hours	2.5 days
Tranylcypromine	2 hours	14 hours
Phenelzine	12 hours	3.5 days
Isocarboxazid	36 hours	10.5 days
Amitriptyline	9 - 25 hours	7.3 days
Lofepramine	12 -24 hours	7 days
Clomipramine	12 -36 hours	10.5 days
Imipramine	9 hours	2.6 days
Trimipramine	23 hours	6.7 days
Doxepin	33 - 80 hours (1.5 - 3.3 days)	23 days
Nortriptyline	36 hours	10.5 days
Dosulepin	50 hours (just over 2 days)	14.6 days

Figure 3. Half-Life for common SSRIs, SNRIs, MAOIs, and TCAs.

SAFETY PROFILE OF PSILOCYBIN

As with any drug used in medicine, side effects, and safety concerns must be taken into consideration. With regard to psilocybin, serotonin syndrome, physiological and psychological effects, induced psychosis and mania, and hallucinogen persisting perception disorder will be discussed.

Serotonin Toxicity- Signs and symptoms warranting immediate medical attention include myoclonus, extreme and fluctuating vital signs, agitation or comatose mental state, muscle rigidity, pronounced hyperthermia (fever), and or seizure activity [24]. The risk of serotonin syndrome can be mitigated by tapering psychoactive medications prior to use and avoiding polysubstance use.

Physiological and Psychological Toxicity- Hallucinogens generally possess relatively low physiological toxicity and have not been shown to result in organ damage or neuropsychological deficits. Some physiological symptoms may occur during hallucinogen action, such as dizziness, weakness, tremors, nausea, drowsiness, paresthesia, blurred vision, dilated pupils, and increased tendon reflexes. In addition, hallucinogens can moderately increase pulse and systolic and diastolic blood pressure. However, these somatic effects vary and are relatively unimpressive even at doses yielding powerful psychological effects [20]. Regarding patients developing a dependence on psilocybin, hallucinogens have historically not been associated with withdrawal syndromes, and they are not reliably self-administered in animal studies. In general, patients should be in good physiological health established by routine medical history, physical exam, 12-lead ECG, blood chemistry profile, hematology, and urinalysis. For reference, while excluding patients with a systolic blood pressure above 140 and diastolic above 90 (mmHg) averaged over four measurements across 2 days, no increases in blood pressure resulting in the administration of an anti-hypertensive have occurred in one university's trials [20].

The largest risk with psilocybin administration is psychological distress, as hallucinogens are physiologically well tolerated. Emotions are experienced more strongly while under the influence. Disturbing experiences are colloquially described as a "bad trip". To handle this risk, psychedelic compounds should be administered in a safe environment that does not allow for self-harm. In addition, adequate preparation about handling negative emotions while under the influence can mitigate the risk of psychological distress. Patients need to approach negative emotions without resistance or fear and with an open mind. They can be counseled that negative emotions will arise in the same way that they do every day. Instead of trying to suppress negative thoughts, they should be accepted and examined with compassion, as this can be a powerful opportunity for self-exploration.

Psychosis- There is a risk of catalyzing a psychotic episode via the administration of psilocybin. Most cases have been in the setting of unsupervised administration, which increases the risk of polypharmacy and unsafe settings. Psychosis has been seen with LSD administration at a rate of .8/1000. This rate was obtained after a single incident out of 1200 LSD administrations in which the patient had an identical twin diagnosed with schizophrenia [25]. As such, patients with a history of schizophrenia or a first-degree relative with schizophrenia should avoid psilocybin in a non-clinical setting. Until more research involving psilocybin and the schizophrenic population is done, psilocybin should be reserved for schizophrenic patients with severe depressive symptoms (e.g., a score of 31 or higher on the Beck Depression Inventory).

Mania- Although there is little research involving psilocybin and the bipolar population, it would be wise to exercise caution

when using psilocybin in patients prone to mania. The rationale is that psilocybin is a potent serotonergic antidepressant which have been known to carry the risk of inducing mania. About 25%-33% of bipolar patients may be inherently susceptible to antidepressant-induced manias [34]. Bipolar patients with a strong genetic loading for bipolar illness whose initial illness begins in adolescence or young adulthood (typically Bipolar 1) and those with prior episodes of antidepressant-induced mania may be especially at risk [26]. Epidemiologic studies suggest that the risk of induced mania or psychosis is quite low. In a study of approximately 22,000 individuals, hallucinogen use did not predict subsequent mania, psychosis, or mental health treatment [27]. Of 130,000 doses of ayahuasca, four subsequent psychiatric diagnoses were labeled 'bipolar affective disorder; psychotic manic episode.' These researchers concluded that the number of psychosis and other cases from this sample is slightly less than expected in the base rate of the population [28].

Several case studies have been documented regarding the use of psychedelics and subsequent cases of mania or psychosis [29]. In summary, there were a total of 17 case studies in which a psychedelic compound could have contributed to the precipitation of a manic episode. Establishing a causal relationship is difficult due to polysubstance use, family histories positive for bipolar disorder, and those with a diagnosis of bipolar disorder may have been at risk for developing mania regardless of substance use. In 9 of the 17 cases, subjects used psychedelics multiple times in a short time-period. In 5 of the 17 cases, subjects used other substances. Of note, there were no studies in which an individual with bipolar disorder ingested a psychedelic and died due to an accident or suicide. When looking at the epidemiologic studies and case studies, there seems to be a risk of inducing mania, even if the risk is small. Despite this, the risk can be reduced even further by avoiding risk factors: polysubstance use, using psychedelics many times in a short time-period (i.e., recreational doses more than once in 72 hours), avoiding use in individuals displaying symptoms of mania or hypomania, and supervised use in a safe setting for individuals with a strong family history of bipolar disorder.

Hallucinogenic Persisting Perception Disorder(HPPD)- HPPD consists of perceptual disturbances (usually visual) while no longer under the influence of a psychedelic. To be considered a disorder, these disturbances must disrupt the individual's day-to-day life. HPPD has an incidence of about 4.2% of 2455 responders to a web-based questionnaire claimed to have visual disturbances prompting them to seek treatment [30]. There are case reports describing successful treatment with oral risperidone, neuroleptics, anticonvulsants (lamotrigine), benzodiazepines, and clonidine [12, 35, 36]. Given the evidence of multiple classes of medications alleviating HPPD symptoms it is difficult to establish a possible mechanism. The current hypothesis is that HPPD is due to chronic disinhibition of visual processors and subsequent dysfunction in the central nervous system [37]. It is important to note that HPPD is more common in recreational use and is rarely seen when psychedelics are used in a clinical setting [35].

SET AND SETTING

Set and setting (referring to the environment, music, and people involved with a psychedelic user's experience) have been posited to be crucial to the outcome of a psychedelic experience. Music is an important component of an individual's setting. A study at Johns Hopkins comparing Western Classical music to Overtone-Based Music did not show any significant differences between the groups when looking at biologically verified tobacco

cessation [31]. This finding in combination with the lack of research on music choice, suggests that it would be more optimal to have patients create their own playlists lasting 6-8 hours or select from a list of genres.

Concerning setting, it has been shown that the setting of an MRI or PET scanner has led to dissatisfactory experiences [6]. This suggests that the environment should be familiar and welcoming and not in a clinical setting. Successful studies have put subjects at ease via a living-room style room. It is important to include activities (e.g., paper, pens, paint, crayons, books, poetry, tv, movies, knitting supplies, fidget toys, simple video games, etc.) to allow personal expression and play therapy. It is also important to allow subjects to move about as they wish to limit feelings of claustrophobia and boredom.

DISCUSSION

The nature of microdosing requires chronic administration, which has not been adequately researched in humans. Some risks include potentially irreversible schizophrenic changes to brain physiology and 5-HT2B mediated negative cardiovascular effects. These risks are largely theoretical and need to be evaluated in a research setting. There is currently much more research available surrounding macrodoses, and thus is assumed to be safer. The initial hypothesis that microdosing may be a more accessible but equally effective treatment method was found to be inaccurate. In comparison to the standard acute administration of a macrodose of psilocybin in a safe clinical setting, microdosing has several theoretical risks that have not been disproven. =

Although microdosing may not currently have a role in treating depression, several case studies demonstrated efficacy for neuropathic pain. There is also evidence for the treatment of migraines [32] at .143mg/kg and cluster headaches [33]. The mechanism for this is not fully understood, but these studies warrant further research. This is especially important given the conflicting evidence that psychedelics indirectly improve cardiovascular health and reduce inflammation. If the cardiovascular risk is found to be minimal, microdosing will allow for more access to psychedelic treatment, as microdosing requires fewer resources and less observation for safety. As a result, macrodosing may be preferred by clinicians at this time as it is more likely to produce acute results, requires less follow-up visits for dose titration and symptom evaluation, and is less likely to have negative cardiovascular outcomes.

