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Psychedelics
The Journal of Psychedelic and Psychoactive Drug Research

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Cover Art

An urban twilight scene depicting the intersection of modern society and psychedelic medicine's emergence into mainstream healthcare. The glowing digital display showing "5.1M" symbolizes the mid-range estimate of 5.1 million patients with major depressive disorder who could potentially benefit from psilocybin-assisted therapy according to research findings. The cityscape at dusk—with its gradient purple-orange sky and illuminated buildings—represents the transitional period in which psychedelic treatments are moving from experimental research into regulated medical practice. The taxi in the foreground suggests the journey toward new therapeutic destinations, while the various digital screens and urban elements reflect the complex healthcare system through which novel treatments must navigate. This visualization connects to the paper "An estimate of the number of people with clinical depression eligible for psilocybin-assisted therapy in the United States" by Syed F. Rab et al. on pages 26-30 in this issue, which analyzes potential patient populations for this emerging treatment modality.

This issue is now available at https://url.genomicpress.com/6rarafbd.

Genomic Press

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Recent publications cover topics such as the economic and public health implications of psychedelic therapies, the effects of ayahuasca on fear and anxiety, psychedelic treatment for anorexia nervosa and body dysmorphic disorder, and advancements, challenges, and future directions for treating resistant depression with psilocybin-assisted psychotherapy.

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EDITORIAL

Counting the uncountable: The critical quest to quantify psychedelic medicine's reach

Psychedelics March 2025;1(2):1–2; doi: https://doi.org/10.61373/pp025d.0005

In this second issue of *Psychedelics* (1), we feature on our cover the thought-provoking study by Rab, Raison & Marseille (2). That paper presents the first rigorous estimate of the potential demand for psilocybin-assisted therapy (PSIL-AT) in the United States. As psychedelic medicine moves from the periphery of psychiatric research toward the possibility, and now the reality, of approval by national drug regulatory agencies,[1] this analysis could not be more timely (3, 4). Understanding the size of the potential patient population eligible for PSIL-AT informs pharmaceutical development and the broader healthcare ecosystem, preparing to accommodate this emerging class of therapy.

By establishing a range of estimates, the authors bring welcome nuance to their methodology, steering clear of hyperbole and undue pessimism. They avoid overly broad assumptions that would be impossible to meet and exclusion criteria so implausibly narrow they are unlikely to occur in actual clinical populations. Their approach provides a credible framework for estimating incidence in a relatively narrow yet clinically relevant setting. Rab and colleagues' finding—that between 24% (using stringent criteria) and 62% (after adjustment for comorbidities) of individuals with major depressive disorder (MDD) or treatment-resistant depression (TRD) may be eligible for PSIL-AT—offers a crucial starting point for healthcare planning, one that has been sorely needed (2).

This study advances the conversation on psychedelic medicine in several ways. First, it acknowledges that not every individual with a depression diagnosis is automatically a candidate for PSIL-AT, pushing back against overly enthusiastic claims of psychedelics as universal remedies. Second, it illustrates how exclusion criteria can act as barriers to access, highlighting that decisions about who receives treatment are not merely clinical—they are public health decisions. Third, it draws a clear line between theoretical benefit and practical implementation: the potential of a treatment cannot be separated from the real-world constraints on its delivery.

Rab et al. identify alcohol and substance use disorders as key factors limiting eligibility in clinical trials. Their analysis is particularly sharp on this point. By showing that removing these exclusion criteria would significantly expand the eligible population, they raise a critical question: Should these conditions automatically disqualify patients—especially given emerging evidence that psychedelics may help those with substance use disorders?

While methodologically strong, the study does have limitations worth noting. The assumption that demand will arise primarily from those already receiving care may underrepresent broader interest once PSIL-AT becomes widely accessible. Additionally, the analysis treats exclusion criteria as binary—present or absent—whereas, in clinical practice, these are often subject to more nuanced judgment.

The authors are careful to emphasize that they are estimating potential demand. But between potential and access lies a complex landscape: insurance coverage, provider training, geography, and cultural attitudes. As Oregon and Colorado lead the way with state-level frameworks for psilocybin therapy (5), these estimates are no longer just statistics. They are planning tools, policy triggers, and moral signposts.

Oregon became the first U.S. state to legalize psilocybin for therapeutic use through Measure 109, which was passed in November 2020. The law established a regulated system for psilocybin services, including licensed service centers where individuals aged 21 and older can access psilocybin under the supervision of trained facilitators. Colorado followed in 2022 by passing Proposition 122, which decriminalized the personal use, cultivation, possession, and sharing of psilocybin mushrooms for adults 21 and over. It also legalized psilocybin-assisted therapies at licensed healing centers.

Yet, history offers a cautionary note as the field edges toward mainstream legitimacy. New therapies—especially those imbued with the allure of innovation—tend to reach the privileged first. Inequities are not incidental; they are systemic. Equity must be engineered, not merely hoped for. Future research must explore who qualifies for PSIL-AT and who receives it.

There are urgent next steps. Longitudinal tracking of real-world implementation in Oregon and Colorado can help validate or refine these projections. Cost-effectiveness analyses stratified by patient subgroups can support rational policy and reimbursement decisions. Clinical trials must evolve to include populations historically excluded—not recklessly, but with careful oversight—so that "evidence-based" does not become a euphemism for exclusion.

Rab et al. have done more than quantify potential demand. They have mapped out a terrain that psychiatry must now navigate—not only with data but with conscience. As we face an epidemic of depression and a crisis in psychiatric innovation, we cannot afford to miscalculate either our reach or our resolve.

What's at stake is not merely regulatory approval but a reimagining of what psychiatric care could become—when informed by innovative science, shaped by society, and governed by ethics.

Julio Licinio[1]

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[1]The Australian Therapeutic Goods Administration (TGA) approved the use of psilocybin for treatment-resistant depression and MDMA for PTSD, effective on 1 July 2023.

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INNOVATORS & IDEAS: RISING STAR

Alaina M. Jaster: Bridging the gap across preclinical and clinical disciplines in the psychedelic sciences

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Keywords: Psychedelics, serotonin 2A receptor, neuroplasticity, biomarkers, depression, substance use disorder, pharmacology, endocannabinoids, fear extinction, endocannabinoids, adolescence

Dr. Alaina M. Jaster is a postdoctoral scholar in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University. She currently serves on the trainee editorial board of *Psychedelic Medicine*, the journal for the International Society for Research on Psychedelics (ISRP), and is part of the Society's Diversity Equity Inclusion and Accessibility committee. Jaster is also part of the Science Policy Committee of Students for Sensible Drug Policy (SSDP) and co-founded a scientific communication website and podcast, *Psychedelic Brain Science.* Her research aims to understand the underlying molecular targets and mechanisms of neuropsychiatric disorders and substance use disorders. Her PhD dissertation focused on the serotonin 2A receptor's modulatory role in rewarding aspects of opioids and neuroplasticity across sexes. Most of her work uses translational methodology related to Pavlovian conditioning combined with techniques to measure and manipulate pharmacological factors involved in these diseases. Her current work focuses on the involvement of endocannabinoids in fear extinction, biomarkers of familial risk of depression, and psychedelic use among adolescent populations. Dr. Jaster is excited to engage in the Genomic Press Interview, looking deeper into her life inside and outside the lab.

Figure 1. Alaina M. Jaster, PhD, Wayne State University, USA.

