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# The Journal of *Psychedelic Psychiatry*



- Educational Pathways for Psychedelic Practitioners
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- Response to ICER and the FDA Advisory Committee on MDMA Approval



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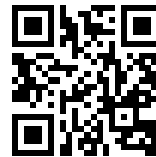
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# Educational Pathways for Psychedelic Practitioners

Raquel Bennett, Psy.D.

## **Abstract**

As the psychedelic renaissance continues to proliferate, there is a tremendous need to increase the number of skilled providers for psychedelic services. This article describes and compares several possible pathways for educating and supervising psychedelic practitioners, including certificate programs and creating a new credential (license to practice). This article also considers the needs of psychedelic practitioners who are already licensed healthcare professionals, as well as the needs of practitioners who were formerly underground guides during the psychedelic prohibition. The objectives of this article are to help readers understand the structural components of different educational pathways and the essential vocabulary for discussing this topic.

## **INTRODUCTION**

As the field of psychedelic medicine continues to erupt, the community at large continues to grapple with several essential questions about the use of these substances and the provision of psychedelic services. Do clients actually need a skilled practitioner to help them navigate this terrain, or is it okay to just hand out visionary medicine and let people figure it out on their own? If a skilled practitioner is needed, who is qualified to work with visionary medicines in a safe way? In other words, what training is essential for psychedelic practitioners? Further, what structures need to be in place to support the educational needs of these practitioners, ensure consistency across different training programs, and generally support safe practices in the field?

Discussion about the training and oversight of psychedelic practitioners is often hindered by semantic confusion. What exactly is the difference between being accredited, credentialed, certified, or certificated? These words are sometimes used interchangeably, but actually have different meanings and implications. I was inspired to do a deep dive into researching possible educational pathways for psychedelic practitioners and the essential terminology associated with this

conversation <sup>[1]</sup>. I have summarized my findings below.

## **OPTIMAL VS. ADEQUATE CARE**

First, as we start thinking about creating infrastructure for psychedelic services on a large scale, it is necessary to pause and consider a foundational issue: making an explicit distinction between "optimal" care and "adequate" care. **Optimal care** is the best care that we can provide <sup>[2]</sup>. Optimal care often involves highly skilled labor, and it is often expensive. Sometimes it is necessary to accept a lower standard of care for financial and/or logistical reasons. **Adequate care** is "good enough" care, and it is almost always sub-optimal. So before we create new programs and structures, it is essential to contemplate whether we are intending to train practitioners to provide optimal care or adequate care? This is a philosophical question with far-reaching implications.

## **EXISTING STRUCTURES**

Next, it is important to understand the existing structures that are pertinent to healthcare practitioners. **DEA** is a federal agency that determines which molecules or substances are allowed to be studied, prescribed and

utilized. **FDA** is another federal agency that assesses the safety and efficacy of each molecule or intervention for a specific clinical application. The **insurance industry** looks to the FDA to decide what services will be covered (allowed and/or paid). **State boards** are responsible for issuing, renewing, and overseeing a healthcare provider's license to practice. State boards also receive, investigate, and take action on any complaints about the practitioner's professional behavior. **Malpractice insurance companies** provide financial coverage for practitioners in case of an adverse event. There are often narrow terms and conditions for what a malpractice insurance company will cover. If a malpractice insurance company refuses to cover a particular service, or if it is deemed that the practitioner operated outside of the scope of their license and training, this can be financially disastrous for the practitioner. In a nutshell, it is nearly impossible to create a credentialing program that does not take these existing structures into consideration.

## EDUCATIONAL PATHWAYS IN GENERAL

What exactly is a credential? A **credential** signals that the applicant has engaged in a course of study, demonstrated competence for a specific skill set, and has earned official permission (from local government) to offer that skill set as a professional service. A credential (or license to practice) is not a concept that can stand alone. Instead, credentialing is typically the endpoint of a training trajectory with multiple steps involving several independent entities:

First, trainees enroll in a **comprehensive training program**. Comprehensive training programs are designed to provide trainees with an intellectual grasp of the subject matter as well as a substantial set of practical skills. They typically value both breadth and depth of knowledge. Further, comprehensive

training programs typically have the following components: entrance requirements (prerequisites to apply); didactic coursework; supervised practical experience; and multiple assessments throughout the training to check the trainee's grasp of the material. Upon successful completion of the training program, the trainee is awarded a **diploma**. (For example, think of medical school, graduate school for psychotherapists, or nursing school.)

A diploma is more meaningful, and perceived to be of a higher caliber, if it comes from an **accredited** training program. Accreditation is awarded by an accrediting body to a program or institution; accreditation cannot be awarded to an individual. The accrediting body must be an independent organization which ensures the quality of a training program and consistency across similar programs.

The trainee can then use their diploma to apply to a **licensing body** for a license to practice (or credential). The licensing body may also require the trainees to pass an **external (independent) examination**. Licensing bodies typically also have a Code of Conduct for affiliated practitioners, and an Ethics Board for responding to complaints. They maintain a publicly visible list of affiliated practitioners and a list of disciplinary actions. (For example, think of the state boards.)

After a practitioner becomes licensed, they become eligible for **membership** in a professional organization. Professional organizations play an important role in providing networking opportunities, continuing education, and political representation for practitioners. (Many professional organizations also offer guidance and mentorship to pre-licensed trainees.)

Alternately, in the healthcare world, a **certificate** is added on to an existing credential. It could indicate that the trainee has completed a comprehensive training program, but more often it means that the trainee has completed a single course or a brief training<sup>[3]</sup>. A

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certificate indicates that supplementary training was completed, but it is not a credential by itself, because the educational organization lacks the necessary structural components to regulate practitioners. (An example of a professional certificate was the buprenorphine waiver, which essentially was an extra class that physicians needed to take if they wanted permission to prescribe that specific medication.)

Another option is to create a **specialty**, **sub-specialty**, or **fellowship** to further develop and refine a practitioner's skill set. A professional specialty is an additional certification that attests to advanced training. Again, it is added on to an existing credential; specialty training is not a credential by itself for the same reason that a certificate cannot be a credential. (Some contemporary examples include the Integrative Medicine specialty for physicians <sup>[4]</sup> and the Contemplative Medicine fellowship for healthcare providers <sup>[5]</sup>.)

A final option is to move an educational component away from being an optional add-on skill, and incorporate the skill set into the **required standard curriculum** for all practitioners. (An example of this is the shift away from having an additional buprenorphine waiver toward incorporating knowledge about opioid agonists into the required training for all prescribers <sup>[6]</sup>.)

### EDUCATIONAL PATHWAYS FOR PSYCHEDELIC PRACTITIONERS

Now that we have clarified the difference between a certificate and a credential (above), we can begin to grapple with what is needed in the exploding field of psychedelics. After surveying the educational landscape, I have concluded that different kinds of practitioners need different things at different times. In the short term, it would be wonderful to have accredited certificate programs for licensed healthcare professionals who want to work

with psychedelic medicines in their clinical practices. In the long term, it is extremely likely that education for working with visionary medicines and altered states of consciousness will be incorporated into graduate level training for all mental health professionals, and possibly for all healthcare professionals and allied health workers. Meanwhile, we should discuss the possibility of creating an alternate pathway to licensure for practitioners who were formerly underground psychedelic guides during the psychedelic prohibition.