This article aims to make a clinical judgment based on the limited evidence available. Given the available research, if a patient is microdosing of their own accord, it is important to advise them. Based on the available research, it would be prudent to limit microdosing schedules to no more than twice a month in patients with an ASCVD (Atherosclerotic Cardiovascular Disease) risk <5% if the goal is to alleviate depressive symptoms. If ASCVD risk is >5% but < 10%, once a month is more reasonable. Patients should be evaluated to assess the need for future doses every 3-6 months, but patients should also be encouraged to titrate their microdose in consultation with their psychiatrist. Treatment should be stopped or reduced in frequency as symptoms decrease. This schedule would minimize cardiovascular risk while also catering to the chronic nature of unipolar depression.

If the goal is to manage chronic pain, the lowest dose that alleviates 80-90% of pain should be used and at the lowest frequency. If patients have chronic neuropathic pain as well as an ASCVD risk over 5%, each decision should be on a case-by-case basis considering the cardiovascular history and pain intensity.

CONCLUSIONS

The suggestions summarized below are based on the findings in this literature review for a treatment plan involving a macrodose.

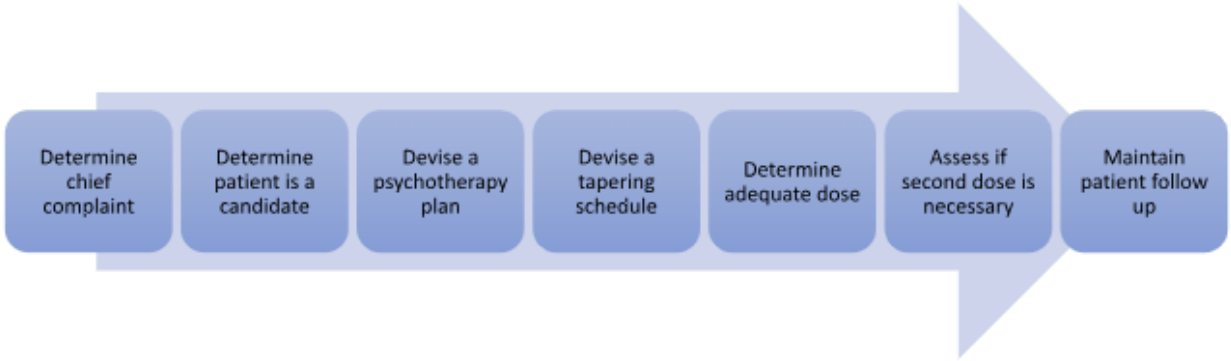

Figure 4. Flow diagram of sample psilocybin treatment plan for depression.

1. Determine the chief complaint, which will likely be a depressive episode that has not resolved with conventional therapies;
2. Determine whether the patient is a candidate (diagnosis of depression, physiologically fit for a psilocybin session, not showing signs of mania/hypomania, no history of antidepressant-induced mania, displaying signs of severe depression if diagnosed with schizophrenia or a first-degree relative with schizophrenia);
3. Devise a psychotherapeutic treatment plan for before and after psilocybin sessions (sessions leading up to psilocybin session should include education and managing expectations about psilocybin experience);
4. Review medications and devise a tapering schedule (monitor for Antidepressant Withdrawal Syndrome and adjust schedule);
5. Decide on a dose after assessment of personality type, experience with psychedelics, and patient comfort level;
6. Assess if a second dose is necessary and conduct an analysis of why the first session did not produce results. Some reasons for an unsatisfactory experience could be incorrect dose, poor relationship with the chaperones, inadequate attention to set and setting, incorrect expectations surrounding the experience, or inadequate psychotherapy prior to the session; and
7. Maintain patient follow-up

This article is limited by the lack of research on psychedelic substances (particularly microdosing) due to federal policies and widespread misconceptions. It is difficult to make recommendations on treating the bipolar population, the cardiovascular disease risk associated with psilocybin, and comparing microdosing to macrodosing. However, between medicalization and an increase in people turning to psychedelics to self-medicate as the standard treatment algorithms have failed them, the need for treatment algorithms to guide psychiatrists in the safe practice of psychedelic therapy is greater than ever, even if there is limited research to do so. More research is needed to evaluate the safety of microdosing, which will allow for safer recommendations regarding the practice. Despite this, as with any new therapies, the research

must be looked at through a clinical lens, and a treatment plan must be developed regardless of the amount of research available. This article serves as the first reference of information that will be helpful for clinicians who are tasked with developing their own treatment plans for treating depression via psilocybin.

AUTHOR INFORMATION

Kevin Enabulele, M.D. (kevin.enabulele@umassmed.edu)

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Article

On the Role of Mysticism in Psychedelic Therapy and Research

Richard H. Jones, Ph.D.; J.D.

Abstract

Should mysticism be excluded from psychedelic therapy and broader scientific research on psychedelics? One camp argues that it should be because experiences are not part of what produces positive effects in psychedelic therapy and because the language of mysticism is inexact and makes psychedelic research appear unscientific. The other camp argues that a mystical experience is needed for the most substantial effect in psychedelic therapy and so must also be studied in psychedelic science. It is argued here that there is evidence that these experiences appear to be a necessary part of the best effect of psychedelic therapy. Unless that data can be refuted, psychedelic-enabled experiences cannot be dismissed from therapy or scientific research on psychedelics. In such circumstances, these experiences must also remain a topic within consciousness studies. Moreover, "mystical" is appropriate for depicting some psychedelic experiences.

Keywords: psychedelics; psychedelic therapy; mysticism; mystical experience; naturalism; consciousness studies

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The beneficial therapeutic effects of classic serotonergic psychedelics have been generally accepted [1]. Psychedelic therapy has also gained widespread attention since Michael Pollan's *How to Change Your Mind* [2]. However, unlike other psychotropic drugs, psychedelics may have a drastic effect on the phenomenology of a subject's consciousness. This leads to the issue of whether it is the *chemical effect* of the psychedelic substantives alone or the enabled *mystical experience* of a loss of a sense of self that is the principal cause of the long-lasting psychophysical benefits. Several recent articles have debated whether research on the therapeutic effects of psychedelics should exclude references to mysticism to gain more scientific respectability. One camp [3-5] argues that the positive therapeutic effects result only from the drugs' direct pharmacological actions on the brain. Thus, the subjective experiences sometimes enabled by the drugs are only therapeutically unimportant byproducts of the chemical reactions. Using "a mysticism framework creates a 'black box' mentality in which researchers are content to treat certain aspects of the psychedelic state as beyond the scope of scientific inquiry" [5] can be eliminated from psychedelic therapy and any scientific research on psychedelics. Thus, talk of mystical experiences should play no role in psychedelic therapies. The opposing camp [6-10] argues that the experiences are essential to the positive (or at least best) psychological results, and so should remain part of psychedelic therapy. Thus, for this camp, any altered state of consciousness (ASC) experiences enabled by the drugs should also be included in psychedelic therapy and broader research. This dispute affects neuroscience and pharmacology, as well as psychology.

Two points will be argued here. First, unless the effects of these drugs can be shown to be strictly chemical, which at present has yet to be shown, the discussion of the experiential dimension in psychedelic therapy remains necessary and thus cannot be expunged. Proponents of decoupling psychedelic therapy and mysticism must base their case on empirical evidence and not simply on the basis of a contentious assumption that

only the chemical effects can be significant. Second, the language of mysticism best captures the experiential dimension for many types of psychedelic-enabled experiences. These positions also impact broader scientific research on psychedelics and models of consciousness.