Part 1: Alaina M. Jaster – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

This question is always tricky to answer because I did not realize the pivotal moments until I was already doing science. I did not link my personal history to my drive until I was well into college, but it makes sense now. I have a family history of addiction and have firsthand experience with drug use, including what it does to families and to people I care about. So, when I went to college and decided to study neuroscience and substance use, I did it because that's what I knew about, and I wanted to understand why some people choose drugs over other values and why some people don't have any issues with recreational use. I learned it is a lot more complex than that, but my entire life led me to this passion for learning about the mind and proving that your circumstances do not have to be the end-all-be-all.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

My trajectory is a little interesting because I did not really know I wanted to be a scientist, as I was never really exposed to that option. I knew about medicine because my mother was a nurse, but I wanted to be an artist in high school. I had little interest in sciences at school, except for my AP psychology class. So, in my senior year, I ended up touring Central Michigan University, where they showed a presentation on their neuroscience program and talked about the brain, which I thought was interesting. I told myself I could do it and wanted to prove I was not my family history. At the end of my undergraduate experience, I was trying to decide on being a counselor or going for a PhD in clinical psychology. Eventually, I decided through experiences working at an inpatient psychiatric facility that I was not ready for direct patient care. However, I still wanted to help people who were suffering from these horrible psychiatric illnesses. I ended up with a research assistant job at Wayne State University, where I worked with human postmortem tissue and genetics of opioid use, along with toxicology and pharmacology projects. This solidified my interest in drugs and how they change the brain.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

Honestly, ever since I was in high school, I thought psychedelic drugs were fascinating. The clinical trials with smoking cessation and decreased drinking following psilocybin came out when I was in my undergraduate degree, and I was just so excited to see psychedelics being used for treating substance use disorders that I knew I had to find a way to study this

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Figure 2. Alaina Jaster explores "Hilltop Trine," one of Thomas Dambo's "6 Forgotten Giants" sculptures in Hvidovre, Denmark (2017). The photo was taken during downtime from her summer neuroscience course in Copenhagen when she participated in an artistic treasure hunt to discover these large-scale public art installations throughout the city's western municipalities. This image captures one of Alaina's many explorations beyond the laboratory.

myself. Now, my studies are broader, focusing on the cannabinoid system as well, but it is just as interesting because cannabis has been shown to help a lot of folks with neuropsychiatric illnesses like depression.

What impact do you hope to achieve in your field by focusing on specific research topics?

I hope to expand our current knowledge of why and how drugs like psilocybin or cannabis have profound effects on people. It is essential to dig into those who respond and those who do not respond and figure out if some specific biomarkers or pathways are involved in these clinical outcomes. With this knowledge, we can better inform treatment strategies and drug policies that make sense.

Please tell us more about your current scholarly focal points within your chosen field of science?

The use of multidisciplinary approaches to understanding disease has only recently taken off, where many studies within the field of neuroscience focused solely on behavior or molecular pharmacology. However, with more people in the field and novel techniques, we can probe for things like biomarkers, the influence of specific cell types and their projections, and alterations in brain connectivity — all at once. My current focus is on using translational techniques and bridging the gap between preclinical and clinical research on neuropsychiatric and substance use disorders.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I am currently in my postdoctoral position, where I am learning so much about coordinating and leading clinical trials, teamwork, and positive work environments. Across my PhD and now my current position, one thing that I have found most important is allowing myself to enjoy the things I love outside of science. Another thing I have found across positions is that keeping a great lab notebook is an invaluable habit.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I think there is a shift in the community where people are becoming more tolerant and accepting of all walks of life, but there is still much work to do. A lot of folks go into science because they have a personal connection to their research questions, but a lot of people with lived experience (specifically with substance use and neuropsychiatric disorders) are turned away from the field or do not have proper access to the tools and help they may need to thrive within the scientific community. I think instead of hiding our personal experiences, we should foster a community that applauds openness and not refuse students or trainees because they would be "difficult" to work with because of their mental health or disabilities.

What do you most enjoy in your capacity as an academic or research rising star?

The best part is all the opportunities to make a difference. There are so many unanswered questions and so many opportunities to collaborate with others inside and outside my specific expertise to answer these questions. In addition, the ability to inspire others is always great. It is very exciting to hear that someone read my work, listened to my podcast, or saw me on a panel, and it got them excited about science.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

On the day-to-day, after work, I love coming home to my cats and putting on some music while I cook with my fiancé. I also love sitting down with a good book and a cozy blanket to spend my leisure time. I also really enjoy traveling and going to see live music, so when I am able to do these things, I always take up the opportunity as shown in Figure 2.

Part 2: Alaina M. Jaster – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Perfect happiness does not exist. Life is all about embracing things as they come and finding joy in the small things.

What is your greatest fear?
The world ending due to climate disaster.

Which living person do you most admire?
Not a single person but all the people who have been dealt a crappy hand and keep on going despite all the things moving against them.

What is your greatest extravagance?
I do not feel quite extravagant, but I do enjoy a fun statement piece from time to time, like a big, colorful fuzzy coat or a fun hat and giant sunglasses.

What are you most proud of?
I am most proud of myself overcoming a lot to get where I am today.

What is your greatest regret?
I do not think I have one.

What is the quality you most admire in people?
Sense of humor.

What is the trait you most dislike in people?
Dishonesty and arrogance are tied.

What do you consider the most overrated virtue?
They all have value and require balance in every individual.

What is your favorite occupation (or activity)?
My favorite activity is dancing at a concert.

Where would you most like to live?
I would love to live somewhere warm with mountains. I would also enjoy moving around Europe and living in a new place every few months.

What is your most treasured possession?
My cats.

When and where were you happiest? And why were so happy then?
I am happiest whenever I see the world and am in nature. Exploring and letting our curiosity run wild is what we are meant to do.

What is your current state of mind?
I am grateful for my experiences and opportunities and for the health of my loved ones.

What is your most marked characteristic?
My determination.

Among your talents, which one(s) give(s) you a competitive edge?
I am really good at time management, and that makes it easier for me to get a lot done in a short time frame.

What do you consider your greatest achievement?
To date, probably taking the US Drug Enforcement Agency to court challenging the scheduling of psychedelic research chemicals DOI/DOC.

If you could change one thing about yourself, what would it be?
Nothing. People are changing all the time, every day.

What do you most value in your friends?
Comfortability, knowing you can be your whole self around them.

Who are your favorite writers?
I am a big fan of Charles Dickens, J.R.R Tolkien, Ta-Nehisi Coates, and Carl Hart.

Who are your heroes of fiction?
I do not think I have any.

Who are your heroes in real life?
My mom comes to mind first; she really is a "super-mom."

What aphorism or motto best encapsulates your life philosophy?
In omnia paratus, a Latin phrase that means "prepared for all things" or "ready for anything."

Detroit, Michigan, USA
30 November 2024

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[1] In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

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INNOVATORS & IDEAS: RISING STAR

Fayzan Rab: What are the economic and public health implications of psychedelic therapies?

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Keywords: Psilocybin, FDA, economic demand, public health estimate, exclusion criteria

At the intersection of medicine, psychedelics, and social impact stands Fayzan Rab, an MD Candidate at Emory University School of Medicine who brings a fascinating blend of experiences to his current role as a clinical researcher at the Emory Center for Psychedelics and Spirituality. His research explores crucial questions surrounding the emerging psychedelic therapy landscape, from understanding minority communities' perspectives to examining the broader public health and economic implications of these groundbreaking treatments. Before pursuing medicine, Fayzan carved out a distinctive path that included leading product development at tech giants Google and Mindstrong Health, followed by grassroots political organizing in the Bay Area. Today, alongside his research, he channels his leadership experience into executive coaching, helping entrepreneurs refine their communication skills and presence. When he is not exploring the frontiers of psychedelic medicine, Fayzan enjoys life in Atlanta with his fiancée Shua and their cat Bella, where you might find them hunting for fresh produce at their neighborhood farmer's market or hosting spirited game nights with friends. In this Genomic Press Interview, he shares his insights on the transformative potential of psychedelic therapy in modern healthcare.

Part 1: Fayzan Rab – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

Both my parents are physicians and while we never explicitly debated the merits of the scientific method, it was baked into the DNA of my upbringing. A few classes in college that looked at epistemology and the history of science reinforced in me the value of science as a neutral arbiter in deciphering reality. In my first career as a product manager at Google, we used principles from science (breaking problems into first principles, validating results, seeing what was reproducible) to build technology products for users. By the time I started medical school, I had a blended philosophy around science. I wanted to use the scientific method to rigorously test and examine questions that were pertinent in the real world. I have been surrounded by mentors who have encouraged that inquiry in developing my relationship with science and using it as a powerful instrument to bring clarity to topics that I feel are important to answer.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

My interest in psychedelic science began during a series of mini-lectures at UCSF designed for the public. I was contemplating a career switch from Silicon Valley to medicine, and I was blown away by some of the clinical research on psychedelic therapies for hard-to-treat conditions like PTSD and depression. The statistics were compelling, but the transformative, qualitative accounts from participants captivated me.