### CERTIFICATES FOR LICENSED CLINICIANS

Creating a psychedelic certificate program is not structurally complex. The main thing that is required is the creation of a core curriculum (or standards <sup>[7]</sup>). This psychedelic certificate would be an optional add-on to the practitioner's license to practice, which would remain under the purview of the existing state boards. While this is the simplest solution, there are several noteworthy challenges. First, getting different certificate providers to agree on educational standards may be difficult because some treat their training materials as proprietary intellectual property. Next, a certificate for psychedelic medicine(s) could be recommended but not required unless there was collaboration with the state boards. But as things stand now, there is no mechanism for enforcing a certificate requirement; instead, holding a certificate would indicate a high level of training (similar to the FACS designation for surgeons <sup>[8]</sup>). Also, it would be good to create an alternate mechanism for assessing and certifying licensed practitioners who have many years of experience in working with psychedelic medicines already, so that they are not forced to enroll in costly and redundant training programs (i.e., a Grandfather Clause). An interesting question here is whether there would

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be one certificate for working with all visionary medicines or if there would be a separate certificate for each psychedelic medicine? Lastly, each state board would need to become knowledgeable about the special concerns and clinical issues that arise when a client is chemically induced into an altered state of consciousness (ASOC). A national consultation service could be really useful for this purpose.

Accreditation for psychedelic certificate programs is essential to ensure consistency across educational offerings <sup>[9]</sup>. Without accreditation, a certificate is essentially meaningless. Currently, a quick online search finds numerous psychedelic certificate programs that vary in length from seven hours (one day of study) to two hundred hours (one year of study). Obviously these programs are not comparable. As an interim solution (before accreditation is in place), it would be good practice for practitioners who completed a certificate program to clearly name the training organization and the number of contact hours.

### **CREDENTIALS FOR UNDERGROUND GUIDES**

Creating a legitimate credentialing program for unlicensed practitioners is much more structurally complex because it necessitates the formation of multiple other entities. It also needs to be mindful of the existing structures, which tend to be territorial for economic and political reasons. Nonetheless, it might be possible to create a comprehensive training program specifically for psychedelic guides with the same structural components mentioned above: entrance requirements, didactic classes, supervised practical experience, opportunities to demonstrate competence, and a diploma. Eventually it would be desirable to have accreditation for the training programs, but a collaborative council could work as a temporary solution. The

guides could then apply to be credentialed through an organization that has a Code of Conduct, an Ethics Board, and a list of credentialed practitioners. As various psychedelic medicines move toward legalization, it becomes more viable to create these structures. Note that the credentialing process needs to be attentive to technical skills and ethical conduct (behavior that does not cause harm to an individual or community).

In this vision, it would also be important to create a system where practitioners with many years of experience could request an exemption from each specific component of training. A portfolio model of assessment (as opposed to an examination model) might work well for this. (For example, portfolios are often used in the assessments of educators and professors.) This process would need to be done extremely thoughtfully because of the illicit nature of this work. It would likely be labor-intensive which would make it costly. Nonetheless, it should be possible to build a process that is rigorous, fair, and respectful of different ways of acquiring knowledge including formal education, apprenticeship, and/or personal experience <sup>[10]</sup>.

Note that no one in this country can legitimately claim to be "credentialed" as a psychedelic practitioner at this time, because the structural components for a credential simply do not exist.

### **MANY PATHS, ONE DESTINATION**

Currently, there is much debate about creating programs and structures to support practitioners who want to work with psychedelic medicines. How can we ensure that practitioners are competent, skillful and ethical? How can we include practitioners from many different backgrounds? While it is tempting to want to create one credentialing pathway for all psychedelic practitioners, this is not possible nor desirable. First, the practice of psychedelic medicine cannot be clearly



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delineated for a healthcare professional who is licensed already. (For example, where does the psychedelic work begin and end when it is embedded in the context of an on-going psychotherapy relationship? Where does medical management begin and end when a psychedelic substance is prescribed?) The edges of the field of psychedelic practice are blurry, and blend into other fields of professional practice, which makes it functionally impossible to have a separate licensing board just for psychedelic services. Next, it may not be possible to give official permission to a healthcare worker to practice outside the scope of their professional license. (For example, would the state boards allow a psychotherapist to assess and treat a medical emergency, even if they took a special class? Would the state boards allow an internist or a surgeon to offer psychotherapy services, even if they took a special class? Would the state boards allow an unlicensed guide to provide services that overlap with medical or mental health care?) As noted above, the existing structures are unlikely to tolerate professional cross-over.

Instead, there needs to be parallel educational tracks for practitioners from different backgrounds. There is substantial precedent for this already in healthcare. For example, there are multiple pathways to providing mental health services: one could train as a clinical psychologist, psychotherapist, or social worker. Similarly, there are multiple pathways to providing physical health services: one could train as a doctor of allopathic medicine, doctor of osteopathic medicine, physician's assistant, or nurse practitioner. Different kinds of practitioners in the same field largely do similar things in their everyday clinical practices despite having different academic degrees. Building on this precedent, it makes sense to have multiple pathways to providing psychedelic services, at least as an interim solution until these skills

are integrated into graduate level training more broadly.

## CONCLUSION

As psychedelic medicine moves from an obscure practice to a booming industry, it is clear that new standards and regulatory structures are needed for the benefit of both clients and service providers: the field needs mechanisms for ensuring a consistent standard of care and an appropriate level of professional conduct. This paper outlined multiple possible pathways for training and supervising psychedelic practitioners. One option is to create a full credentialing pathway for unlicensed practitioners; this would necessitate the formation of multiple organizations to provide the necessary structural components. Another option is to offer accredited certificate programs for practitioners who already hold a license to practice; this is the most pragmatic strategy for licensed healthcare professionals. I advocated for the co-existence of different pathways for different kinds of practitioners, based on the precedent that exists already in healthcare. Note that I have deliberately focused on the structural frameworks for the required components, not the content of the trainings nor the management of the organizations that are needed.

Ultimately, we need to acknowledge that psychedelic substances constitute an entirely new category of "experiential medicines." These psychoactive materials have the potential to create powerful alterations in perception, emotion, identity and/or somatic awareness. As such, the context in which the medicines are ingested becomes an important consideration in the overall experience. (This is unlike most conventional medicines, which probably work the same regardless of context.) The community clearly needs new training programs and educated regulatory bodies to assist with the safe provision of experiential medicines.

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### **ENDNOTES**

1. I participated in a panel discussion about credentialing psychedelic practitioners at the Psychedelic Science conference in Denver, Colorado in June 2023. The other participants in this panel were Nicole Buchanan, PhD (Chair); Angela Allbee, MPA; Shannon Hughes, MSW/PhD; and Scott Shannon, MD.
2. There is much active debate among providers as to what optimal care actually looks like for different psychedelic substances and for different sub-populations of clients.
3. Being "certified" means you have earned a certification of completion, whereas being "certificated" means that someone else has checked and confirmed your certification status.
4. Integrative medicine eligibility requirements. *American Board of Physician Specialties*. April 2023. <https://www.abpsus.org/integrative-medicine-eligibility>
5. Contemplative medicine fellowship. *New York Zen Center*. April 2024. <https://zencare.org/contemplative-medicine-fellowship>
6. The X waiver is officially dead. *Med-Page Today*. January 5, 2023. <https://www.medpagetoday.com/special-reports/features/102520>
7. As a starting place, I would look at this historic article: Phelps, J. (2017). Developing guidelines and competencies for the training of psychedelic therapists. *Journal of Humanistic Psychology*, Vol. 57, Issue 5. <https://doi.org/10.1177/0022167817711304>
8. Fellows (US and Canada). *American College of Surgeons*. April 2024. <https://www.facs.org/for-medical-professionals/membership-community/member-services/join/fellows>
9. There are several established entities that offer accreditation to healthcare trainings, including ACHC.
10. Much of what I know about working with ketamine was informed by my experience as a client in the psychedelic underground. I also studied psychedelic medicines under the mentorship of several teachers, and I earned a doctoral degree in Clinical Psychology. None of these experiences alone were sufficient to become a competent ketamine practitioner, but rather it was a combination of a broad knowledge base, specialized instruction, and personal experience that seem vital to skillful and ethical practice.