THE DISPUTE

As part of the "psychedelic renaissance" that began in the 1990s, the therapeutic use of some well-known psychedelics (in particular, psilocybin) has proven that in certain doses, these drugs have long-term benefits for patients dealing with depression, anxiety, post-traumatic stress disorder, cancer, end-of-life distress, and drug or alcohol addiction. Psilocybin-aided therapy has proven helpful in cases resistant to conventional therapies [9]. The beneficial well-being and quality of life changes may last years [11]. Negative symptoms are reduced, and positive traits connected to well-being and optimism are increased after one or a few sessions. There are indications that the positive effects are greater with psychedelics than with other drugs or traditional talk therapies [12]. How the drugs affect the brain is currently not fully known. Indeed, the scientific study of psychedelics and consciousness is still nascent [13]. So, psychological knowledge of ASC experiences is still in its infancy [8]. Some current theories are that the drugs bring about change by disrupting specific serotonin receptors in the brain and that the drugs may disrupt the default mode network underlying our ordinary states of consciousness or that they have broader network effects [4] thereby allowing other types or levels of consciousness to be manifested in waking consciousness.

Proponents of disengaging mystical language from psychedelic therapies argue that, at best, the subjective experiences are irrelevant to the drugs' effectiveness, and at worst, the experiences are often dangerous.[1] Thus, reference to experiences should be ended — only the chemical effects on the brain of these psychoactive drugs bring about positive changes. Psychedelics are psychoplastogens that alter neural structure over time — they "rewire" the brain — and this chemical effect by itself accounts for the beneficial psychological effects. David Olson [3] points out that MDMA promotes structural and functional neural plasticity that effects long-lasting changes in most subjects but only a small percentage of the subjects have even extremely mild perceptual alterations. The effects of the drugs as catalysts that bring about the growth of key neurons in the prefrontal cortex would explain the beneficial changes in a person's behavior long after the compounds have been cleared from the body [3]. So too, the positive effects last after the experiences have faded and, in fact, sometimes grow. Thus, even a sense of well-being or the significance of being must be only a useless byproduct of the chemical effect, not an actual cause of the psychological transformation. Correlating the greater intensity of the experience with better results [14] does not mean that the experiences were the causes but only that the drugs had a greater effect on the patient's well-being and also produced a more intense byproduct. This camp can also point to the fact that even the short-lived negative "bad experiences "bad trip" psychedelic experiences — or in therapeutic language, "challenging experiences" — may lead to *positive,* cathartic effects later [15], suggesting that only the chemical effects are what produce the positive results rather than the subjective experience during the drug session.

Negative experiences enabled by psychedelic drugs (and meditation) are less often reported than positive experiences and are usually downplayed in scientific reports [16]. In particular, ego-dissolution can cause anxiety and dread. Even when the context is limited

to therapy, many participants experience anxiety, which would have a very negative effect. Such negative experiences affect the issues of whether experiences result from chemical effects on the brain alone and whether the chemical effects alone are responsible for therapeutic outcomes.

The fact that some experiences may be correlated with specific brain states does not mean that the *caused* them — correlation does not imply causation in one direction or the other. So too, correlating changes in brain states with mystical experiences does not explain either the brain activity or the "felt" nature of experiences but only adds one more thing that needs explaining.

This leads these researchers to conclude that the experiences associated with the biological effects are only epiphenomena of the neurobiological mechanisms and have no causal power. That is, these particular experiences have an interesting phenomenology but do not work. Thus, they argue that the actual science of psychedelics should be disentangled from all talk of mysticism, and the focus should be on brain chemistry. Olson [3] believes the "hallucinogenic" and psychoplastogenic effects can be decoupled through careful design but that work still needs to be done to determine if positive therapeutic responses can be produced without inducing behavioral effects characteristic of classic psychedelics. Companies in the United States funded by the government also want to alter psychedelics or develop new drugs that produce the beneficial effects without the mind-altered subjective experiences [3]. This would radically change the nature of psychedelic therapies. Nevertheless, even if the non-hallucinogenic analogs of psychedelics fail in therapy, Olson suggests that they "will provide a wealth of information about the fundamental neurobiology underlying both compound-induced neural plasticity and hallucinogenic effects [3]."

However, those who advocate retaining experiences as part of psychedelic therapy readily acknowledge that a reorganization of a brain next work is produced by chemical effect of the drugs on areas of the brain connected to a sense of "self," a sense of boundaries and a sense of emotional importance and that this rewiring is part of the causes of positive therapeutic effects, but they also affirm a mediating role for experiential effects [6]. Moreover it, it may be the mystical experiences that are responsible for structural changes in the brain [17]. These advocates point out that analyses suggest that mystical-type experiences play an important role apart from the overall intensity of the drug's chemical effect [17]. It may be that the *intensity* of the experiences accounts for their potential transformative effect [12]. One meta-analysis found that "mystical-type experiences" are associated with positive long-term changes in subjects after the drug sessions and that these changes are not just the result of the chemical action of the drugs but from causation by the experiences [18]. In anecdotal accounts of psychedelic treatments, meaningful insights and belief changes are also frequently cited by patients as fundamentally important to enduring positive outcomes [6].

Researchers are now experimenting with low doses of drugs ("microdoses" of perhaps 10% of a normal dose taken several times a week) that produce no psychedelic experiences but hopefully would still have a transformative impact on a sense of well-being. Microdosing can touch off some experiences connected to mysticism — increased awareness and sensations — but not the more robust experiences affecting perception [19]. In one recent study, the microdosing did not produce experiences that affected the emotion-related symptoms and processing of the patients [20, 21]. At best, they are no more effective than a placebo [3]. However, this does not affect the claim by the proponents of decoupling that in the proper doses,

psychedelics' chemical effect is all that matters. These proponents, however, still have the problem noted below that placebos can enable some therapeutic-level ASC experiences.

Advocates of the role of experiences in these therapies believe that the case is "compelling" for "the subjective effects playing a major role in the enduring beneficial effects" [6] or "a profound, potentially transformative psychological experience is critical to the treatment's efficacy [9]." They argue that having a mystical-type ASC experience in therapy sessions is a reliable predictor and "key determinant" of long-term positive psychological changes [8]. The fact that these drugs, unlike other psychoactive ones, enable *experiences* may indicate an important role for them. So too, the correlation of high results with the presence of altered state experiences should not be dismissed out of hand [9]. The philosopher Chris Letheby [22] argues that the central mechanism in psychedelic therapy is a psychological factor, not the chemical stimulation of the brain, and this factor correlates with an ASC experience. Proponents of decoupling talk of mysticism can point out that the experiences being an indicator or predictor of therapeutic change does not mean that the experiences are a *cause* in the process. Nevertheless, at least one advocate of decoupling talk of mysticism in therapy, David Olson [3], is also willing to accept that the experiences may be needed to achieve the psychedelics' maximal efficacy.

Thus, advocates for retaining a role of experience argue that, unlike for most drugs, it may be the case that with psychedelics, it is the experiences and not the chemical changes in the brain that are most important for producing the psychological benefits and for those benefits to be lasting. The experiences often lead the experiencers to see the world and their lives as more satisfying, purposeful, and meaningful, even if no exact meaning of life is given. Participants often rate their experiences as *the* most meaningful ones in their life or among the top five [11, 23, 24]. In one study [23], two-thirds of the participants stated that it was the most meaningful experience of their lives or among the top five and the equivalent in impact to such things as the birth of a child or death of a parent. That impact, not only the psychedelic's chemical effects, is the source of the therapeutic change. The experiential mechanism may be complex: it may be that the ego-dissolution that lasts only for the short period of the psychedelic experience is not the direct cause of the therapeutic benefits but rather the resulting sense of connectedness to other things cultivated through meditation is the cause of lasting benefits [25, 26].This would remove the physical triggering of chemical changes in the brain by the drug two steps from the changes in the sense of self involved in the therapeutic changes.

In addition, the neuroscientific community today studying the bases of ASC experiences in brain activity is coming to accept that mystical experiences are not merely products of our imagination or emotional embellishments of ordinary experiences but are based in distinctive neurological events [27-29]. That they are "real" or "genuine" experiences does not necessarily mean that transcendent realities must be involved in some mystical experiences or that mystical experiences provide knowledge of reality but only that ASC experiences are not merely some more ordinary experiences that have simply been Interpreted mystically. Furthermore, if these ASC experiences have causal power, these experiences may be able to produce enhanced effects on a person's well-being. Thus, the experiences may hold the key to the most effective therapies.