Figure 1. Fayzan Rab, MD Candidate, Emory University, USA.

Emory established a Center for Psychedelics and Spirituality during my third year of medical school, which provided a natural playground to explore some of the questions arising in the burgeoning psychedelic ecosystem. While many researchers focused on clinical trial outcomes, I saw an unmet need to explore questions around implementation—such as public health needs and real-world operating models. This realization led me to create a research team to address these critical issues.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

So often, I would drive home at the end of a psychiatric clinical service and be saddened by the way the healthcare system treats some of the most

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vulnerable and mentally ill in our society. These are the patients that many general providers often feel some aversion to wanting to treat. The current treatments we have do not seem to reach the patients with the worst mental illness or provide a sustained impact that changes the trajectory of their outcomes.

It would be a fool's errand to say that psychedelic therapies alone would change that. Treating mental illness will require changes within clinical practice but also investments into social safety nets, re-employment opportunities, and affordable housing.

Psychedelic therapies are one of many ingredients that could make a significant difference. I am fortunate to see a whole new field of medicine emerge at this stage of my clinical training. Some of the questions we get to ask about psychedelics, such as reimbursement models, diversity and inclusion, and public health, provide entry points to re-examine many fundamental aspects of the way mental healthcare occurs in the United States.

What impact do you hope to achieve in your field by focusing on specific research topics?

Many questions are well-intentioned in academic research for mental illness: how do we incorporate more minorities, what would improve access to all groups of people, and how do we measure or make a dent in growing rates of mental illness in the United States? However, many existing healthcare systems are structured in a way that makes it hard—if not impossible—to change these inequities. My hope in psychedelic science is that we get to integrate those questions early on while psychedelic therapies are in their infancy. By addressing and planning for them now, I believe these therapies could reach and become more accessible to those generally excluded from treatment innovations.

Please tell us more about your current scholarly focal points within your chosen field of science?

My research within psychedelic science encompasses several interconnected areas of focus. I examine the public health and economic implications of psychedelic therapy approval, particularly regarding patient eligibility and broader health outcomes. Another crucial aspect of my work investigates how cultural and religious minorities, with a specific focus on Muslim communities, relate to and might benefit from psychedelic therapies – this research aims to create more inclusive therapeutic frameworks. I am also deeply interested in expanding the clinical applications of psychedelics beyond traditional mental health conditions. While current trials predominantly focus on treatment-resistant mental illnesses, I am exploring potential applications for diverse populations, such as cancer patients and those with postpartum conditions, as well as different therapeutic targets, including OCD and chronic pain.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

In leading my research group, I am guided by two fundamental principles that shape our approach. The first centers on maintaining a narrow focus while seeking broader applications – each research question we pursue must connect specific inquiries to larger implications within the field. A prime example is our study that estimated potential patient demand for psilocybin therapy in depression treatment. While we focused on determining eligible patient numbers, this research illuminated broader aspects of medical eligibility criteria, FDA approval processes, and public health outcomes.[1] The second principle emphasizes valuing progress over the pursuit of perfection. Academic work can often stall when researchers become overly focused on achieving perfection. Instead, I encourage my team to view peer review not as a test demanding perfection but as a collaborative opportunity to refine and enhance our ideas. As demonstrated in our recent publication (Rab, Raison & Marseille, 2024, doi: 10.61373/pp024r.0025 – in this issue), this approach has enabled us to contribute meaningful insights to the field while maintaining scientific rigor.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

The scientific method holds immense potential to address society's most pressing challenges, yet science is often conducted in isolation from community providers. I would love to see more direct collaborations with organizations and providers to identify the most pertinent real-world questions. In one of my research areas—Muslims and psychedelics—the majority of hypotheses are developed in coordination with local providers. By grounding research questions in partnerships with on-the-ground organizations, we can ensure that the results and discoveries are relevant and meaningful to those in the field.

What do you most enjoy in your capacity as an academic or research rising star?

At a fundamental level, it is validating. Sometimes, venturing outside the comfort zone of the conventional questions being studied can feel risky. Already, many clinical peers raise eyebrows when I mention I am studying psychedelic therapies. In addition, most researchers in the psychedelic space are not diving into the questions I am studying; it can be a lot to be with at times. To have our publication accepted and then widely publicized can be affirming for that initial instinct that had me venture in this direction.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I believe that leisure is an important part of any creative research process. Asking unconventional questions, getting inspired, and playing with ideas were all made possible because I created dedicated, uninterrupted leisure time. Leisure's non-utilitarian nature takes the pressure off for it all to feel useful and paradoxically makes the inquiries I ask feel more organic and natural.

For me, leisure consists of some structured stream-of-consciousness writing (check out the morning pages concept from *The Artist Way*), playing pickleball with friends in my local community, and spending quality time with my fiancée and cat.

Part 2: Fayzan Rab – Selected questions from the Proust Questionnaire[2]

What is your idea of perfect happiness?

Celebrating the moments in my life that are already joyful such as my morning walk, watching a movie with my fiancée, and relishing that I get

[1] Rab SF, Raison CL, Marseille E. An estimate of the number of people with clinical depression eligible for psilocybin-assisted therapy in the United States. *Psychedelics*. Published online September 13, 2024. doi: 10.61373/pp024r.0025 – in this issue.

[2] In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

Figure 2. Fayzan Rab with his cat, Bella Donna.

to ask the questions and work on the problems I organically love to think about.

What is your greatest fear?
To live a life that is not authentic to who I am.

Which living person do you most admire?
Bernie Sanders. He is willing to be misunderstood to serve what he believes will benefit humanity.

What is your greatest extravagance?
I love a good spa day. One of my good friends and I will make it a habit to visit a local Korean spa for a whole evening.

What are you most proud of?
I met a great life partner and had the courage to propose to her.

What is your greatest regret?
Staying too long in a job where I felt like my manager was personally putting me down.

What is the quality you most admire in people?
Pioneers who are invested in bridging disparate worlds.

What is the trait you most dislike in people?
Self-righteousness.

What do you consider the most overrated virtue?
People who take much pride in saying they are busy. Busyness does not equate to progress or value.

What is your favorite occupation (or activity)?
I love coaching people who are facing personally meaningful challenges in their life.

Where would you most like to live?
A home that is based around a lot of wildlife and nature but still close enough to a large urban center.

What is your most treasured possession?
My grandfather's stethoscope.

When and where were you happiest? And why were so happy then?
The weekend I proposed to my fiancée: a total surprise to her. Our close friends and family came into town the following day and surprised us again with a full-blown celebration.

What is your current state of mind?
I am a bit sad about current events in the world, but I am also calm, present, and grateful for what's next.

What is your most marked characteristic?
Deep listening and not being afraid to take the conversation one level deeper.

Among your talents, which one(s) give(s) you a competitive edge?
My ability to distill multiple, diverse perspectives and synthesize them into a path forward.

What do you consider your greatest achievement?
Cultivating a close set of friendships and mentors whose relationships have not succumbed to the busyness of life.

If you could change one thing about yourself, what would it be?
I would have more faith during times of uncertainty in the path I am charting for myself.

What do you most value in your friends?
I am lucky to have an empowered and accomplished set of friends. However, none of them conflate their resumes for what is most important: relationships.

Who are your favorite writers?
John Steinbeck, Haruki Murakami, and Jhumpa Lahiri.

Who are your heroes of fiction?
I love the character Yusuke Urameshi from the 1990s Japanese anime *Yu Yu Hakusho*. He is a high school student who dies in a car crash only to be resurrected to fight invisible battles with spirits, demons, and villains. The show is surprisingly deep about redemption, remembering the day-to-day joys, and being willing to put everything on the line for something you believe in. I regularly watch clips from that show for inspiration when I encounter setbacks or uncertainty.