## Image Literacy: Preparation during Psychedelic Psychotherapy

Andrée Salom, MPS, ATR

### Abstract

The images that arise with classic psychedelics have an affinity to artistic expressions, for they involve the five senses. This text raises questions about the usefulness, for the client or participant, of exploring personal history (respecting imagery), familiarizing with images and non-verbal language, and developing comfort around images before a psychedelic experience. It also offers themes and concrete prompts regarding image literacy to consider during psychedelic psychotherapy preparation to facilitate the integration. Concerning imagery, choices and resources are available every step of the way.

**Keywords:** Imagery, preparation, integration, psychedelics, psychotherapy

### INTRODUCTION

Visual images converse without words and communicate through how they affect. Think of green, for example, and its range of expression in various hues alone: pistachio, lime, pear, pickle, mint, basil, olive.

Tensions establish an artistic composition in relation to content and style and are also present in psychedelic imagery: luminosities and shadows, centers and peripheries, sharpness and diffusions. There may be color, tone, line, shape, volume, texture, direction, movement, and size in both.

Classic psychedelics have an affinity with artistic expressions. The bond is visible in the petroglyphs of mushroom-topped figures, in the porous contours of ancient stone sculptures, in ritual objects made of clay, wood, and gold, and in outfit, ornament, and altar configurations; in the textures of textile arts and fresco paintings (Allegro & Swain, 1970)<sup>[1]</sup>; and in the work of visionary artists (Alex Grey, Allison Gray, Victor Escobedo, Android Jones, David Normal, Pablo Amaringo, etc.).

Not all imagery is visual, although, visual or not, it is intimately linked to sensations. Writers rely on language to create mental impressions emanating from our sensory experiences. Describing bitterness, softness,

mustiness, and pitch, besides intensity, can evoke memories and sensations and offer meaning. Accordingly, psychedelic aesthetics are also present in the non-visual-arts. They are, in the wisdom of storytelling and myth, in the literature of the members of the Club des Hashischins (Charles Baudelaire, Victor Hugo, Alexandre Dumas, Gerard de Nerval, Honore de Balzac, etc.) and in the writings of the Beat Generation (Jack Kerouac, William S. Burroughs, Allen Ginsberg, etc.). The psychedelic-image connection is palpable in traditional drumming, singing, *Icaros*, jazz, and dances worldwide.

Numerous studies have explored the connection between psychedelics, artistic expression, and creativity, encompassing a wide range of participants, including non-artists, visual artists, musicians, writers, architects, creative thinkers, scientists, and college volunteers<sup>[2-13]</sup>. Psychologist Betty Eisner incorporated post-session art as part of integration in psychiatric hospitals. Joan Kellogg (in Thayer<sup>[14]</sup>) classified mandalas, including those drawn after holotropic breathwork sessions, into 12 categories related to the life-death-life cycle. Stanley Krippner<sup>[15]</sup> studied the impact of psychedelics on the content, approach, and technique of art pieces. He gathered queries that analyzed art processes,

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production, and creative problem resolution before, during, or after psychedelic sessions.

Leo Zeff (in Stolaroff <sup>[16]</sup>) asked his clients to gather a series of biographical photographs before attending an individual psychedelic session. Baby ones, teen ones, and grown-up ones. Alone, bonding, family ones.

“Look at it a little while. You may not experience anything. It’s all right. Put it aside, pick up the next one, then look at it. If it provokes any memories, kinda sit with the memories a little bit, let them go where they want to go. Whatever feelings you have, allow them to be there. (p. 66).”

Zeff said that by gathering the prescribed list of pictures beforehand, individuals arrived at the session already “in the middle of their trip <sup>[16]</sup>” (p.66.) After the psychedelic experience, once again, he asked clients to contemplate their images of self. Biographical images started and ended voyages. They prompted content and then gathered it.

It is natural for psychedelics to be closely related to the arts. Imagery in the psyche (psychedelic, mental, somatic, oneiric, imaginative) or the paper carries symbols and metaphors. Alternatively, perhaps symbols and metaphors shape imagery –whisper, shout-out, meanings, or suggestions–. An image is an informer primarily through foreground, background, distance, closeness, heaviness, or wisp. It uses means to capture our attention, evoke sensation and emotion, and fuel flickers of cognitive thought.

### **IMAGE LITERACY DURING PSYCHEDELIC PREPARATION**

Given the richness of imagery during classic psychedelic journeys, the question posed here is: How can doctors and therapists assist clients in embracing their personal connection with images (and with their nonverbal languages) before embarking on a

psychedelic experience? Beginning with image literacy from the moment of preparation and doing so according to the uniqueness of each client may ease the experience and the posterior integration. Clients can discover that images are portals. However, images need not necessarily be used to induce content unless specific evocations are planned for and desirable. Familiarity with psychedelic images can encompass various domains.

### **PERSONAL HISTORY WITH IMAGES**

First, therapists can inquire about clients' previous engagement with images. We have alliances and animosities to artworks, dreams, memories, mental representations, and reflections from a mirror. Some of us can easily see or hear phenomena in our mind's eye or ear. Others of us can not. We may be able to easily grasp the theme of changing imagery or not, eagerly link images to spirituality, or, quite the opposite, understand them as unfavorable idolatry.

Whether we have effortless or challenging relationships with images and their meanings, they warrant exploration. Images will likely arise during a psychedelic journey, influence our mood, and carry personal information. An empathic stance towards the client is also empathic towards the client's history with images and the images themselves. Any content in an image may be welcome if there is trust that the content can be incorporated or worked through.

Accordingly, the therapist can reflect, help titrate, paraphrase, propose resources for emotional regulation, or encourage skills for meaning-making while embracing what shows up.

### **IMAGES AND ALTERATIONS DURING THE JOURNEY**

Second, decisions must be made about what information to offer clients about psychedelic imagery. Who will benefit from knowing the kinds of phenomena and alterations that can arise? Who might welcome the surprise? Psychedelic visions can vary widely and encompass bursts, squiggles, figures, kaleidoscopic displays, or no visual visions at all. Sounds range from nuanced, overblown, unintelligible, vibrational, or even silent. Touch, smell, and taste may be pleasant, painful, amplified, intensified, fluxing, or heightened. The senses can mix and combine during journeys (as in synesthesia), and perceptions from each of the senses (or from their combination) can be hallucinatory, according to Benny Shanon<sup>[17]</sup>.

Compassionate conversations can focus on managing expectations, potential disappointments, concerns or fears, and or on being available to explore what arises with curiosity. Acknowledging psychedelic phenomena as naturally unfolding and autonomous, can prompt relaxation. However, the readiness for biographical, spiritual, or vacuous themes may be explored.

Given the particular disposition of each participant, it may be useful to discuss the limits of mental imagery –their inability to physically harm the body, their immateriality, for example–. Regardless of the vividness, images remain just that: images.

### **RELATING TO IMAGES**

Third, mental imagery (and images) are inherently relatable, and we may learn to befriend them, even when they seem daunting, perplexing, and deeply felt.

Understanding alternatives may enhance trust, especially if an image is frightening or uncomfortable. Clients can learn that an image may be sought from a different perspective: closer, from above, shrunken, or diffused. Alternatively, images can be greeted and turned from (towards an image of

something else). Journeymen may appreciate the option of approaching images –rather than running from them–: to actively become part of a psychedelic experience –by opening the doors, riding the dragons, or going inside them “through the pupils” according to Cosimano, Richards, & Richards (2023)<sup>[18]</sup>,-- By being the energy. “The drinker may be outside the scene of the vision, statically inside the scene, or in movement within the scene<sup>[17]</sup>”, wrote Shanon (2002, p. 101). Again, there are options and resources in relation to images throughout. The following sections expand on the attunement to clients’ preferences and opportunities.