TESTING THE COMPETING POSITIONS

Thus, the question now stands: Are ASC experiences the *cause* of the positive (or at least the best) changes, or are they only an expendable *side-effect* of the chemical actions that produce those changes? That the experiences last long after the drugs have left the body is interpreted by proponents of decoupling to mean that the drugs have rewired the brain. At the same time, proponents of retaining talk of mystical ASC experiences interpret this to mean that, while the drugs may both enable the experiences and rewire the brain, the ASC experiences are also a causal factor in the enduring positive therapeutic results. Both camps can cite data favoring their side, but both concede that more research is needed.

Can the two options be directly tested empirically? That the power of a disputed subjective effect makes testing extremely difficult. However, David Yaden and Roland Griffiths [6] propose a test to determine the relevance of subjective effects. They claim that the only definitive study that could disprove the importance of the subjective effects would be one in which a psychedelic is administered to individuals who were fully unconscious at the time (e.g., via deep anesthesia) and who subsequently report no memory of psychedelic experiences and yet have the positive psychological effects. They suggest that positive psychological effects will not occur in such an experiment [6]. Chris Letheby concurs: "almost all relevant clinical trial evidence suggests that a full-blown psychedelic experience is necessary for a complete therapeutic response [22]." If no changes occur to these patients or only relatively minor changes occur and the patients affirm that no experiences occurred, the case for decoupling mysticism and psychedelic therapy is damaged since advocates of decoupling would predict that the benefits would accrue even to unconscious patients. However, if no changes occur, proponents of decoupling may contend that such a test only shows that psychedelics affect the brain differently when the subjects are awake than when they are asleep. They would then have to find independent evidence establishing that.

Also, note that this dispute over ASC experiences should *not* be seen as a broad dispute between materialism and nonmaterialism on the nature of the mind. Proponents of decoupling need not deny that consciousness has causal powers — they may merely treat *consciousness as physical* in nature and mental causation as material in nature. Instead , proponents may not dismiss all experiences as having causal powers but see only psychedelic-enabled ASC experiences as a type of experience with no causal power and thus treat these specific experiences as extraneous and useless side effects that can be ignored. For them, psychedelics are like any medication in which the patient's mental state is irrelevant. The burden then is on materialists to make a compelling case that these particular experiences play no causal role, and such a case cannot be limited to results of studying the brain's hardware. All neuroimaging can show is what the brain is doing or not doing during an experience. However, it cannot examine the ASC experiences themselves and thus cannot tell us anything about their role or nature.

However, those materialists who treat consciousness as nonmaterial and deny mental causation in favor of the causal closure of the material have a further problem. When all we have are the reports of material activity in the brain during these experiences, what could neuroscientists who adopt an eliminationist metaphysics take as evidence of an ASC experience being a cause of brain activity? Their metaphysics may preclude the possibility of finding evidence that consciousness is a separate causal power from the psychedelic's chemical effects. However, if finding evidence for something is precluded in advance, then *not* finding evidence cannot be evidence against its existence. Thus, no experiment could rule out a conscious event,

such as an ASC experience, as a cause guiding neural activity in the brain. Consciousness may be like software guiding the course of events in the hardware (the brain), but all we can see in any experiment is the activity of the material brain. The problem is how to devise an experiment where consciousness might or might not be a cause.

But until the proponents of decoupling have made a case for excluding psychedelic-enabled ASC experiences as causes, treating them as causes are warranted. Those denying ASC experiences as a cause of positive therapeutic outcomes are not in a position to prove that ASC experiences are not causes in the brain events, and until then, proponents of decoupling can never rule out ASC experiences as possible causes of therapeutic results for experiment-based reasons. In such circumstances, the best course of action is, as Joost Breeksema and Michiel van Elk suggest, "acknowledging the varieties and weirdness of psychedelic experiences should be at the heart of any research program on the topic [7]." In addition, considering that neuroscientists currently do not have complete knowledge of the workings of the brain or how psychedelics affect the brain, or the basic nature of consciousness, common sense suggests that the safer course at present is still to include ASC experiences in psychedelic therapies. This is especially so since, at present, patients attach great significance to the experiences. Thus, therapists should not ignore, dismiss, or downplay the experiences since the patients would not be helped as much — the explicit or implicit denial of the therapist may negatively affect the effectiveness of the therapy.

In sum, as things stand today, non-pharmacological factors appear essential to a positive therapeutic outcome. All who adopt naturalism should remain open-minded until convincing empirical evidence is presented. (As noted below, a positive naturalist interpretation of mystical experiences is possible.) Moreover, including ASC experiences in psychedelic therapy makes it an important topic for study in psychedelic and consciousness research.

THE VARIETY OF SUBJECTIVE RESPONSES

One problem for proponents of ASC causation is that *there is no universal psychedelic altered state of consciousness or experience*. That is, there is no generic "psychedelic state of consciousness" following the ingestion of these drugs [30]. The research shows that psychedelic drugs enable a variety of psychedelic experiences and states, including a variety of mystical ones, even though researchers routinely refer in the singular to "*the* psychedelic state" and "*the* mystical experience [31]." The psychologist Stanislav Grof [32] also makes the point that LSD has no one invariant pharmacological effect, nor is there one inevitable experience associated with it — rather, he asserts, LSD is a catalyzer that amplifies and brings into consciousness dynamics that are within the person's subconscious.

Contemporary researchers have found many nonmystical ASC experiences enabled by psychedelics. These include visual, auditory, and tactile experiences, kaleidoscopic and fractal visions, seeing two-dimensional pictures as animated and three-dimensional, synesthesia, and alterations of the perception of time and the body. So too, there is no one mystical experience but significantly different types of mystical experiences [16]. Different psychedelics have different effects on brain activity — e.g., LSD appears to enable more visions than psilocybin. Different dosages of a given drug may also produce different neurochemical states that ground different experiences. In addition, the same person may have psychedelic-enabled experiences that fit the characterization of "mystical" given below and some that do not. Even

during one session, there are various states of consciousness under the chemical actions of the psychedelics [30]. Moreover, *no alteration of consciousness at all* may occur. William Richards reports that a substantial number of people have ingested psychedelics on many occasions without experiencing any profound alteration of consciousness [30]. Indeed, he notes that people can take psychoactive drugs hundreds of times without encountering anything deemed "sacred [33]." J. Harold Ellens [34] found the same: many persons have taken psychedelics repeatedly and never come close to experiencing profound states of consciousness, spiritual or otherwise.

If a one-to-one correlation of mystical experiences and psychedelic triggers were established, advocates of decoupling would not have a problem: such a *correlation* does not prove psychedelic-enabled experiences are active *causes* rather than powerless *side-effects* but only that they appear together. However, there is no one-to-one relation between different triggers and different types of experiences: based on the phenomenological accounts of mystics and experimental subjects, different psychedelics, meditation, and other natural (and perhaps non-natural) triggers produce some experientially indistinguishable experiences. The same trigger may produce different experiences, and the same experiences may come from different triggers. It is not as if different triggers "enter" the experiences and produce experiences unique to that trigger. (If multiple significantly different types of experience are associated with the same neural state, there would be the inverse of the "multiple realizability" problem in the philosophy of mind — the same brain state would underlie different mental states. Of course, it may be only that our contemporary technology is not sensitive enough to detect differences in what appears to be the same neural state for different experiences.)

Differences in therapeutic benefits for those with different experiences or no experiences would be significant for the question of whether the chemical effects of the drugs are all that matters. But if the same benefits accrue despite differences in experiences, this presents a problem for advocates of the retention of a role for ASC experiences. Thus, this presents an empirically testable issue: if different experiences give rise to different positive therapeutic outcomes or if some have no effect, this suggests that some ASC experiences play a role in the outcome; but if all ASC experiences or no changes in consciousness have the same effect, this suggests that only the chemical effect of the psychedelic is all that matters.