Who are your heroes in real life?
Dr. Tom Insel for his willingness to reinvent; Bernie Sanders for his commitment to serving the common person, and my grandfather for his ability to connect deeply with others and amazing storytelling abilities.

What aphorism or motto best encapsulates your life philosophy?
"Amor Fati."[3]

Atlanta, Georgia, USA
4 December 2024

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[3]"Amor Fati" is a Latin phrase meaning "love of fate" or "love of one's fate" that was particularly embraced and popularized by German philosopher Friedrich Nietzsche in the 19th century. However, the concept has earlier roots in Stoic philosophy, especially in the writings of Marcus Aurelius and Epictetus.

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Psychedelics

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INNOVATORS & IDEAS: RESEARCH LEADER

Charles L. Raison: Elucidating the role of conscious experience in the therapeutic effects of psychedelics as a means to optimize clinical outcomes

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Keywords: psilocybin, psychedelics, consciousness, depression, inflammation

Charles Raison, MD, is a Professor of Human Ecology and Psychiatry in the Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison. Dr. Raison also serves as Director of Clinical and Translational Research for Usona Institute, as Director of the Vail Health Behavioral Health Innovation Center, Director of Research on Spiritual Health for Emory Healthcare, and as Visiting Professor in the Center for the Study of Human Health at Emory University in Atlanta, GA. Dr. Raison's research focuses on the examination of novel mechanisms involved in the development and treatment of major depression and other stress-related emotional and physical conditions, as well as his work examining the physical and behavioral effects of compassion training. More recently, Dr. Raison has taken a leadership role in the development of psychedelic medicines as potential treatments for major depression. He was named one of the world's most influential researchers by the Web of Science for the decade 2010–2019. With Vladimir Maletic, he is author of *The New Mind-Body Science of Depression* published by W.W. Norton in 2017. We are happy to share Dr. Raison's perspectives on his life and career with our readers.

Part 1: Charles L. Raison – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

My childhood was dominated by a love of science, especially astronomy. In sixth grade, I started my own stargazing magazine (with the printing help of my parents, who owned a small-town newspaper). My interest in science lapsed in my teenage years and was replaced by a search for spiritual answers to life's mysteries. My journey back toward science began not with science but in the humanities when I discovered psychoanalysis not in a clinical context but while working on a Ph.D. in English. Spurred on by this and a first encounter with the power of psychotherapy in my own life, on Christmas Eve 1984, I had a "road to Damascus" type experience on a forlorn highway in South Texas when I suddenly decided that I should change my life's direction and become a psychiatrist. This required that I return to school to complete all the pre-med-type classes I had studiously avoided as an undergraduate. The beauty of physics ravished me, and I might have stepped away from my medical plans had I the talent; however, lacking the requisite mathematical gifts, I did become a doctor and a psychiatrist. But I was still a ways away from spending a life in science as my early years after residency were spent as a full-time clinician.

It is interesting how life brings things back around. My long-term interest in spiritual traditions launched my life in science. In the mid-90s, I had the good fortune to befriend the Dalai Lama's sister, who, in turn, introduced me to several brilliant Tibetan Buddhist monks. These gentlemen taught me much about esoteric meditation practices, which fascinated me. I became obsessed with understanding what these practices did to the brain and body from a Western scientific perspective. I was especially interested in the effect of these practices on body temperature, as raising body temperature is central to these techniques, as odd as that sounds from our Western perspective.

Figure 1. Charles L. Raison, MD, University of Wisconsin-Madison, USA.

As wonky as these considerations sound, they motivated me to leave a clinical faculty position at UCLA, throw caution to the wind, and move to Emory University in Atlanta in hopes that I could leverage the university's strengths in Tibetan Buddhist studies and mind-body medicine to pursue the studies I wanted to commence.

Just as life brings things back around, so does it move forward in paradoxical ways. I became a researcher at Emory under the tutelage of my friend and mentor, Andrew Miller. However, I could never conduct the studies of advanced Tibetan Buddhist meditation practices that had been my initial impetus for retooling my career toward research. A pivotal moment came early on at Emory when I was still trying—but struggling to do the work I wanted to do—when Andy said, "While you are fiddling with this meditation stuff, how about doing some real science in the meantime?" This was his offer to join him in studying how inflammation affects the brain and body to produce depression. I was interested in thermoregulation and body temperature because of my

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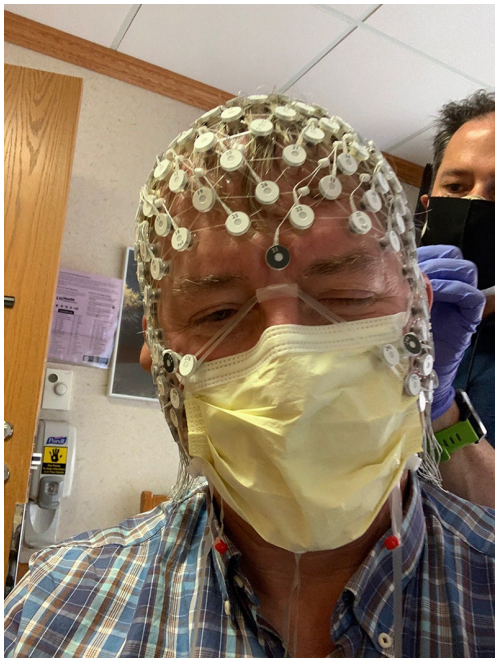

Figure 2. Charles L. Raison volunteering to "beta test" an EEG protocol.

interest in a meditation technique called tummo (made somewhat famous recently by Wim Hof). Inflammation increases body temperature, so I thought, "Why not?" and joined Andy's research team. Had I said "no" and insisted on my more narrow focus, I would never have been gifted with a life in scientific research. This is an important point and a profound challenge for young scientists. On the one hand, you do not want to go so far away from your interests that the work is tedious; however, if you are too rigid, tremendous opportunities will sail past.

My experience has been that research is like following a fascinating trail of breadcrumbs through the forest. If one maintains a felt sense of what one is looking for, things often circle back. Although I never did the studies I had initially hoped to do, over the years, I have been fortunate to conduct meditation studies and, in the last decade, studies that harken back to my long-term interest in body temperature/thermoregulation and mood.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My leadership roles, such as they are, were something other than what I actively pursued. I realized many years ago that I prefer to occupy a "vice president" type role, being second in command in a research group. I was never more productive than when I existed in this type of relationship at Emory University with Andy Miller. I am an excellent "wingman". But years pass, one ages, and over time, one is faced with a choice: to either step into leadership or step aside. I have generally stepped in. I have had several leadership positions over the last decade, but I will focus on two here. In 2017, George Grant, MDiv, PhD, asked me to become the Director of Research on Spiritual Health for the Woodruff Sciences Center at Emory University. Because my primary academic position is—and was then—at the University of Wisconsin-Madison, I realized early on that the best way I could lead from a bit of a distance was to bring in as much research talent as possible and then disperse leadership amongst these researchers. I consider this one of my primary leadership accomplishments because I have been remarkably successful (if I can brag) at bringing remarkable younger scientists to Emory as faculty working in Spiritual Health. More recently, a defining moment in the last several years occurred when I was invited to take on the role of Director of the new Vail Health Behavioral Health Innovation Center, a new institute situated within a larger consortium that has been established between UW-Madison and Vail Health. I took this position because it promises to bring many of my research interests and colleagues together into one place to explore the implementation of novel treatments for depression, anxiety, and substance use disorders.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

I have always had two deep interests that have formed an undercurrent in all my work. One of these is the ability of the body to influence mental states. The other is the potential of particular mental states to promote profound and sustained wellbeing. These two are—of course—related: the body can be used to drive the mind into certain mental states, and certain mental states can profoundly affect bodily function. As I described above, I came into research because I was fascinated by the possibility that certain esoteric Buddhist meditation practices might be equivalent to deep brain stimulators to induce profoundly positive mental/emotional states. More lately, my work with psychedelics has induced in me a profound interest in the question of whether consciousness has actual causal power in the world (as opposed to being epiphenomenal to more basic non-conscious brain processes).

What impact do you hope to achieve in your field by focusing on specific research topics?