### **DISCUSSION: ENGAGING WITH IMAGES TO SUPPORT SAFETY, FROM THE START**

Broadening the repertoire of interactions that a person can have with psychedelic images, from the start, may facilitate both the journey itself and the subsequent integration, irrespective of the emotional charge of the imagery. Artistic expression is not the point. Exploring possibilities and understanding individual needs and inclinations in relation to interpretation can provide congruence for both client and therapist. Decisions must be made according to the uniqueness of each person’s essentials for wellness, engagement, and relaxation. Some, but not all, individuals may thrive with an in-depth array of information. A thoughtful selection regarding image literacy may support centered, safe, and serene states.

### **CHOICES FROM THE START**

Images during psychedelic psychotherapy are often regarded as life-affirming. They serve as a path towards wholeness whether they offer insight, crucial information, a new perspective, or exalted experiences.

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Clients may benefit from recognizing images' relationship with each of the five senses as a way to explore them. Inviting clients to connect to rising sensations may be useful before translating images into verbal narratives. On the other hand, images with high contextual content (memories, beliefs, expectations, intentions, etc.) can be slowly translated into emotions and sensations from higher-order cognition, according to Aquil & Roseman (2023)<sup>[19]</sup>.

Journeymen may want to engage with an image in empirical ways: "To participate in it, to enter into its imagery and mood, to want to know more about it, to understand, play with, live with, carry, and become familiar with [it]—as one would do with a friend<sup>[20]</sup>" (Hillman, 2013, p. 179). This approach may be appealing to animistic-minded individuals. It has some similarities with Native American and African cultures, which view images as from the spirit world: carriers of sacred information for the individual or the collective; they may be prophetic, healing, initiatory, or guiding.

Regardless of the approach towards meaning-making (and there are many: Freud<sup>[21]</sup>; Grof & Grof<sup>[22]</sup>; Hillman<sup>[20]</sup>; Jung<sup>[23]</sup>, etc.), it is essential to remind participants that they can decide what to share, how to share, how much to share, whom to share with, and when to share. They choose when to reveal an experience and when to keep it private (like a cherished gift).

Individuals may ask for questioning and prompting or very little intervention. Regardless of what they prefer, therapists can remind them to tend to what they need, for they always have options respecting imagery.

Concrete prompts for relating to visions before a psychedelic session (and after) may comprehend basking in their presence, free-associating, or visually contemplating<sup>[Table 1]</sup>. The bond may happen by animating dialogues with the images, giving them a voice, analyzing them, writing descriptions, or

developing artistic works about them (or as them). Literature that produces mental imagery, picture taking, art appreciation, image making or guided imagery, can be used as exploration and preparation tools. Like all articulation, image literacy leads to informed alternatives.

Individuals will require attuned, active listening and unconditional positive regard for their images. Compassionate present-moment witnessing can lead participants to trust their resourcefulness, personal voice, and innate wisdom. Furthermore, deep therapeutic bonds can be strengthened through common images in our minds. The terror or the transcendence lived, may be thus conveyed non-verbally. Images are doors to empathy.

### **PATIENCE IN THE PROCESS OF MEANING-MAKING**

Relating to images may be straightforward, random, or take time and patience. Knowing this may prevent post-journey disillusionment.

Some evocations are epiphanies and make sense quickly. They speak directly to the psychonaut, the dreamer, the maker, and the seer. Beyond or preceding the need for rational or linear thought, they yield an extraordinary experience. They emboss an imprint. An inkling may lead to action, a breakthrough, or change. Relating to an approachable image provokes an unfolding of meaning or a welcomed pleasantness.

Other iconographies, like the ones in enigmatic visions, take time to assimilate or to connect. It may be useful to inform clients that images may stem from unknown cultural traditions. That, maybe, we are foreign to the languages they propose. They might speak in a variety of tongues that include thoughts, emotions, feelings, sensations, impulses, and movement (Gendlin, 1998)<sup>[24]</sup> or be void-like and indescribable. Clients may appreciate knowing that the messages of some images

emerge slowly –as if in the intricate process of a pointillistic painting– or that parts of their content may be hard to interact with (we have all encountered monsters). Addressing charged topics with the proper care, time, and support is integrative.

Engaging with images intimately takes engagement and consistency, as does any relationship. In the face of gentleness, interest, or affection, images deliver substantial information during and after the experience. They may do so in subtle ways, perhaps sub-perceptual, perhaps in time. There is no rush, and not knowing is valuable. Despite the uncertainty, by developing comfort in, or tolerance of, their presence and influence, psychedelic imagery becomes approachable.

### **PERSONAL INTERPRETATIONS**

Explaining the therapist's frameworks and personal foundations around imagery provides clarity throughout. Nevertheless, the guiding premise should be about the approaches that serve the client best.

Clients can consider prioritizing personal interpretations rather than relying on those from a therapist, external diagnosis tools, or superimposed definitions. This may grant personal agency and celebrate innate healing intelligence. Meaning-making may be developed between an image and the individual who experiences it. Then, a camaraderie may unfold, an active engagement with personal visions, and possibly a commitment to them.

However, in certain contexts, external guidance may be clarifying, asked for, or even central: symbols are passed down generationally, discussed with the community, or taken to an elder for interpretation. A conversation about preferences can give the client a sense of agency in meaning-making from the start.

### **ONGOING RELATIONSHIPS WITH IMAGES**

Images may be both passing and, simultaneously, long-lasting. Understanding paradox may ease confusion. Information about psychedelic images' ephemerality can come as a relief. Therapists can teach clients to actively alter an image tangibly by working with a permanent marker over a photograph or drawing or through the process of collage. But imagery can also be altered in the mind. A memory may be touched on lightly, given a different outcome, visited with a protective part, seen in slow motion or very fast and or explored in the empathic presence of another.

Delightful psychedelic images' elusiveness can come as sad news. Some people may need reminding that an image's after-taste can be beckoning, lasting, more vivid than waking, or even life-altering. Depending on the goals of the client and the beauty of visions, therapists may emphasize that images can be incorporated into the mind and heart. If they are not captured, like a photograph, they may evaporate. Gratefully, images are like fluttering in aesthetics. Linking them to creative action will help keep them alive: Imagining, calling, describing, contouring, printing, or bonding them to a haiku or a three-dimensional object. Keeping images available (in perceptible form) can strengthen the dynamic relationship and maintain a connection for future reference. Images can be keepsakes and memory keepers, and when in need of a token or of a resource, they may be summoned.

Ongoing relationships with images, past the initial conversation with them or the first appreciation of them, can promote their integration or their ongoing flavor. Self-discovery, through exploring an image, can be fostered over time as meanings and resilience evolve. Not everyone knows, from the start, that images may lead to the change of a trait: images may remind us to saunter in nature,

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call a loved one, or feel into who we really are. Yet, encountering imagery and understanding the actions they insinuate can be learned. A newfound commitment and an awareness of lasting value can be fastened through their acquaintance

### *Consider Image Literacy During Preparation*

During psychedelic psychotherapy preparation, consider the following:

- Ponder on your relationship to images in general.
- See if symbols or iconographies have ever helped you transform moods or habits.
- Consider the pros and cons of looking at images before a psychedelic experience. If you decide that it is beneficial, choose the images carefully.
- Look into your patterns of meaning-making in relation to the non-verbal (pictures, songs, dance). Know that you can access the patterns that serve you and/or develop new ones.
- Think about your recollection of sensory details and emotion in relation to images (Do you remember your dreams? Do you have vivid memories?). Practice expanding your recall by looking at an apple and then drawing it without looking.
- Examine your grasp of a common theme in the face of changing phenomena—practice summarizing the main theme of a picture, a movie, or a text in one sentence. Title your dreams. Then, title your psychedelic journey. It may have more than one title.
- Look at an art image from a magazine, a movie, a dream, listen to music, or taste a dish. Notice what the experience of observation brings up in relation to smell, touch, taste, sound, and sight—practice describing the experience in writing.
- Use active imagery as a practice. See how you relate to imagery, and if trust in emerging phenomena can be further developed.
- Investigate your alliance to dreams, daydreams, nightmares, flashbacks, mental images, pictures, images aroused by texts, and your personal bond with metaphors.  
Recognize or develop strategies useful for dealing with difficult images so that you may have exercises available when you need them
- If a mental image is frightening or uncomfortable, you may approach it from a different perspective: get closer, see it from above, shrink it in your mind, change its color, or shift between it and an image of beauty and joy.
- Describe, in detail, an image that has served as a resource in the past. See if you can find more images that are resources from the psychedelic experience after.
- Notice and describe the effects of an image from a dream or painting on your body. You may choose to do the same with psychedelic images to explore the somatic information.
- See if doodling on big pieces of paper, or small, can shift your bodily sensations. Explore the difference between making round, linear, angular, vertical, and horizontal traces. What soothes you? What materials work best?
- Develop openness towards your reading of an image. The meaning may expand.
  - Practice free-associating around an image.
  - Animate a dialogue with an image and give it a voice.
  - Speak as the image.
  - Write descriptions or develop artistic projects about it.
  - If you wish, analyze it cognitively. Ask yourself what the image can



## Image Literacy: Preparation during Psychedelic Psychotherapy

teach you about yourself, others, or the world.

- Explore the sensations, emotions, and thoughts about an image (in that specific order or vice versa).

Draw a circle and, in it, a sketch, a painting, or an illustration of an experience. You don't need artistic ability, just oil pastels, crayons, or pencils. Perhaps start with a texture, a color, a trace. Trust the process.

- Decide if it is beneficial to translate an image into art, and plan how to do so, and when. There is no rush for additional actions; waiting before making any important life decisions is advisable. Micro-steps in change can lead to new destinations (Mary Cossimano, 2023)<sup>[25]</sup>.
- If you wish, have images available (in perceptible form –make them, write about them, record them, recollect them, document them–), for future reference.
- Consider the pros and cons of telling about a psychedelic image versus keeping it private for self-care. Consider who to share with, if anyone, when, and how much to share. If you do, share an image and explore the mutuality around it.
- Consider, with trust, your own interpretations and your felt sense of an image.
- If you want others' interpretations of an image, take what serves you and let the rest go.
- Offer images spaciousness.  
Give yourself time to relate to an image.  
Let your relationship with images evolve

### CONCLUSION

In psychedelic psychotherapy, a person-centered approach can provide choices (and resources) related to image literacy from the start to support a sense of safety and comfort. Exploring relationships with images makes it possible to diminish fears, increase agency and trust, fine-tune expectations, develop skills for the journey, make sense of what

may arise post-experience, and understand the possibilities of reshaping images or having ongoing bonds with them. Image literacy can focus on the benefits of being curious in the presence of any mental and somatic phenomena that may occur.

Whether in matter, in the mind's eye, or produced by molecules, images are holdable, watchable, tastable, smellable, and hearable. They reverberate through various dimensions and can synthesize somatic, emotional, mental, social, ecological, animistic, cross-cultural and or spiritual themes. Through a relaxed familiarity, imagery can be an agent for “altered traits,” expanding transformation, and past altered states (Smith, 2003, p. 97)<sup>[26]</sup>. Being conduits for participation, they provide an expanded array of experiences for change.

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# Anti-inflammatory Effects of Ketamine in PTSD: A Review

Ashu Agarwal, M.D.

## INTRODUCTION

Post-traumatic stress disorder (PTSD) is a mental health condition that affects people who have experienced a significant traumatic event. Current pharmacotherapies offer small to modest benefits over placebo, and residual symptoms are to be expected. In recent years, ketamine has been studied as a potential treatment for PTSD. Clinical trials have found that ketamine can provide relief from PTSD and PTSD-related conditions with minimal side effects.

The pathophysiology of PTSD involves dysregulation of the stress response pathway. Ketamine has been shown to modulate the stress response pathway, which may contribute to its therapeutic effects in PTSD. This review aims to explore the current literature surrounding ketamine's potential to reduce PTSD symptoms through modulation of the stress response pathway.

## BACKGROUND

### PATHOPHYSIOLOGY OF PTSD-STRESS RESPONSE PATHWAY

PTSD is a psychiatric disorder that can develop after experiencing or witnessing a traumatic event, characterized by symptoms such as intrusive thoughts, avoidance behaviors, and hyperarousal. Symptoms of PTSD are hypothesized to represent the behavioral manifestation of stress-induced changes in brain structure and function.

Stress regulates and can cause dysregulation of the stress response pathway, which includes the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system (ANS), and the immune system. These systems interact extensively to maintain homeostasis in the face of stress on the individual.

PTSD symptoms result when an acutely traumatic event causes an over-reactive adrenergic response, creating abnormal and maladaptive neurological patterns in the brain. These patterns can persist long after the event that triggered the fear, making an individual hyper-responsive to future fearful situations.

## HPA AXIS CORTISOL

Although it is colloquially known as the "stress hormone," cortisol regulates the body's response to stress, affecting several aspects of the body. Individuals with PTSD following a single traumatic event tend to have lower basal cortisol levels than healthy or trauma-exposed individuals without PTSD<sup>(1)</sup>. This is in contrast to those suffering from depression or chronic stress, for whom cortisol levels are found to be higher than the average population<sup>(2)</sup>.

Amongst its many functions, cortisol is responsible for negative feedback on the HPA axis, downregulating the production of corticotropin-releasing hormone (CRH) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary. Studies of individuals with PTSD find low secretion of cortisol and high secretion of catecholamines in urine, with a norepinephrine/cortisol ratio consequently higher than comparable non-diagnosed individuals<sup>(3)</sup>. Due to cortisol's negative feedback functions in restoring homeostasis, a lower level of cortisol perpetuates a longer and more distressing response to trauma, increasing the likelihood of developing PTSD. The blunted cortisol response in PTSD is attributed to an enhanced HPA feedback function<sup>(4)</sup>. Lower basal levels of cortisol increase the sensitivity of glucocorticoid receptors (GR) in PTSD, leading to a progressive sensitization of the HPA axis<sup>(5)</sup>.

### **PTSD INFLAMMATION**

Cortisol plays a role in suppressing immune and inflammatory reactions, protecting from an excessive immune response, and reducing inflammation-related tissue damage. Dysregulation leads to hyperactivity of the immune response in the face of a stressor. Furthermore, Immune signaling contributes to regulating the HPA axis and other neurobiological processes that modulate affective behavior in the face of stressor exposure. Elevations in proinflammatory cytokines, including interleukin 1 $\beta$ , interleukin 6, tumor necrosis factor  $\alpha$ , and interferon  $\gamma$ , are associated with PTSD <sup>[6]</sup>.

Cortisol binds GR on immune cells, inhibiting further transcription of pro-inflammatory cytokines and limiting inflammatory damage. However, stress-induced HPA disruption may result in decreased cortisol-mediated inhibitory feedback of cytokine production with subsequent prolonged exposure to inflammatory cytokines and disruptions to multiple neuronal functions <sup>[7]</sup>. Another consequence of the combined HPA axis dysregulation and pro-inflammatory state may be to compromise the glia function responsible for maintaining synaptic glutamate homeostasis, resulting in neurotoxic elevations of extrasynaptic glutamate levels <sup>[8]</sup>.