Outside of the dispute, researchers today agree that all psychedelic experiences are not simply products of chemical changes alone. As Huston Smith stated, "there is no such thing as the drug experience per se — no experience that the drugs, as it were, secrete [35]." That is, differences matter in an experiencer's mental "set" (i.e., background beliefs, preparation, expectations, disposition, propensity for altered states of consciousness, personality traits, mood, and past experiences with drugs) and the "setting" (i.e., the social and physical environment) when a drug is ingested [8]. For example, a subject's disposition of a "willingness to surrender" is associated with "stronger" mystical experiences [8, 37], and meditation prior to a psilocybin experience can yield beneficial results [8].These are important to whether psychedelic experiences occur and what type of experience occurs. Their differences at least partially account for the great variation in the experiences enabled by the drug. As discussed below, a frame of mind that is prepared for, or expecting, some religious experience to occur or for the possibility of a mystical experience occurring combined with a religiously-inspiring physical and social environment enhances the likelihood of such an experience, even if the resulting visionary or mystical ASC experience is not what the

experiencer anticipated. A laboratory setting may negatively impact the possibility of a mystical experience and its phenomenological content. Even a researcher calling the drug an "entheogen" ("generating God within") or a "hallucinogen" ("generating hallucinations") can affect the experiencer's mental set through an expectancy bias one way or the other. So too, researchers must inform participating subjects that they may receive a mind-altering drug and that may affect the experiences that result.

Thus, every psychedelic experience appears to result from a mixture of at least three ingredients— the drug, set, and setting [35]. The particular dosage is also a factor in the mix [18]. Genetics and demographics [37] and the propensity to become wholly absorbed in an experience [8] are among other possible factors. In addition, although mystical experiences occur with a higher frequency with a psychedelic than with a placebo, in all of the controlled experiments cited here, some participants who were given only a placebo also had mystical experiences. In one study of placebos, 61% of the participants reported some effect from the placebo — some effects with magnitudes typically associated with moderate or high doses of psilocybin [3]. The drugs disrupt the neurology underlying our baseline state of consciousness and make the experiencer more susceptible to the effects of set and setting but do not set up any one altered state of consciousness. Instead, our subconscious or other factors complete the experience. Thus, our underlying mental set may be responsible for the differences in experiences in a person's altered state of consciousness, not a drug's chemical effects on the brain. For example, if one expects a life-changing experience, one will often get it; if one does not, one will not. This, it is argued, is why expectation and the rest of the set and setting are so important; thus, studying those also in connection with placebos is valuable [38]. However, proponents of decoupling must explain the placebo effect here if the chemical effect of psychedelics is all that matters. Even if the placebo effect is explained through a participant's expectations, still the proponents would have to explain this when there is an apparent lack of a prior chemical alteration in the brain.

One problem with determining the long-term effects of psychedelics (and meditation) will arise if most subjects in these studies are self-selected participants who are members of particular religious traditions or unaffiliated "seekers" already seeking a religious experience.

This would predispose the participants toward a religious understanding and a lasting religious impact. If so, it is difficult to determine if any changes in values or ways of living are the results of chemically-induced neural changes or the participants' prior religious beliefs or continuing training — do the lasting effects result from new brain conditioning alone or a mixture of a memory of the experience and the subject's beliefs? Drug study participants may also adjust their impressions of the realness of spiritual experiences over time [17]. Thus, the long-lasting effects of these experiences on one's character may result not from rewiring the brain but from the impact of an experience on how the experiencer decides to live. So too, with the waning of the psychological effects. That is, even if there may be some lingering chemical effect of the drugs on the brain, changes in character as a result of the experience account for the increase in some positive effects over time.

Two further problems are that non-psychedelic drugs (e.g., alcohol) can disrupt the default mode network operating in our consciousness without producing psychedelic experiences and that psychedelics cause more comprehensive network changes than merely disrupt the baseline mental state [4].

All of this complicates the picture for those who believe psychedelic-enabled

experiences matter: Does the variety of subjective responses to psychedelics mean that those responses are irrelevant, or does it mean that the chemical reaction of the drugs is irrelevant and the particular psychedelic response that a particular subject experiences is all that matters? Or is there a combination of the two? If there is no therapeutic benefit from an ASC experience arising from a placebo, that would point to the importance of the chemical effect of the psychedelics. On the other hand, if psychological benefits accrue from experiences occurring when placebos are given or when ASC experiences occur through meditation or spontaneously (i.e., without any preparation or expectation), then the impact of the chemical effects of psychedelics on the brain falls into question. There is an apparent disconnect of the experience from chemical changes in the brain that proponents of decoupling must explain.

It may be that no one mechanism accounts for the therapeutic efficacy of psychedelics and that a pluralistic approach to analysis and explanation may be needed [39]. Nevertheless, it does appear that the psychedelic drugs in certain doses *open up the mind* to different states of consciousness by *disrupting the everyday state of mind* that sets up a subject/object duality and conceptualizes multiple objects. The drugs have the same disrupting effect on all subjects' neural configurations, but what happens after our baseline state is disrupted *does not depend on the drugs* but on other factors. Different psychedelics may disrupt different brain networks, just to facilitate different types of ASC experiences. In sum, psychedelics enable various ASC experiences to occur but do not mechanically produce, induce, or trigger any experience or determine an experience's significance for the individual experiencer or an experiencer's sense of meaning, and it may be those experiences that matter at least as much as the neural changes in any therapeutic outcome.

Spontaneous mystical ASC experiences have not gained the attention in scientific circles that they should. The differences between them and psychedelic mystical-type experiences are not well described [40]. Spontaneous ASC experiences may result from triggers (e.g., the fatigue of long-distance running) that affect the brain the way that psychedelics do, but that would have to be established empirically.

CHARACTERIZING MYSTICISM

The last section brought up some ASC experiences that researchers labeled "mystical," and this leads to the second issue for this article. If it is accepted that psychedelic-enabled experiences play a necessary role in psychedelic therapy, should at least some of these ASC experiences be characterized as *mystical*? [5] argue that talk of "mystical experience" is too inexact to be scientific and that use of that language biases the reports that patients give of their experiences; it is also an unwarranted and risky "blend of mysticism and science" that "risks damaging the credibility and potential of psychedelic science" and may lead to misinterpreting the findings of psychedelic research or to being seen as advocating a role of a transcendent reality [5]. In addition, patients who need help may avoid getting treatment because of the stigma attached to mysticism in the general populace. On the other side, [7] argue that:

1. Critics have an incomplete understanding of mystical experiences as a scientifically validated and rigorously studied domain of human experience.
2. Experiences that are especially mystical in nature are clinically and scientifically highly relevant.
3. Good methodological tools are available for studying these experiences.

4. The scientific community ought to embrace these "weird" experiences and that it would be unscientific to ignore mystical frameworks and language simply because they supposedly are incompatible with the metaphysics of naturalism since the experiencers themselves take mystical frameworks seriously — mystical experiences are part of the therapy, and their effects must be noted

Critics are correct about the vagueness of the words "mystical" and "mysticism." (It should be pointed out that the words "experience" and "consciousness" are also hard to nail down.) Moreover, the term "mysticism" also has a negative connotation in today's culture. This has led to the term being used for a wide range of phenomena that are generally looked down upon and applied in academia to anything academics today generally deem flaky. Even those who advocate a role for experiences in psychedelic therapy and research dance around the term "mystical" — they use "mystical-*like*" or "mystical-*type*" experiences or phenomena "*related*" to mysticism [6] rather than accept that the experiences, in fact, *are* mystical. At best, "mystical experiences" are treated as only a subcategory of positive "self-transcending" experiences [41].

Unfortunately, researchers in the dispute who employ the term "mystical" often do not define the term or characterize what is deemed "mystical." It often means any ASC experience or only "union with God." But a fairly tight definition of "mystical experience" can be seen as applicable to some of the psychedelic-enabled ASC experiences that appear to have a positive effect in psychedelic therapy. That is, "mystical experiences" in the sense of experiences involving a loss of a sense of a distinct "self" separate from the rest of reality and a resulting sense of connection to something deemed more real; conceptual distinctions, in general, are also loosened [16]. The state of consciousness loses the duality of subject and object. As noted above, this may occur introvertively or extrovertively.

Moreover, the subjects' self-reported phenomenological accounts in these research reports — i.e., first-hand accounts of the "felt" content of the experience without any interpretation of what was experienced — contain language central to any strict definition of "mystical experience." Researchers have been following or elaborating on Walter Stace's summary account of the defining characteristics of mystical experiences [42] to characterize "mystical-type" experiences: feelings of unity, transcendence of space and time, a noetic quality, ineffability, paradox, and sacredness, as well as positive feelings of bliss, joy, wonder, and awe and a sense of ego-dissolution and an enhanced perception of emotions [39]. Any loss of a sense of self or "ego-dissolution" would necessarily disrupt our ego- driven baseline state of consciousness, thereby producing an altered state of consciousness. In a recent review of the reports on meditative experiences, researchers have found that experiencers of "pure consciousness" (i.e., one empty of all thoughts, images, concepts, perceptions, and feelings) retained some content after the experience: stillness, silence, simplicity, naturalness, calm, relaxation, rest, bliss/joy, a sense of knowing, freedom, wholeness, security, unity, depth, and profundity [43]. A sense of "oceanic boundlessness," derived from Freud (see Jones 2021, pp. 98-99), is also gaining use when the ego is dissolved. Broader definitions of "mystical experience" would include such experiences as visions and locutions that were mentioned above under the variety of subject responses that involve a sense of a duality of subject and object.