On a more fundamental science level, I would like to use psychedelics to explore the question of whether consciousness has causal power. On a clinical level, I hope to conduct studies that identify and optimize novel treatments for depression and anxiety, especially those that build upon ancient practices that are often also adaptive stressors.

Please tell us more about your current scholarly focal points within your chosen field of science.

I am currently up to my eyeballs in five major studies for which I have primary responsibility. Four of these studies focus on trying to understand better the role of conscious experience in the therapeutic effects of psychedelics and, via this understanding, to optimize outcomes. One of the studies focuses on whole-body hyperthermia. This study seeks to understand whether the therapeutic effect of heat can be expanded by combining heat with cold exposure. This study also seeks to follow up on prior work that has identified a potential immune-based antidepressant mechanism of action of whole-body hyperthermia.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

A primary value is never to set out to prove what I already know to be true—a trait that is too often present in people who study mind-body type interventions like meditation or novel treatments like psychedelics. Years ago, I was told by a wise person, "If you are scared of the truth, get out of science," and I have taken that to heart. I start studies with hypotheses but am always ready to abandon these and listen to what the world is trying to tell me through the actual results of a study. The most exciting studies I have done have been those that disproven my initial hypotheses.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I have become increasingly concerned about data falsification within science, as it has become sadly and increasingly clear that this is a real issue. As much as anyone, I understand the terrible pressure researchers are under to produce positive "catchy" results. Nevertheless, the entire edifice of science is built upon our ability to trust results. Failed studies do not add much to one's career in any straightforward sense. However, my best ideas generally come from results that contradicted my easy initial hypotheses.

What do you most enjoy in your capacity as an academic or research leader?
I enjoy the opportunity to devise and implement studies that attempt to address questions that most interest me and are essential for human wellbeing.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?
I take a "Swiss Cheese" approach to work and leisure. Because of my many responsibilities, I work all the time, meaning I start the day with work, and late into the evening, it is usually the last thing I do. Nevertheless, like Swiss Cheese, I leave holes in the constant work stream to do fun things with family and friends. So I work, off and on from 7 a.m. to 10 p.m., but during that period, I will also take a couple of walks with my partner or kids. When I travel for work, I often try to leave a few extra hours open for what I have called "targeted travel," a brief excursion that transforms a work trip into something fun and memorable. If I had more of a choice in my time, I would eliminate email. Far too much of my time is spent just culling through all the details that emailing makes it so easy to become bogged down.

Part 2: Charles L. Raison – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I want to explore somewhere new and fascinating on a perfect summer's day with the people I love.

What is your greatest fear?
Dying after the people I love.

Which living person do you most admire?
I greatly admire many people. But I know my partner Christine Whelan best and admire her most.

What is your greatest extravagance?
Green Chartreuse.

What are you most proud of?
The wide variety of amazing people I have been honored to know as friends, colleagues and family.

What is your greatest regret?
Not meeting my partner sooner in my life.

What is the quality you most admire in people?
Highly competent/talented people who don't toot their own horns.

What do you consider the most overrated virtue?
Over the years, people have complimented me on being a risk-taker, which I appreciate because, in fact, I am rather cautious and conservative at heart.

What is your favorite occupation (or activity)?
Walking in a new and exciting place with my partner.

Where would you most like to live?
Walnut Creek, CA

What is your most treasured possession?
My copy of "The Handbook of the Yokuts."

When and where were you happiest? And why were so happy then?
I am the happiest I have ever been right now. Later in life, I met the love of my life, and we have five children together who are the light of my life. My work is stressful but fascinating and meaningful.

What is your most marked characteristic?
Wide-ranging curiosity about life and the world we find ourselves in.

Among your talents, which one(s) give(s) you a competitive edge?
Ability to public speak and write.

What do you consider your greatest achievement?
Raising my two teenage boys.

If you could change one thing about yourself, what would it be?
I would be more organized.

What do you most value in your friends?
Kindness, intelligence, passion, and vision.

Who are your favorite writers?
John Spivey (The Crying Dance, The Great Western Divide), Rilke, Whitman, TS Eliot (Four Quartets).

Who are your heroes in real life?
Franklin Delano Roosevelt, Eleanor Roosevelt, Buddha, Samuel Johnson.

What aphorism or motto best encapsulates your life philosophy?
"Old men ought to be explorers
Here or there does not matter
We must be still and still moving into another intensity
For a further union, a deeper communion."

Charles L. Raison, MD[1]
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[1]In the late nineteenth century various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

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Psychedelics

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COMMENTARY

Psilocybin-assisted psychotherapy: Advancements, challenges, and future directions for treating resistant depression

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Keywords: Psilocybin-assisted psychotherapy (PAP), treatment-resistant depression (TRD), psychedelics, psilocybin

Depression is a global public health challenge that represents the world's largest cause of disability, especially in the context of traditional treatments. One potential solution being explored is psilocybin assisted psychotherapy (PAP) which shows promise for treating depression. A recent study by Rosenblat et al. explores the use of psilocybin in clinical mental care with promising results (1).

The increase in major depressive disorder (MDD) cases particularly since 2005 and worsened by COVID-19 is alarming (2). While monoaminergic antidepressants have been used as a treatment since the 1980's, they often take two to four weeks to show effects and may not work for up to one-third of patients (2). Additionally, side effects lead up to 50% of patients to stop treatment (2, 3). Therefore, there is a growing focus on finding better ways to address depression.

Responding to the need for antidepressant options, psychedelic compounds have garnered attention in recent times. Despite past disapproval due to recreational drug use, there is now renewed interest in exploring psychedelics like psilocybin for their therapeutic potential (2, 4).

Psilocybin, a naturally occurring psychedelic compound found in certain mushroom species, has been found to have a profound impact on consciousness by interacting with serotonin 5HT2A receptors (2, 3). Research on animals suggests that psilocybin is associated with an increase in brain derived factor (BDNF) which influences plasticity, neurogenesis and dendritic growth (5). Interestingly, lower levels of BDNF have been linked to depression in several studies (6). While the exact pathways through which psilocybin benefits conditions is still up for debate, there is promise in using it to help treat treatment-resistant depression (TRD) when combined with psychological support (3, 7).

The idea of PAP has been gaining traction as a supported method for addressing depression symptoms in individuals with bipolar II disorder as noted by Aaronson and colleagues (8). However, determining the combination of therapy sessions and dosage levels for effectiveness remains an area of concern.

One important area of concern is the critical issue of adverse reactions, which are particularly important in the light of reports of psychedelics-induced mania that could paradoxically indicate their effectiveness as antidepressants (9). A very germane point is that effectiveness and safety must be well ascertained in order to avoid investing in therapies that may not work. This is particularly relevant for long-term psychotherapy in combination with psychedelics (10). One of the frustrations experienced by clinicians is that most of the evidence supporting the use of psilocybin for depression comes from studies with very strict eligibility criteria, which makes it unclear if the findings from those rigorous trials are applicable in real-world settings, where conditions like personality disorders and suicidality (which tend to be clinical trial exclusion criteria) are highly prevalent (11).

In a March 2024 article titled "Psilocybin assisted psychotherapy for treatment depression: A randomized clinical trial (RCT) evaluating repeated doses of psilocybin," Rosenblat and colleagues shed light on these issues in the field of PAP research (1). This new RCT provides evidence supporting the use of psilocybin dosing in a population dealing with complex psychiatric issues such, as TRD bipolar II disorder (BPII) or other comorbid conditions.

In the study conducted by Rosenblat and colleagues, participants had an average Montgomery-Asberg Depression Rating Scale (MADRS) score of 30.5, experiencing depression for 18.3 years, and having gone through approximately 11.27 failed medication trials. Interestingly 40% of them had experience with electroconvulsive therapy or ketamine infusions. This trial involved 31 individuals with TRD; most were initially diagnosed with MDD (26 participants), while only four were diagnosed with BPII. Each participant also had at least another co-morbid psychiatric diagnosis. One participant withdrew before the study began. The trial aimed to evaluate the feasibility of using psilocybin in combination with therapy to address TRD. Participants were split into two groups: one receiving treatment ($n = 16$) and the other on a waitlist control ($n = 14$). Over six months all treated participants received one to three doses of psilocybin at 25 mg each along with preparatory and integration psychotherapy sessions over a six-month period.