### **KYNURENIN PATHWAY**

The kynurenin pathway is responsible for the production of coenzyme (NAD<sup>+</sup>). Tryptophan is one of the primary metabolites in this pathway, accounting for 95% of tryptophan catabolism <sup>[9]</sup>. Inflammation, as seen following an acute traumatic event, induces activation of the kynurenine pathway, resulting in less availability of tryptophan for the biosynthesis of serotonin and, instead, a shift towards the production of kynurenine and downstream neurotoxic metabolites. This leads to decreased available serotonin and neurodegeneration.

Inflammatory cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , are known to upregulate the enzyme indoleamine-pyrrole 2,3-dioxygenase (IDO), which converts tryptophan into kynurenin <sup>[10]</sup>. The activation of IDO results in a decrease in tryptophan concentration and an increase in several metabolites, including neurotoxic quinoline acids <sup>[11]</sup>.

### **KETAMINE IS AN EFFECTIVE AGENT IN THE REDUCTION OF PTSD SYMPTOMS.**

Ketamine is a dissociative anesthetic that has been used for decades as a pain reliever and anesthetic. It is a non-competitive inhibitor of the glutamate N-methyl-D-aspartate (NMDA) receptor. In recent years, ketamine has been studied as a treatment for mental health conditions. While a majority of research involving ketamine as a psychopharmacological agent has explored the treatment of depression, several clinical trials have investigated the use of ketamine in the treatment of PTSD.

Clinical studies of ketamine for the treatment of PTSD have found a significant reduction in PTSD symptoms with minimal side effects. A proof-of-concept, randomized clinical trial (RCT) published in 2014 found that ketamine infusion was associated with a significant and rapid reduction in PTSD symptom severity, compared with midazolam, when assessed 24 hours after a single IV infusion <sup>[12]</sup>. A follow-up RCT in 2021 examined repeated ketamine administration for chronic PTSD, which found that sixty-seven percent of participants in the ketamine group were treatment responders. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions <sup>[13]</sup>. PTSD symptoms reduced by ketamine in these trials include hyperarousal, avoidance behaviors, and intrusive thoughts. Furthermore, ketamine has been found to be protective against recurrences of PTSD <sup>[14]</sup>.

## **KETAMINE**

There are several mechanisms by which Ketamine may reduce PTSD symptoms through effects on the stress response pathway.

## **KETAMINE DECREASES HPA SENSITIVITY**

Research has shown that ketamine can modulate the hypothalamic-pituitary-adrenal (HPA) axis, which may contribute to its therapeutic effects. In mouse models, Ketamine increased GR expression in the hippocampus of stressed mice, thus normalizing HPA axis responses <sup>[15]</sup>. Recent separate pre-clinical studies have reported how ketamine reduces HPA axis hyperactivity by decreasing the corticosterone response in male mice <sup>[16]</sup> and that ketamine (but not fluoxetine) reverses stress-induced GR receptor impairments and dendritic branching loss in the ventral and dorsal dentate gyrus regions <sup>[17]</sup>. Ketamine also increased cortisol levels in a double-blind, placebo-controlled study. In this study, low-dose ketamine produced a dose-dependent increase in cortisol production, with a twofold increase at a concentration of 165 ng ml<sup>-1</sup> <sup>[18]</sup>.

## **KETAMINE MODULATION OF THE INFLAMMATORY PATHWAY**

Studies have found that Ketamine can decrease heightened inflammation in animal models and human blood in vitro <sup>[19]</sup>. Rodent studies provided strong support for ketamine-induced decreases in pro-inflammatory cytokines, namely in interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$  <sup>[20]</sup>. In human models, Ketamine was shown to inhibit immune reaction-induced proinflammatory cytokine production, including nuclear factor  $\kappa$ B, and to decrease blood levels of tumor necrosis factor- $\alpha$ , interleukin 6 (IL-6), C-reactive protein, and inducible nitric oxide synthase <sup>[21]</sup>. Ketamine exerts its anti-inflammatory actions

by directly affecting immune cells and inhibiting the production and release of inflammatory biomarkers, including pro-inflammatory cytokines <sup>[22]</sup>.

## **KETAMINE KYNURENINE PATHWAY**

Studies have examined the effects of ketamine on the kynurenine pathway, which reduces available tryptophan for serotonin synthesis and produces neurotoxic metabolites. Findings suggest that ketamine's anti-inflammatory properties reduce the activity of the kynurenine pathway. Ketamine-induced reductions of inflammatory markers were observed most commonly for the cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . The effect of ketamine in decreasing pro-inflammatory cytokines leads to the dampened activity of IDO and other enzymes in the kynurenine pathway, leading to increased availability and synthesis of neuroprotective kynurenic acid and a decrease in neurotoxic quinolinic acid <sup>[11]</sup>.

A systematic review of the effect of ketamine on inflammation and the kynurenine pathway in depression found that ketamine appears to induce anti-inflammatory effects in at least a proportion of depressed patients <sup>[23]</sup>.

## **DISCUSSION**

Ketamine has emerged as a safe and effective treatment option for those suffering from PTSD. While the mechanisms by which ketamine alleviates PTSD are a topic of ongoing research, current models suggest a large contribution from ketamine's modulation of the stress response pathway, aiding in the restoration of homeostasis between the HPA axis, autonomic nervous system, and the immune system.

Ketamine regulates the stress response at several points. Low basal cortisol levels are implicated in sensitization of the HPA pathway, i.e., increased glucocorticoid receptor sensitivity, following an acutely traumatic

event. This leads to the upregulation of subsequent inflammatory activation in PTSD. Ketamine, in mouse models, has been shown to effectively “reset” the sensitivity of the HPA axis by decreasing the corticosterone response. Ketamine has been shown, in a double-blinded, placebo-controlled study, to increase cortisol levels, which may contribute to the downregulation of GR sensitivity. With decreased HPA axis sensitivity comes an attenuation of the unregulated feedback loop of neurotoxic inflammation and adrenergic response.

Ketamine has also been found to exert anti-inflammatory actions by directly affecting immune cells and inhibiting the production and release of inflammatory biomarkers, including pro-inflammatory cytokines. By binding GR on immune cells, ketamine inhibits further transcription of pro-inflammatory cytokines and limits inflammatory damage.

The kynurenine pathway, which forms the coenzyme NAD<sup>+</sup>, is the primary metabolic pathway of tryptophan metabolism. This pathway is upregulated with increased inflammatory signaling, as seen in PTSD, which leads to the depletion of tryptophan necessary to synthesize serotonin and increases the synthesis of quinolinic acid, an endogenous neurotoxin with multiple targets [24]. Ketamine is implicated in the downregulation of cytokine-induced activation of the kynurenine pathway, leading to increased serotonin and decreasing quinolinic acid, improving the neurochemical imbalance in individuals who have PTSD.

While this review focuses primarily on ketamine’s modulation of the stress response pathway seen in PTSD, there are several other mechanisms by which ketamine may reduce PTSD symptoms. Other areas of investigation include ketamine’s effects on the glutamergic system, BDNF release, and cholecystokinin release [25]. At the same time, efforts to elucidate the underlying mechanisms of ketamine continue trials press on to examine the

full therapeutic effects, risks, and optimal dosing to treat PTSD.

## **CONCLUSION:**

In conclusion, ketamine has shown promise as a safe and effective treatment for PTSD in several clinical studies, with the underlying mechanisms of these effects under investigation. PTSD pathophysiology is driven by dysregulation in the homeostasis of the stress response pathway. Ketamine may improve symptoms of PTSD by modulating the stress response pathway in the brain at several points, including desensitization of the HPA axis by regulating GR sensitivity, inhibition of pro-inflammatory cytokines, and regulation of the kynurenine pathway. While more research is needed to fully understand the effects of ketamine on the stress response pathway in PTSD, ketamine represents a promising avenue for the treatment of this debilitating disorder.