"Ineffability" is central to modern philosophical characterizations of mysticism.

However, it should be noted that when classical mystics used the term, they usually meant only that what is experienced is *more than* can be described, not that it is completely *indescribable* and that terms designating ordinary phenomena can only be applied metaphorically [16]. The term is a type of emphasis for the otherness of the experiences and the reality allegedly experienced. So too, people who have had mystical experiences can characterize the felt phenomenology of the experiences themselves in some terms [44].

What exactly is meant by a "loss of a sense of self" (LOSS) in psychedelic and meditative experiences is a matter of debate in neuroscience, and there are different phenomenological features for different types of states labeled "loss of self [45, 46]." The LOSS may lead to the best long-term results, but patients often dread the dissolution of a sense of self. From a psychological point of view, there is little reason to suspect that a LOSS would be anything other than negative—terrifying even—and yet LOSS in psychedelic-enabled experiences is often reported to be "profoundly positive [44]." In mysticism, it is not a matter of merely not being aware of a subject sensing something (most experiences are like that), but that during the experience (or looking back at it later) it seemed to lack ownership or being attached to the person. Sometimes LOSS results in a state of consciousness that does not seem personal or temporal and leads the experiencer to believe there is no personal or individual survival of death. However, it is not a loss of subjectivity. In Theravada Buddhism, the no-self (*anatta*) doctrine does not mean that there is no subject to our experiences. Only that there is no discrete entity in the phenomenal realm. There is still an impermanent and conditioned configuration of sensing, feeling, and thinking, even though no separate "self" is ever found in our experiences. That is, only the reality of a substantive "experiencer" in addition to our actual mental content is denied, not subjectivity or a subjective point of view. Similarly, in advanced states of mindfulness, there is no "subject" as a separate reality or a dualism of subject and object. Nevertheless, a subjective element need not be denied.

However, those who equate "mystical experience" with "union with God" will not want to label such a loss and connection as a "mystical experience." The basic problem in the rejection of mystical language may be only a discomfort with the term "mystical experience," not a denial that a loss of a sense of "self" sometimes results in a mystical experience. Some types of mystical experiences appear more easily facilitated by psychedelics than others. Introvertive experiences that are free of all differentiated content are less common with psychedelics than extrovertive experiences and visions and voices [23, 24]. A resulting increase in mindfulness has also been associated with ingesting psychedelics [47, 48]. Researchers in psychedelic studies will have to examine the different types of mystical experiences as related by experiencers for their therapeutic impact, if any. If the different mystical experiences have a different impact, this will point to the issue noted above of whether the uniform changes in the brain produced by the chemicals are the sole source of the psychological effects. Thus, studying mysticism may inform better research on the "subjective" side of psychedelics

Those researchers who reject any role for ASC experiences in psychedelic therapy or research on consciousness, of course, want to disavow any connection to mysticism, but that does not mean that the term "mystical experience" is not appropriate to some of the experiences enabled by psychedelics in therapy sessions. Some researchers may seek to use another term without religious connotations, such as "transpersonal experience" or a "quantum change experience" [40]or simply a generic "therapeutic experience [49]" Using

"self-transcendent experiences [17]" may be confusing: it sounds as if the experience transcends itself rather than referring to experiences that transcend a sense of self. Perhaps a new term derived from Greek or Latin may be invented, but the phenomena covered by that term will still be covered by the term "mystical." Thus, some ASCs could still be labeled "mystical."

That being the case, a simpler route would be to retain the term "mystical" but advance an exact stipulated definition of the term for psychedelic studies. Researchers could then work out a typology of mystical and nonmystical psychedelic-enabled experiences and their effects in therapy. The study of mysticism may inform better research in this regard. Then the term could be utilized in scientific research for the limited range of phenomena covered by that term. Nor should the negative attitude of the general public be a deterrence. After all, the general public has a generally negative attitude toward "psychedelics" because of its history, and yet the term has gained respectability in scientific circles. Furthermore, it should be noted that notions of "naturalizing" mystical experiences and of a "secular mysticism" removing alleged transcendent implications are taking root in our culture today [50]. Thus, mystical experiences are not inherently tied to a metaphysical belief of realities transcending the natural realm. Thus, this removes some of the religious and transcendent overtones of "mysticism" that secularists want to overcome. In the end, it is not surprising that the term "mystical experience" is becoming common in psychedelic research [17].

The danger that participants may mischaracterize their experiences in light of the researchers' questions cannot be overlooked. They may not have had any ASC experience. Brain scans can at least indicate whether the participant's brain activity was unusual or not during an alleged ASC experience.

THE PROBLEM OF MYSTICAL AND ANTI-MYSTICAL LANGUAGE

If therapists and researchers accept psychedelic-enabled experiences as part of therapy and that mystical language is appropriate, how should the experiential component be presented? The wording of questionnaires given to subjects in therapy and broader research on psychedelic-enabled ASC experiences should be scrutinized [51]. Researchers may be interested more in the experiences themselves than in their therapeutic effects. However, the questions advanced by them may be related to specific metaphysical beliefs and not to the phenomenological content of the experiences themselves. Instead, questions related to the phenomenological content alone should be included and should be first. But when it comes to therapy, patients may see these experiences as provoking the "big questions" of philosophy and science concerning what is real and what is meaningful in life. Then questions about what the experiencers believe they experienced must also be included [4]. Psychedelics may indirectly lead to being more open to such questions because of the shock of the unexpected in ASC experiences or the temporary disruption of the normal state of mind. Moreover, experiencers may not clearly distinguish the experience and what they think was experienced — their description of the former may be in terms of the latter. Questions cannot be limited to only those that naturalists think are appropriate and are expressed in naturalist terms — questions should be phrased in such a way that they do not limit the opportunity of respondents to express themselves in their own terms, which are often in terms of their religious tradition's transcendent realities in order to let the participants have a wide latitude of responses. Experiencers also often modify their beliefs about transcendent realities and express them in more abstract

terms, not in terms of a theistic personal god and doctrines of the respondent's culture and tradition. The beliefs are still religious even if they do not reflect the doctrines of a specific tradition. Scientists are not constrained by the participants' responses in the *explanations* that they give mystical experiences. However, participants should be afforded the opportunity to express their understanding and description of the experiences and what was allegedly experienced in an open-ended form in order to gain the fullest accounts of the alleged content of these experiences.

Thus, questionnaires should be phrased as neutrally as possible and not predispose respondents toward either transcendent or natural realities and should allow respondents to describe the phenomenology of the felt aspects of an experience without reference to what supposedly was experienced. However, in addition, they also should permit experiencers to express their beliefs about what was experienced. Having a strictly secular questionnaire can be seen as neutral when the researcher is looking only at the phenomenology of the experiences but not when looking for the impact of the experiences on the respondents. On the other hand, the risk of monotheistic bias is particularly significant when it comes to transcendent realities — nonpersonal and deistic realities and naturalistic alternatives, must also be options. Furthermore, religious language can be used without tending to elicit a particular response if used with other options. Thus, resorting to mystical terminology should not be ruled out by fiat.