Results showed significant reductions in depression severity in the full sample, with further MADRS score reductions from repeated doses. The results showed a reduction in depression severity across all participants after receiving repeated doses of psilocybin. The treatment was well tolerated without any reported events. The high retention rates and manageable side effects emphasized the effectiveness of this approach for individuals struggling with TRD.

The unique aspect of the research study conducted by Rosenblat and team was their method of dosing, which involved administering psilocybin based on relapse indicators. This sets it apart from studies that typically followed a fixed single dose protocol (4, 7, 9, 11, 12). As a comparison, in a study by Goodwin et al., a single dose approach was used to evaluate the effectiveness of psilocybin doses along with support for TRD (12). In this study, a 1 mg dose served as a reference point compared to doses. The findings revealed that the 25 mg dose improved participants symptoms after three weeks whereas the medium 10 mg dose did not show symptom reduction. Interestingly the control dose of 1 mg did not yield benefits. While this research emphasized the importance of dosing strategies it only observed patients for 12 weeks indicating the need for longer trials to fully understand the lasting effects of psilocybin treatment.

Following the examination of dosing frequency, the Rosenblat et al. study broke new ground by extending the follow-up period to six months and allowing for a schedule with doses given as needed (1). Evaluating outcomes two weeks post each dose, the study found that the primary depression measure, the MADRS, was significantly lower at the last post-dose follow-up compared with baseline. The authors conclude that their

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results indicate that when depression is recurrent, as it often is, treating it as one would treat the recurrence of other episodic disorders makes more sense than sticking with a more rigid fixed-dose schedule that may not be personalized to the needs of the patient.

I found that the approach taken in the Rosenblat et al. study to dosing was better than what other studies have shown. However, while the research by Rosenblat and colleagues shows promise, there are some limitations to consider. The fact that it was an open label study had a sample size. Using waitlist controls instead of a placebo group are significant issues that could make the antidepressant effects seem stronger than they actually are. Additionally, this study differed from ones by providing preparatory and integration psychotherapy, which might explain why the antidepressant effect was not as strong as seen in studies like Goodwin et al., where there was a greater reduction in MADRS scores (1, 12).

In studies involving psilocybin, including the one led by Rosenblat et al., participants receive support through three phases: preparation, dosing session and integration (1, 13). For patients with TRD, therapy is believed to enhance the effects of psilocybin and help individuals process their dosing experiences (5). This dynamic relationship makes it difficult to determine whether improvements in symptoms are due to psilocybin itself or the psychological support provided alongside it.

The effect of psychotherapies used in PAP trials on the effectiveness of treating depression has yet to be determined by researchers. Clinical trials vary in the number and type of preparation and integration sessions provided (14). As we noted previously, the range of background training for the therapists is equally diverse (13). These PAP trials have not tried to standardize either the psychotherapies or the therapists.

As we move forward, the integration of PAP into practice may present some real challenges. While there are those who believe that psilocybin therapy could well provide some lasting benefits when compared to ketamine, the potential cost of these therapies has some professionals concerned. If the cost of these therapies rises, it becomes an even bigger barrier to access. Right now, a couple of different efforts are exploring group therapy and virtual therapy as potential alternatives that could save people money, but the safety and efficacy of those therapies are not yet established. Another thing that is perhaps less frequently discussed is the huge importance of setting in enhancing the effects of these therapies. In short, places matter; and you need to have an accessible space if you are going to have a positive effect (15).

To sum up, an important step was taken by Rosenblat and associates when they recently illuminated the subject of psilocybin and its possible use as a treatment for depression. What they did was quite different from what has been done before in this area. They took a group of people who had serious mental health issues (in this instance, depression), in real-life settings that included multiple comorbidities. Future studies will be required to address constraints like an open label design sample sizes and controls.

One could make the case that future research must include larger, placebo-controlled trials over extended time so that we can clearly ascertain the long-term safety aspects of psilocybin and generate the evidence needed to optimize the combination of dosing with psychotherapy sessions. Addressing variations in psychotherapy techniques and therapist training will play a role in enhancing the effectiveness and consistency of PAP. Moreover, logistical and financial obstacles need to be addressed since PAP demands therapist engagement, specialized training and suitable clinical environments. Continuous research is vital to realize the potential of psilocybin as a treatment for depression offering renewed optimism for those struggling with TRD.

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THOUGHT LEADERS INVITED REVIEW

Effects of ayahuasca on fear and anxiety: cross-talk between 5HT1A and 5HT2A receptors

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Ayahuasca is a hallucinogenic substance currently being investigated for the treatment of mood, anxiety, and trauma-related disorders. Evidence from animal and human studies suggest that the effects of ayahuasca involve modulation of neural substrates relevant for emotional processing, especially in regions rich in serotonergic receptors. Moreover, preclinical studies also show that ayahuasca has specific effects on fear-related memories. The serotonergic system has been classically associated to anxiety and fear responses, with selective serotonin reuptake inhibitors being first-class medication to treat mood, anxiety, and stress-related disorders. Here we review currently available data regarding ayahuasca (and its main components) behavioral and functional effects on anxiety and fear-related responses through its modulation of serotoninergic signaling.

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Introduction

Ayahuasca (AYA) is a hallucinogenic beverage traditionally consumed by indigenous groups from Northwestern Amazon and, more recently, by syncretic religious groups present worldwide. The main psychoactive compound in AYA is N,N-dimethyltryptamine (DMT), present in the leaves of *Psychotria viridis*, but the preparation of AYA also involves the *Banisteriopsis caapi* vine, rich in β-carbolines (1). The β-carbolines act as antagonists on digestive system monoamine oxidase enzymes that, otherwise, would degrade DMT before it could reach the central nervous system (2). Harmine, tetrahydroharmine, and harmaline are the most relevant β-carbolines in AYA, which have their own pharmacological properties, adding another layer of complexity to the mechanisms of action of AYA (3).

AYA can be defined as a classic hallucinogen, since it has agonistic effects in different serotonergic receptors, especially the 2A subtype (5HT2A receptor) (4). The subjective and hallucinogenic effects of AYA seem to result from its agonism at 5HT2A receptors; however, it can also act on different receptor subtypes, with the 1A receptor (5HT1A) being of special interest for the discussion proposed by this review (5, 6). The effects of AYA on serotonergic pathways mostly rely on DMT action, since β-carbolines present little to no affinity for most serotoninergic receptors, except for a modest affinity for the 5HT2A receptor (3, 5).

Similarly to what have been happening to other psychedelic substances, AYA properties have been investigated as treatment for numerous psychiatric disorders, such as depression, anxiety, and substance use disorder (7–11). Additionally, preclinical studies have suggested a possible action of AYA on fear processing circuits, which could support possible mechanism for therapeutic effects on anxiety and posttraumatic stress disorder (PTSD) (12, 13). A few observational studies and case reports have already been published about therapeutic effects of AYA on trauma processing and treatment of PTSD (14, 15), with promising results. Nonetheless, until now, clinical trials performed in controlled settings are lacking.

Apart from serotonin receptors, AYA also has effects on glutamatergic, dopaminergic, and endocannabinoid systems (16–18). It is possible that DMT acts as an agonist of *sigma-1* receptors (19), which was already suggested as a possible mechanism for AYA effects on fear processing (20). Moreover, AYA intake can alter neuroendocrine responses as well (21). These complex interactions, however, are beyond the scope of this review. Here, we aimed to concatenate and discuss data regarding AYA effects on fear and anxiety and how it can be associated with its actions on serotonin (5HT) receptors.

Fear Behavior and Anxiety

Fear is an evolutive preserved behavior that acts as a defense mechanism and is usually triggered by threatening and dangerous stimuli. Some stimuli can naturally elicit a defensive behavior, while others can be learned and associated to lifelong responses. This behavioral plasticity is crucial for adaptation to an environment that continuously challenges individuals with new contexts (22). Anxiety, on the other hand, represents a state of increased arousal and vigilance even in the absence of an imminent threat, and it can also elicit behavioral defensive responses (23).