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## Response to ICER and the FDA Advisory Committee on MDMA Approval

Tyler Kjorvestad, MD and Joseph Pullara, MD

On May 14th, 2024, the Institute for Clinical and Economic Review (ICER) published an Evidence Report "Midomafetamine-Assisted Psychotherapy for Post-Traumatic Stress Disorder <sup>[1]</sup>" which stated that "the current publicly-available evidence for MDMA-AP is insufficient." The ICER MDMA report was one of the main pieces of evidence presented at a subsequent Federal Drug Administration (FDA) Advisory Committee meeting on June 4th, 2024. The Advisory Committee concluded 9-2 that the MAPP-1 and MAPP-2 trials did not prove the efficacy of MDMA-AP and 10-1 that the risks outweighed the benefits of MDMA-AP <sup>[2]</sup>. Both these votes are non-binding, but the FDA will take them into consideration at MDMA-AP's priority review session on August 11th, 2024. After the news broke, supporters of psychedelic medicine were rightfully disheartened, but before descending into despair, a critical analysis of the data that led the advisory committee to reach the conclusions it did must be undertaken.

All proponents of psychedelic medicine should read and analyze the ICER report in its entirety. Per ICER, it "is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system <sup>[1]</sup>."

Additionally, ICER asks three fundamental questions of any intervention <sup>[3]</sup>:

- Based on the evidence, how much better is a new treatment at extending or improving patients' lives?
- What would a fair price be, based on the clinical evidence as well as patients' perspectives about the outcomes that are most important to them?
- And how can patients, clinical experts, and insurers translate the evidence into insurance coverage that ensures the best patient outcomes?

Before diving into the actual report, it is essential to recognize these motivations and intentions as they form the foundation for the report's structure and analysis. Comparative analysis of a novel intervention against the current standard of care is a worthy endeavor and, when done well, is an invaluable resource for the entire healthcare industry. However, attempting to determine a "fair price" undoubtedly slants the discussion away from the efficacy of the intervention and toward that of public policy. The FDA rightly does not concern itself with whether a drug will be priced at a "fair price" but rather the trade-off between the risks and benefits of the proposed intervention based on the clinical data <sup>[4]</sup>. The price of a drug, whether deemed "fair" by those at ICER or elsewhere, is a decision that is best left to the market to determine rather than central planners who believe they can account for most or all of the value of an item in their models.

Turning now to the ICER report, the first thing of note is that no Psychiatrist or Psychologist was involved as an ICER Staff or Consultant nor in the modeling group. Being mindful of the appeal to authority fallacy,

having both a Psychiatrist and a Psychologist in the authorship would have added significant credibility, especially because MDMA is a novel psychiatric drug and MDMA-AP is a novel psychotherapy approach. The lack of familiarity with psychiatric and psychological interventions and the shortcomings of psychiatric clinical trials was highly evident when reading the report. It should be noted that one of the three expert reviewers was a Psychiatrist but disclosed that he is the inventor of a competing augmented reality intervention for PTSD management. No psychologists were reported as expert reviewers. The following were the primary concerns identified in the ICER report regarding MDMA-AP:

- Ethical Concerns
- Trial Design and Conduct
- Safety Concerns
- Frequency of Benefits and Harms

Examination of these concerns in greater detail, from the most valid to the least valid, will follow.

Regarding ethical concerns this was the most concerning aspect of the report, specifically the misconduct and abuse of a clinical trial subject in 2015. The two therapists assigned to the patient deviated from the protocol during the clinical trial and allegedly engaged in a physical relationship with the patient after the trial was over. To their credit, the Multidisciplinary Association of Psychedelic Studies (MAPS), which sponsored the trials, reported this to Health Canada, the FDA, and IRBs and banned the therapist from all future trials. They also made significant changes to their policies, training practices, and reporting standards. Any time a patient is harmed by a practitioner, the processes and standards that allowed this to happen should be thoroughly evaluated, and substantial changes should be made to reduce the likelihood of an event like this happening again. However, before jumping to the

conclusion that a breakthrough therapy should not be approved, it is prudent to place this boundary violation in the context of the broader Psychotherapeutic enterprise. The MAPP-1 and MAPP-2 Trials collectively enrolled 194 total patients, only the patient above experienced a boundary violation for a rate of 0.5%. This rate should be compared to the rate of boundary violations within the general psychotherapy environment. A 2007 article<sup>[5]</sup> found the following: "Most research has involved self-report surveys of mental health professionals and has demonstrated a prevalence of 0.9–12% with a median figure of about 6%. Generally, male therapists are more involved in these violations than are female therapists with a ratio of about 3:1."

The ICER report also raised other ethical concerns, including research participants feeling pressured or encouraged to suppress adverse outcomes and overreport the positive attributes of MDMA-AP. However, while ICER claims they had firsthand and secondhand reports, they do not offer any other corroborating or substantive information. When pressed on this issue, ICER has responded by saying their refusal to make the public the source of the information "does somewhat decrease the transparency we would typically want in an ICER report" and that "We cannot be certain that these reports were accurate<sup>[6]</sup>." Taking all of this in totality, it is difficult if not impossible, to determine what is hearsay and what could be a credible piece of information. The FDA, through its standard monitoring programs, should be able to identify and thoroughly investigate these issues, but until such time that this information is validated, it should not be used as a rationale to prevent the approval of MDMA-AP. Lykos should have every right to address the criticism as well as note any particular credibility issues that any of the anonymous whistleblowers might have, and the FDA can then weigh those arguments and make an informed decision.

## Response to ICER and the FDA Advisory Committee on MDMA Approval

Moving on to Trial Design and Conduct concerns, the ICER report takes particular aim at the use of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [7]. Again, this highlights the paucity of psychiatric and psychological involvement in the write-up of this report. As things currently stand, the CAPS-5 is the most well-validated scale to use for PTSD symptoms and is considered the gold standard for clinical trials in PTSD. The ICER report expressed the following concern: "We heard from multiple people that the CAPS-5 measures of improvement failed to capture participants overall response to MDMA-AP. ... we repeatedly heard about participants experiencing improvement or resolution in the single trauma identified for the CAPS-5 measurements while new issues became overwhelming following MDMA-AP." What ICER appears to be missing is that most patients can and do have multiple traumatic events, but in both research and therapeutic settings, the researcher must specify their aim before they begin the intervention or treatment. Therefore, only one index trauma or one specific series of traumatic events may be selected for research purposes or targeted in the initial therapeutic sessions. Commonly, patients will experience an initial worsening of index trauma symptoms early on in trauma therapy as they voluntarily confront past events. This is an extremely common phenomenon across all exposure therapies, and patients are often counseled that this will be the case. Trauma therapy can involve going through the worst moments of a patient's life with a fine-tooth comb, and reliving those experiences may be nearly as difficult as living through the event itself.

Additionally, as a patient progresses through the index trauma, symptoms specific to the index trauma, such as re-experiencing symptoms or avoidant behaviors, will improve. However, if other non-index-related traumas are present, these may occupy or contribute more to the trauma symptom

burden. This likely occurs as a result of greater insight and the patient realizing just how much the traumatic events have impacted their lives.

It should be noted that this is not a drawback to the therapy but a necessary step in the healing process for the patient. Failure to adequately process trauma results in continued and often compounded symptom burden. As several of the therapists involved in the MAPP-1 and MAPP-2 trials wrote in response to these specific ICER complaints, "the accusation that it undermines the validity of the Phase 3 data supporting the use of MDMA-AP for PTSD could be leveled against any other clinical study using this outcome measure—which again, though flawed, is the gold-standard in the field of PTSD clinical research. We do not dispute that some participants may have experienced worsening psychological distress; however, secondary outcome measures (e.g., the Sheehan Disability Scale, the Beck Depression Inventory) and adverse event reporting (e.g., exacerbation of anxiety, suicidality, insomnia) would have captured that distress, even if it was not associated with the index trauma identified on the CAPS-5. Results from these secondary outcome measures did not show statistically significant worsening in the MDMA group; on the contrary, those results tended to favor active treatment with MDMA [8]."