A related problem is the physical setting of therapy sessions and research labs. As long as ASC experiences are accepted as a necessary part of psychedelic therapy, a purely secular setting [3] is not "neutral" or "more scientific." A religiously sterile room may bias participants against where their mental framework would otherwise lead them. So too, for settings that intentionally point in the direction of a general spirituality or transcendent realities. A therapist should not inadvertently advocate or discourage any type of experience or any understanding of the significance of the experiences. Even different settings may be seen as suggesting either a mystical experience or a naturalist understanding. The setting should be neutral between interpretations to the extent that is possible in terms of experience, lighting, music, and so on to not interfere with the experiential process and its aftermath. As Matthew Johnson [4] states, "[t]he goal of a clinician should be to create an open and supportive environment where the patient can make her or his own meaning, if any, from such experiences" — and "open" does not mean religiously sterile. The fact that a setting that makes the participant comfortable, including symbols from his or her religious tradition, may lead to more mystical experiences while a setting void of religious symbols may lead to fewer mystical experiences neither proves that mystical or other psychedelic-enabled experiences are purely hallucinatory nor that only the chemical effects of the drugs have an impact — it only points to the importance of the role of one's mental "set" and the "setting" in these experiences. Finding a truly open setting may prove difficult — a hodgepodge of multiple religious and secular elements may not be best for removing any anxiety a participant may have and setting a mood that is open to having a mystical experience. It may offend or alienate the nonreligious and even members of a Western religion who think they are being indoctrinated into an Eastern religion or some formless "perennial philosophy." However, the object of therapy is to help people, and there is some evidence that a purely secular standpoint diminishes the effectiveness of psychedelic therapy and is ill-suited to help people process the ontological shock that may be associated with psychedelic-enabled experiences

[8]. Arguably, the secular approach is harmful to the religious (since it may create a conflict in their mind) rather than helpful. As noted above, at this early stage of research mystical experiences are the best indicator of a positive therapeutic outcome, and so a setting inducive of mystical experiences should be preferred. But the problems just noted show how difficult it may be to determine the best setting.

The participants' and the therapists' mental framework can also impact what occurs in the ASC experience themselves and the experiencer's post-experience understanding of what was experienced. The state of mind during an experience can be distinguished from the experiencer's post-experience understanding, even though both are "subjective" and may not seem distinct to experiencers but two phases of the same event. So too, the questionnaires should reflect this distinction. A mental framework preconditions experiencers to follow a certain mental track and may predispose them to certain understandings. For example, theistic beliefs may direct experiencers to interpret the felt sense of nonduality or pure consciousness (i.e., a state of consciousness empty of differentiated content) to be the ground of only the soul or to be merely a powerful hallucination and not indicate an actual unity to a "wholly other" creator god who is by definition unexperienceable. Alternatively, theists' expectancy bias may direct experiencers to take any psychedelic experience as a "taste" of transcendent knowledge or a "glimpse" of God. The philosophical issue of whether mystical experiences are, in fact, cognitive of reality [52, 53] can be ignored for the question of therapeutic benefit, but another issue arises: if the patient *believes* the psychedelic-enabled experience is cognitive, is the therapeutic effect different than for a patient that does not believe that?

It may be that the beliefs one holds at the time of the experience do not matter for a transformative effect — all that may matter is the experience, and the experience leads to changing one's beliefs. It may be that ASC experiences do not introduce new beliefs but only alter a person's existing beliefs and their impact (McGovern et al., 2021). Psychedelics open healthy volunteers up to greater suggestibility [8, 15] and magnify whatever meaning they bring to the experiences. Under the recently proposed REBUS ("RElaxed Beliefs under pSychedelics") model [55], psychedelics weaken the control of one's beliefs, thereby permitting more influence from experiential input and making experiencers more flexible in their resulting beliefs. Indeed, psychedelics do not necessarily make an atheist into a theist, but there may be "significant decreases in identification as atheist and agnostic and significant increases in belief in ultimate reality, higher power, God, or universal divinity [57,58]." It does appear that psychedelic-enabled experiences tend to cause a shift in the experiencers' metaphysics away from "hard" materialism or to accepting transcendent realities [22, 59]. Part of the problem is how "atheist" is defined and its contrast to traditional Western monotheism [58], but psychedelics do appear to have a "robust tendency to make users believe in *some* other (non-physical) Reality that puts this one in the shade [58]." Theists may also change their beliefs to embrace panpsychism, cosmopsychism, or a transcendent consciousness or a nonpersonal "Ultimate Reality" that is the ground of the natural universe. A single psychedelic experience may also have a lasting effect on how the person views consciousness [60]. Such effects on beliefs are correlated with positive mental health changes and a sense of well-being, and the metaphysical changes may be long-lasting [59]. Psychedelics can occasion strong but short-term and reversible disruptions of self-consciousness. However, the long-lasting effects on well-being do not appear to be necessarily mediated by intense experiences but

rather by the training of different cognitive mechanisms through meditation [45].

This points to the need for sensitivity to how mystical language and religious symbols are handled in psychedelic therapy and research. If mishandled, the resulting experience or lack thereof may be misconstrued as evidence for the researcher's own position on the issue of mysticism and psychedelic research.

IMPOSING NATURALISM

As discussed above, it is essential to realize the influence of expectations, dominant discourses, and social and cultural beliefs in both the set and setting of psychedelic-enabled experiences and the post-experience understandings. However, it must not be assumed that only the religious have a mental set that affects their experiences and post-experience understanding. Naturalists routinely recognize the danger in scientists and clinicians unconsciously imposing their personal religious or spiritual beliefs in the practice of psychedelic medicine and condemn introducing their own "nonempirically supported beliefs [4]." Clinicians without explicitly endorsing supernatural beliefs may still impose them [4] when gaining a rapport with the participants. Nevertheless, the danger that *naturalists* may unknowingly impose their own unacknowledged naturalist beliefs also must be recognized. Nonreligious, antireligious, and agnostic naturalists are in the same boat as those who are antinaturalists in their metaphysics — their position is as metaphysical as the ones they reject, but naturalists often think that their beliefs are dictated by science and therefore are in a privileged position. However, naturalists often think that their beliefs are dictated by science and thus are in a privileged position. Thus, they believe that imposing their beliefs is permissible.

These changes in metaphysical beliefs occur after the experiences. Thus, the new beliefs are not psychological factors in the therapeutic effects related to the experiential dissolution of a sense of self [58].

Naturalism, too, is a matter of metaphysics and cannot be equated with science or deduced from scientific findings. It is a worldview based on taking science alone as answering the fundamental questions on the nature of the world. In naturalism, all that exists is open to scientific examination, and thus all that is real is the natural world (with the possible exception of mathematical entities). However, it is not as if science can function unless naturalism is correct. The naturalist position is not neutral for therapy concerning either set or setting, and a naturalist setting or instructions to the participants or in a post- experience session or questionnaire risks biasing participants as much as a religious presentation does — participants may be led to believe that a clinician's presentation in naturalist terms is proven scientific fact.

But Sandeep Nayak and Matthew Johnson [61] have the goal of providing a "common conceptual vocabulary" for psychedelic therapy and advancing a "secular framework [4]" of only naturalist terms [51]. Naturalists believe that only having an "unambiguously secular" framework will enable researchers to describe and explain psychedelic-enabled experiences without seeming to connect science with transcendent realities [5]. This may seem "more scientific" to a naturalist. However, a framework is not neutral that does not give the experiencers' own views an equal status. Imposing such a framework only seems to be a reasonable course of action to one already denying any non-natural options. A purely naturalist framework is one-sided and can distort the experiencers' view of their ASC experiences: providing questionnaires that are devoid of transcendent terms may be taken by the experiencers to mean that the experience cannot be of anything but the natural world — after their experience, experiencers

may reconceptualize their experiences in the preferred terminology even if the experiences did not feel that way. These problems are lessened in research when the focus is only on the phenomenological "felt" content of the experiences alone, but in therapy, this is a problem: the clinician's naturalism may diminish the effectiveness of the psychedelic therapy [8]. So too, it may result in a "spiritual bypass" in which the experiences are not integrated into the patient's life.

Many naturalists disparage the term "mystical" because "it suggests associations with the supernatural that may be obstructive or even antithetical to scientific method and progress [9]." But no experiences per se conflict with science — only possible *understandings* of their nature and significance may conflict. And naturalists may give a naturalist interpretation of mystical experiences in which the experiences are taken seriously as more than hallucinations. Indeed, some prominent naturalists — e.g., the philosopher Bertrand Russell and the physicist Alan Lightman — have had mystical experiences without giving up their naturalism or agnosticism. And positive understandings of mystical experiences as cognitive that are consistent with naturalism have been advanced [22, 62-65]. For example, the sense of oneness is explained in terms of the natural mind simply being empty of content. A sense of connection is explained in terms of the experiencer overcoming a sense of a "self" existing independently of the rest of the natural world — all that happens during a mystical experience is that the area of the brain responsible for a sense of a boundary between the sense of a "self" and the rest of the universe receives less input and the area attaching importance to events is more active, and so mystics naturally feel without a separate "self" and feel more connected to the universe, which in naturalistic metaphysics we in fact are. Broader explanations can also be given. For example, Jussi Jylkkä [64] proposes panpsychism to explain the claim that we are merely "waves on a sea of consciousness" that gives consciousness and naturalized mystical experiences fundamental roles in our understanding of the universe.