Impairments on appropriate fear and anxiety responses are the cause of a variety of psychiatric disorders, such as PTSD, generalized anxiety and panic disorders (24). Efforts to develop better treatment options for patients suffering from these disorders demand the development of tests and paradigms that can assess the behavioral and neural alterations underlying the symptoms.

Paradigms for Assessing Fear and Anxiety Responses

The more frequently employed paradigms to assess fear and anxiety responses in preclinical studies usually are rooted on inherent behavioral characteristics of the animals or on associative learning of conditioned responses to naturally aversive stimuli.

In the first category, the animal behavior is affected by an approach-avoidance conflict between the inherent tendency for the animal to explore the new environment versus fear-driven behaviors. The elevated plus-maze (EPM) and the open field test (OFT) are two of the most famous tasks based on this premise. Animals expressing increased anxiety-like behavior spend more time on the closed arms (EPM) or in the edges of the field (OFT), respectively. Treatment with anxiolytic drugs increase entrances and time spend on the open arms for the EPM, as well as time spent in the center of the arena for the OFT (25, 26).

On the second category, the classical or Pavlovian conditioning is the most widely employed protocol to study fear behavior and memories.

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Through this paradigm, a stimulus once neutral, that is, that does not elicit a behavioral response, is paired to a stimulus that naturally evokes a fear response. Once the animal is trained through simultaneous presentations of the latter (that is called the unconditioned stimulus or US) together with the former (which will be called the conditioned stimulus or CS), an associative memory is acquired and the CS alone is able to evoke the behavioral response (27, 28). Alterations in US intensity and CS characteristics can result in memories with different characteristics, like duration, intensity of evoked behavioral response and generalization (22). The two more frequently employed fear conditioning paradigms are the contextual fear conditioning (CFC) and the tone fear conditioning (TFC). Both apply electric shocks at the animal's paw as the US, but the first uses the whole context where the animal is trained as the CS, and the latter uses a specific sound as the CS, and the animal is tested being exposed to the same sound but in a different context from training (29).

Fear conditioning protocols have been widely employed by preclinical researchers as a tool to understand memory formation as well as how they can be altered or forgotten. Repeated re-exposure to the CS is the base for reconsolidation and extinction protocols (30). If elucidating the fear memory formation is relevant, understanding how already established responses can be altered can be even more valuable to contribute for treating disorders like PTSD (31).

In humans, the behavioral and subjective consequences of fear and anxiety are frequently assessed using specifically developed psychometric instruments. However, there are many tasks as well that can be employed, being especially useful when accessing neural alterations underlying the behavioral responses through neuroimaging techniques.

Social cognition tasks frequently employ emotional relevant stimuli. During tasks involving the recognition of emotions in facial expressions (REFE), subjects are presented to static or dynamic images of facial expressions and asked to recognize pictured emotion. There are many variations in these tasks, but several are based on Ekman's theory of basic universal emotions (32). Performance in these tasks seems to be altered by numerous conditions, especially when responding to negative valence emotions, like fear (33–35). Another task example is the Simulation of Public Speaking Test (SPST), an anxiety-induced task where individuals are asked to elaborate a speech on a random matter and present it in front of camera, mimicking a public speak situation (36).

Neural Substrates Underlying Fear and Anxiety Responses

Multiple brain regions are involved on processing of emotionally relevant stimuli, but a significant part of the available data produced in the last decades focuses on understanding cortical-limbic circuits dynamics. In this section, we will focus on prefrontal cortex (PFC), amygdala (AMY), and hippocampus (HPP) influence on fear and anxiety processing. Later (Section 2.3), raphe nuclei innervations to these structures will also be discussed.

Prefrontal Cortex. The PFC is involved in numerous executive processes. It receives and projects to structures relevant to emotional, cognitive, sensory, and motor functioning, resulting in a central integrative role for behavioral control and flexibility, highly influenced by external cues and internal contingencies (37). Although there is an ongoing debate regarding the homologies between rodent and primate composition of the PFC, the medial PFC (mPFC) from rodents holds similarities in the modulation exerted by human dorsolateral, medial and cingulate cortices over memory, emotional regulation and response control, among other functions (38).

The rodent mPFC includes two main subdivisions, the prelimbic cortex (PL), that together with the anterior cingulate cortex constitutes the dorsal mPFC, and the infralimbic cortex (IL), more ventrally located. Despite being closely located and intimately interconnected, these two regions have different projecting profiles (37, 39). The PL have more efferent connections with the basolateral nucleus of the AMY (BLA), and dorsal and median raphe nuclei, while the IL innervates numerous AMY nuclei, but especially the central AMY nucleus (CeA), and the lateral septum (39).

The PL projections, although not necessary for fear conditioning acquisition, are needed for the consolidation of the associative fear memory (40). The PL is also relevant for freezing expression after TFC, since CS-modulated disinhibition of PL principal neurons (PNs) projections to the BLA is relevant for fear expression during test (41). The IL activity does not influence fear acquisition or consolidation; however, it is essential for fear extinction retention, suggesting a role on behavioral flexibility (42). Optogenetically silencing IL PNs during extinction learning does not interfere with freezing reduction within session, but impaired extinction recall. However, silencing the PNs during extinction test does not impair extinction recall, indicating that proper IL activation is necessary for consolidation of the extinction memory (43).

The mPFC activity exerts a top-down modulation of subcortical structures relevant for emotional regulation (37). Consistent with that, data from clinical and preclinical studies suggest that increased anxiety responses are linked to a hypoactivation of this region, which can also result in impaired cognitive flexibility (44–46). In mice, synchrony between mPFC and BLA activity is related to discrimination of safety contexts during fear learning and anxiety protocols (47). Similarly, when compared with healthy controls, patients with generalized anxiety disorder had reduced ventromedial PFC activation when processing safety signals (48).

Regarding PL and IL, their precise role on modulation of anxiety responses is less well defined, with contrasting results on the literature, that may result from projections' functional heterogeneity (49).

Amygdala. The AMY is a subcortical structure comprising different nuclei and located in the medial temporal lobe. It receives projections from cortical and subcortical structures, essentially acting as an information processing hub that translate sensory inputs to other areas relevant to behavioral control and emotional processing, such as the PFC and HPP (50, 51).

During fear conditioning, the CS and US association depends on an intricate temporal balance of the different AMY nuclei activation (22). The lateral portion of the AMY is the input region for sensory information, and it is also where the CS and US stimuli representations are associated. However, the communication with other AMY nuclei depends on glutamatergic projections leaving from the basal AMY. Since both regions are intimately interconnected, they are often referred as the basolateral AMY (BLA) (52). If the BLA is the main input center, the central AMY (CeA) is the output, projecting to structures relevant for fear expression, such as the hypothalamus and the periaqueductal gray (53). The BLA PNs innervate de CeA directly, but also regulate its activity indirectly through projections to the intercalated cells (ITC), a GABAergic cell mass, that also innervates the CeA (54). AMY activity is necessary for both CFC and TFC, but on the former, the context representation relies on dorsal HPP activity which then indirectly communicates with the AMY through ventral HPP projections (29, 55).

Altered activity in different AMY nuclei is associated to anxiety responses. Inside the AMY, activation of projections from the BLA to CeA have an anxiolytic effect, while selective optogenetic inhibition of these neurons result in an increase of anxiety-like behavior in mice (56). Functional connectivity between these two subregions is also impaired in patients with generalized anxiety disorder (57). When exposed to emotional relevant stimuli, patients with anxiety and trauma-related disorders tend to present increased AMY response (58).

Hippocampus. The HPP is located in the temporal lobe and implicated in multiple cognitive, memory and emotional processing functions. This structure can be functionally differentiated into two distinct areas, the ventral HPP and the dorsal HPP (59).

The dorsal HPP functioning is associated to cognitive performance and is responsible for encoding the representation of the context during CFC, hence why this task is described as HPP-dependent. Lesions on the dorsal HPP impair CFC expression without altering TFC (60).