Another primary concern raised by the ICER report surrounded the concept of functional unblinding, which means that patients and clinical trial staff could determine whether a patient was receiving MDMA or a placebo simply based on the effects of the drug. The adverse effects of the medications themselves mainly drive this. Furthermore, functional unblinding is almost to be expected during a psychedelic clinical trial that uses an active drug vs. a placebo. While placebo-controlled randomized controlled trials are an excellent way to determine if specific interventions are, in fact, effective, they are

not perfect for all therapeutic interventions, and psychedelic trials will likely need alternative trial designs to access efficacy <sup>[9]</sup>, especially within psychopharmacologic trials where placebo responses are noted to be exceptionally high and variable. A recent systematic review and meta-analysis published in May 2024 <sup>[10]</sup> highlighted the potential impact that placebos could have across several psychiatric conditions.

It should be noted that these trials did not include non-placebo arms making it difficult to fully rule out regression to the mean or natural disease course. However, it fits into the more extensive discussion about placebo response to psychiatric medications. A separate May 2024 article <sup>[11]</sup> noted the following: "The third and perhaps most significant factor driving trial failures in psychiatry is the high and growing rates of placebo response. One systematic review of 252 antidepressant trials found a consistent placebo response rate today that is now between 35% and 40%." Additionally, there is no way to blind psychological interventions as both the patient and the clinician are aware of the intervention. Understanding these constraints on psychotherapy research and the placebo issues raises the question of why ICER and others on the advisory committee felt this was such a consequential piece of information. Combining a psychedelic drug with a psychotherapy protocol makes it almost impossible not to have at least some degree of functional unblinding.

Furthermore, the FDA was and is aware of this issue and still chose to greenlight the phase 3 trials. This is based on precedent for other psychopharmacology interventions, including clozapine <sup>[12]</sup> and esketamine <sup>[13]</sup>. Esketamine, being the most recently approved and a psychedelic-like agent in its own right, provided a road map that MDMA-AP followed by utilizing independent third-party raters. Independent raters worked exceptionally well for the esketamine trials "[R]emote

raters practically duplicated site-based findings in MADRS score reductions, yielding a 92.9% predictive value for matching treatment responses and remission rates <sup>[13]</sup>."

The third primary concern identified by the ICER report surrounded the adverse effects of MDMA and the long-term consequences of MDMA, specifically on the cardiovascular system. The only long-term data on MDMA's cardiovascular effects comes from observational studies or murine models. The observational data is predominately from patients who were abusing MDMA or what they presumed to be MDMA. Recreational MDMA cannot and should not be used as an appropriate comparator to pharmaceutical grade MDMA with a predetermined dose-response curve with only 2-3 dosages being given about one month apart. Given its stimulant-like qualities, a suitable comparator for MDMA may be stimulant medications used in the treatment of ADHD. While these medications are typically taken daily or at least multiple times per week, they still do show the potential for longer-term cardiovascular disease. A recent article from November 2023 found the following: "[L]ong-term exposure to ADHD medications was associated with an increased risk of CVDs, especially hypertension and arterial disease <sup>[14]</sup>." While there may be other cardiovascular adverse effects such as valvular disease, arrhythmia, or heart failure, these will likely not appear in the short term of a clinical trial but rather will require diligent monitoring over the long term. The lack of long-term data on these issues, however, should not serve as sufficient rationale to preclude approval. The Risk Evaluation and Mitigation Strategy programs can require advanced cardiovascular screenings and monitoring prior to and during MDMA-AP treatment, and similar to Clozapine, long-term monitoring interventions could be instituted as well. However, like stimulant medications, a risk-benefit discussion between a physician and a patient should

occur, and shared decision-making should follow.

Finally, regarding the frequency of benefits and harm concerns, the ICER reports make nonspecific and veiled comments stating:

"It seems clear that some people with severe PTSD experienced substantial benefit in the MAPP trials. We spoke with some patients who reported experiencing benefits even in the face of important harms and, in speaking with experts, including experts quite skeptical of the safety of MDMA-AP, they reported hearing stories from patients who believe they were greatly helped by MDMA-AP. It is also clear that at least some people who participated in the MAPP trials experienced very severe harms. There seems to be some disconnect between the reporting of these harms in the clinical trials and what we heard from patients; however, it is possible that this is due to the timing of evaluation measures rather than deliberate attempts to suppress these reports [1]."

PTSD is a highly debilitating condition where up to 50% of patients do not adequately respond (a 50% reduction in symptom burden) to psychotherapeutic interventions [15], and only 20-30% of patients on psychopharmacologic agents achieve complete remission of symptoms [16]. Couple that with the necessity to take the medication every day and have continual exposure to antidepressants and their accompanying side effects and then compare that MDMA-AP, which reported a 46.2% rate (loss of PTSD diagnosis and CAPS-5 score <12) roughly 15-25% better than the standard of care antidepressant therapies and in total 71.2% of patients no longer met diagnostic criteria for PTSD. The contrast is incredibly striking, given that these results were after 2 or 3 MDMA dosing sessions and approximately 15 psychotherapy sessions.

Even if a regression to the mean of the effect sizes reported in the MAPP-1 and MAPP-2 trials is allowed, MDMA-AP still shows significant benefits over the current standard of care. As Dr. Thomas Sowell said, "There are no solutions, there are only trade-offs." This idea is at the crux of psychedelic research. Outside of the regrettable and unacceptable boundary violations that occurred with a single patient in the trial and possible but as of yet unsubstantiated concerns regarding biased reporting and influencing of study participants, there is no perfect or ideal form of a randomized controlled trial for the purposes of investigating the efficacy of a psychedelic compound. While other researchers have tried to utilize lower dosages of a psychedelic substance as a control instead of an inactive placebo to combat functional unblinding, this does not guarantee successful blinding and also introduces the possibility that even a microdose of a substance can exert a therapeutic effect. Finally, concerning safety, there exists a continuum from acceptable side effects to life-threatening ones. All MDMA-AP trials have shown that when pharmaceutically manufactured MDMA is taken in a therapeutic environment, it has transient side effects that are generally acceptable. Long-term effects must be assessed in a post-marketing environment, and extrapolations from recreational MDMA studies are confounded by a lack of quality control for the medications and the likely use of supra-therapeutic dosages. Recreational MDMA observational studies can point long term monitoring in a general direction in regard to the area of focus in the post-marketing analyses.

Additionally, the risk of MDMA must be appropriately weighed against the risks of continued antidepressant, antipsychotic, anxiolytic, and other pharmacotherapy used in the treatment of PTSD. Daily usage of multiple medications, often for years in the case of severe refractory cases, results in a

significant burden to patients and raises health care costs. If a medication can help the most severely ill with 2 or 3 administrations and decrease or eliminate the need to take medications daily and indefinitely with limited acute and intermediate side effects, the choice for most patients and providers is evident. Hopefully, the FDA will not lose the metaphorical forest for the trees as they attempt to parse out the data on MDMA-AP. While there are valid concerns, especially about boundary violations, the anonymously reported hearsay and vague indirect critiques leveled against the trial either must be substantiated or set aside. Taking anonymously sourced claims or assuming facts not in evidence is a fool's errand, but going a step further and using that information to discredit multiple studies showing significant benefits for patients with PTSD above and beyond those of the current standard of care would truly prove George Orwell correct when he said: "Some ideas are so stupid that only intellectuals believe them."

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