In his philosophy of psychedelics, Chris Letheby [66] presents a "naturalized spirituality" supported by a neurocognitive theory that can account for the transcendence of the sense of a discrete experiencing "self" (i.e., a theory in which a "self" does not exist but is only a mental construct), feeling connected to others and the world, heightened emotions and awareness, and in which psychedelic-enabled experiences have a transformative impact. This spirituality also presents a meaning of life, all within a "disenchanted" naturalist worldview congruent with science. Thus, psychedelic-enabled experiences may give genuine insights into reality that transform the experiencer [22]. He believes that this will explain why these experiences are the key causal factor giving rise to the sense of well-being and the other psychological benefits of psychedelic therapies, and that also will get around the "comforting delusion objection [67]" that clinicians should not utilize metaphysical beliefs in a therapy session that they believe are wrong regardless of any pragmatic value.

More generally, there now are also "religious naturalists" who reinterpret monotheistic language into naturalist terms — e.g., "God" becomes only the laws of nature. Such naturalists highlight awe and wonder at the majesty of nature, even though mystical and psychedelic-enabled experiences do not appear to play a major role in this religiosity [68].

Sarah Lane Ritchie [69] connects panpsychism to psychedelic-enabled states and spiritual flourishing. Thus, this secular mysticism changes the understanding of mystical experiences. However, it can still support the idea of "mystical insights" as genuine and experiential, even if no transcendent realities are involved rather than as

spurious insights fabricated under the influence of hallucinogens. This may also lead to the general acceptance that the term "mysticism" need not carry non-naturalist connotations. Naturalists rightly point out that mystical experiences are open to the same type of examination as any experience — their religious impact does not make them off limits — and it is epistemologically legitimate for scientists to advance explanations of the mechanics of the brain during the experience that differ in type from metaphysical explanations of the source and significance of the experiences. Mystical and psychedelic experiences are as open to scientific explanations as any other experiences. In principle, neuroscience can give as complete an account of what is occurring during an ASC experience or state as it can for any conscious event. Thus, consciousness research has no "psychedelic exceptionalism [5]." Nevertheless, when it comes to presentations to patients and participants in psychedelic studies, there also is no "naturalism exceptionalism."

THE CONTRIBUTION OF MYSTICAL EXPERIENCES TO THE SCIENCE OF PSYCHEDELICS AND CONSCIOUSNESS

Despite the rise of such positive naturalist understandings of mystical experiences, most naturalists may wish to exclude mystical experiences from consciousness studies as no more than hallucinations that tell us no more about how the brain works than other hallucinations. Mystical experiences for many are simply "metaphysical hallucinations [67]" — experiences are perhaps psychologically convincing to the experiencers themselves but of no more interest to scientists than other hallucinations. Moreover, perhaps therapists should embrace "mystical fictionalism [70]" as long as positive results arise. But can the study of mystical experiences add to general psychedelic and consciousness research?

Mystical experiences are more limited in what they can contribute to psychedelic research and to the study of consciousness than what some advocates of psychedelics claim. In particular, these experiences do not explain the relation of the mind to the body, show the true nature of consciousness, or overcome the "hard problem" of why subjectivity is attached to some physical events. In one study, David Yaden and his collaborators concluded that psychedelics are unlikely to provide information relevant to the hard problem [13]. Mystical experiences are exotic cases that add to the pool of data to be studied. However, they remain merely another type of experience or state, even if they are open to interpretations in terms of transcendent realities. So too, mystical experiences, in general, do not prove that consciousness is independent of the brain or matter in general as long as a naturalist explanation of these experiences in which consciousness is either identical to the brain or is a naturally emerging property is a viable alternative [22, 62]. As Matthew Johnson [4] also concludes, to date, psychedelic science may not have provided substantial advancement in our understanding of either the easy or hard problems related to consciousness. Yaden and his collaborators called for "epistemic humility" on this topic in psychedelic studies [13]. Neuroscientists generally adopt a "methodological materialism" in which they tend simply ignore the hard problem and use the term "consciousness" to refer to a wide array of the contents of the mind in general (e.g., perception, thoughts, and emotions) [13].

But mystical experiences can contribute to the study of consciousness in several ways. Most importantly, the different types of mystical ASC experiences and states of consciousness add to the spectrum of consciousness. Thus, they must be accounted for in developing models of consciousness or models of how the brain works in underlying subjectivity, whether mystical experiences

are cognitive or not. Even if they have no causal properties, their presence must be considered. These experiences may be like the high-energy physics that caused physicists to revise Newtonian physics [71]. In particular, the issue of whether a sense of "self" is necessarily part of all human experiences is debated today in the philosophy of mind [72, 73]. Some research suggests that a sense of "self" is not necessary for consciousness [46]. Chris Letheby [22, 65] also defends the possibility of a truly selfless awareness against the claim that all awareness must be to someone — a sense of ownership or "for-me- ness" to all experiences — and thus there must be an experiencing "self." That is, *subjectivity* is necessary for any experience but not necessarily a separate ontological entity called the "*self*." The sense of "self" may be an illusion. It appears that psychedelics disrupt the neural underpinnings of a sense of "self," and mystical experiences deconstruct the sense of an isolated "self" leading to a possible psychological transformation. Thus, the experiences of selflessness may provide experiential input not only on whether all experiences imply that there must always be some self-awareness, but also on the ontological question of whether there is a phenomenal "self."

There may also be a state of consciousness devoid of all content except consciousness itself — a "pure" consciousness. Whether a state of consciousness truly empty of all diverse content is in fact possible is a matter of debate in philosophy [74]. The study of "pure" consciousness or awareness has become an increasingly important subject of empirical and philosophical research on consciousness [75]. Whether such a consciousness is a core consciousness that is present in all states of consciousness or is only one state of consciousness would be an issue, but in either case studying a state of consciousness by free of the usual content may prove of value for understanding the nature of consciousness.

Mystical experiences can also contribute to science in other ways. First, the brain states underlying introvertive mystical experiences with diverse content may contribute to scientists' understanding of vision (through the vividness of these experiences), how information is integrated, how some cognitions are impaired, the sense of unity to consciousness, and other supposedly "easy" problems of consciousness [76]. Second, the experiences may expose something of the subconscious layers of consciousness. Mystical experiences may also help the study of the brain. For example, the experiences may add to the study of neuroplasticity [77] and neurotransmitters.

All of this is part of the broader issue of the nature of consciousness. Mystical and other psychedelic-enabled states and experiences may require some remodeling of the nature of the mind, even though to date, these states and experiences have done less than many advocates of the claim. Indeed, in the end,, these experiences and states may only increase the mystery of consciousness.

CONCLUSION: SITUATING MYSTICISM IN PSYCHEDELIC THERAPY AND RESEARCH

To sum up: proponents of disengaging mysticism from psychedelic therapy have not made their case, and as long as psychedelic-enabled experiences appear to be part of the beneficial effects of psychedelic therapies, experiences appropriately labeled "mystical" are part of the therapeutic picture and the explanations of the effects. Thus, mysticism cannot now be expunged from broader psychedelic research. Scientists can accomplish their explanatory task without mysticism introducing a collision of science and religion or surreptitiously smuggling non-natural transcendent realities into their explanations. Mystical concepts may need to be clarified for purposes of psychedelic science, but

mystical experiences do not per se conflict with science. Mystical experiences are open to naturalist understandings, but as long as consciousness is part of the picture in psychedelic studies, it is not obvious that these experiences must be seen only in naturalist terms. However, the "applied mysticism" of psychedelic therapy and research has less potential in addressing basic issues of consciousness and the mind than many advocates of psychedelics currently assert — the role of mystical experiences is a subset of the general problems of consciousness, not their solution. Nevertheless, if a "new paradigm" in therapy that treats psychedelic-enabled experiences as causal does become mainstream, the study of mysticism should become part of the training of clinicians and researchers in psychedelics studies.

AUTHOR INFORMATION

Richard H. Jones Ph.D.; J.D.
(rhjones2488@gmail.com)

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