Additionally, HPP is one of the few structures where new neurons can be born in adult brains (61), although there is an ongoing debate whether this property is present in humans (61, 62). Impaired neurogenesis seems to be related to symptomatology of multiple psychiatric disorders, like depression and PTSD (63).

However, this hippocampal region does not directly project to the AMY and the integrations of context representation to sensory inputs to AMY

depends on ventral HPP projections (64). Added to its role on CFC acquisition, dorsal HPP also is relevant for fear memory recall and extinction (65, 66).

The ventral HPP, on the other hand, is more associated to emotional processing, being the only HPP region projecting directly to AMY (64). Additionally, the ventral HPP also seem to be relevant for expression of anxiety responses. Anxiogenic environments increase synchronization of mPFC and ventral HPP, the same not being reported for the dorsal HPP (67). Additionally, lesions on the ventral HPP lead to decrease in anxiety-like responses in the EPM (68).

In humans, PTSD is associated with decreased HPP volume and impaired HPP activation in women performing a verbal declarative memory task (69), and it is also associated with reduced HPP activation to trauma-related stimuli (70). In patients with generalized anxiety disorder, the anterior HPP (analog to the ventral HPP in rodents) had decreased activation to repeated exposure to threat cues when compared with healthy controls (71).

Serotonin Effects on Fear and Anxiety Responses

Studies on human serotonin receptors are intimately linked to hallucinogenic compounds. In 1953, Gaddum reported lysergic acid diethylamide (LSD) antagonistic effect over 5-HT responses elicited in vitro (72, 73) and, since then, seven serotonin receptor classes have been described, mostly represented by G-protein coupled receptors (74). Although hallucinogenic compounds can interact with different 5HT receptor classes, most of the available data focus on the 5HT2 and 5HT1 subtypes, specifically the 2A and 1A subtypes (75).

The 5HT2A subtype is $G_{q/11}$-coupled and abundantly expressed in cortical areas, especially on layer V dendrites of PNs, which are densely innervated by 5HT axons (76). Their activation mostly produces increased membrane excitability through a slow membrane depolarization and inhibition of calcium activated after-hyperpolarization currents (77).

The 5HT1A receptors, on the other hand, are presynaptically expressed on 5HT neurons of the raphe nuclei where they act as autoreceptors and regulate 5HT release (78). However, they are also widely distributed through substrates relevant to memory and emotional processing, such as the HPP, cingulate and entorhinal cortices and AMY, where they are postsynaptically expressed (79, 80). These receptors are coupled to the G_i protein, and their activation induces membrane hyperpolarization through increase in rectifying potassium currents and inactivation of calcium channels (74, 77).

The seemingly opposing effects of 5HT2A and 1A receptors on membrane potential may appear contradictory as they are often co-expressed on cortical PNs (81), but these differences are relevant for stimuli processing. The hyperpolarizing action of 5HT1A alters the sensibility to input-generated excitability, restraining firing frequency, while the inhibition of after-hyperpolarization induced by 5HT2A activation increases excitability, modulating neuronal gain (77). Apart from PNs, these receptors can be expressed on cortical GABAergic interneurons (INs) as well, adding another layer of complexity to serotonergic control over cortical excitatory/inhibitory balance (76, 81).

Through the 70s and 80s many studies explored how 5HT affected punishment conditioned behaviors. At the time, 5HT signaling pathways were thought to regulate these behaviors and promote punishment-induced response suppression. Although further evidence elucidated that this relationship is not as straightforward as initially thought, 5HT role on fear and anxiety neurobiology is still undeniable, with selective 5HT reuptake inhibitors (SSRIs) being the first line of treatment for many stress and anxiety disorders (24).

The theory formulated by Deakins and Graeff proposes that distinct fear and anxiety behavioral responses are controlled by specific 5HT pathways arising from the raphe nuclei. The dorsal raphe (DRN) periventricular tract is responsible to react to acute US exposure, controlling flight or fight responses, and mostly modulating the periaqueductal gray activity. The DRN forebrain bundle tract (DRD/DRC) is activated by acute exposure to CS and controls avoidance behaviors through projections to structures such as the AMY, ventral HPP and PFC. And the median raphe forebrain bundle tract (DRI/MnR) responds to chronic US and/or CS exposure, being responsible to promote resilience or tolerance to chronic stress, projecting to the dorsal HPP and PL and IL cortices, acting mostly though postsynaptic 5HT1A activation (82, 83).

Knock-out mice for the 5HT2A receptor present decreased anxiety-like behaviors, but have normal CFC and TFC, and the reestablishment of 5HT2A signaling in cortical neurons normalized the anxiety-like responses (84). In the BLA, activation of 5HT projections of DRN increases anxiety-like responses through 5HT2A activation (85).

Pretreatment with the 5HT2A agonist TCB-2 or antagonist MDL 11,939 before acquisition and retrieval of conditioned fear memory did not interfere with freezing expression of male mice, while TCB-2 administration posttraining enhanced freezing on CFC and TFC tests. As for the extinction learning, 5HT2A activation is not essential, but facilitates the process (86). Altogether, these data suggest a role for the 5HT2A receptor on plasticity mechanisms altering memory traces and behavioral responses, but that role is limited to already acquired memories and does not seem to influence the establishment of new associations.

Activation of postsynaptic 5HT1A receptors, on the other hand, seems to decrease anxiety and stress responses. Systemic or intrahippocampal treatment with 5HT1A agonist 8-OH-DPAT before CFC impairs fear memory retrieval, without significantly altering TFC memory retrieval. The impairments were not observed when treatment was administered after training. Additionally, WAY 100635, a 5HT1A antagonist, was not able to produce memory alterations when administered alone, but prevented retrieval impairments when combined with 8-OH-DPAT. Opposed to the outcomes observed after 5HT2A manipulation, 5HT1A receptors seem to be relevant for memory acquisition, especially of HPP-dependent memories, like the CFC (87).

Serotonin Receptors' Role on Psychedelic Effects

The behavioral and mental alterations resulting from psychedelic administration are frequently associated to its agonism at 5HT2A receptors. In humans, ketanserin, a 5HT2A/2C antagonist, can be used to reduce subjective effects induced by LSD (100 or 200 μg) (88, 89). Pretreatment with ketanserin also prevents the psilocybin-induced (215 μg/kg) increase in positive affect and the decrease on recognition of negative facial expressions (90). For DMT (0.7 mg/kg, i.m.), pretreatment with cyproheptadine, another 5HT2A/2C antagonist, did not interfere with subjective effects (91). On the other hand, pretreatment with pindolol, a 5HT1A/β-adrenergic receptors antagonist, intensified DMT (0.1 mg/kg, i.v.) subjective reactions, suggesting an attenuation response of 5HT1A receptors activation on DMT effects. The enhancement of subjective effects caused by pindolol could be a result of increased 5HT2A signaling after 5HT1A blockade (5).

Regarding AYA, pretreatment with ketanserin altered the neurophysiological oscillatory patterns induced by AYA (dose adjusted to contain 0.75 mg/kg of DMT) intake and blocked visual effects through blocking AYA-induced decrease in alpha oscillations (6).

Although the available literature mostly attributes the subjective effects of psychedelics to agonism at the 5HT2A receptor, some evidence points out that not everything can be explained by it. In healthy volunteers, pretreatment with ketanserin did not prevent the reduction in attentional tracking ability caused by psilocybin (215 μg/kg), suggesting a role for 5HT1A receptors (92). Combined administration of buspirone, 5HT1A agonist, and psilocybin (170 μg/kg) reduced the acute subjective effects of psilocybin (93). In chronically stressed mice, treatment with ketanserin did not prevent the antidepressant effects of a single dose of psilocybin (1 mg/kg, i.p.) (94).

Preclinical Evidence for Ayahuasca' Effects on Fear and Anxiety-like Responses

Animal studies evaluating the effects of AYA administration are trying to decode how this substance can interfere with behavioral, functional and structural parameters of fear and anxiety-like responses, and how this could be linked to the possible therapeutic effects (Table 1).

A single oral administration of AYA (containing 9 mg/kg of DMT) to female rats decreased locomotion on the OFT and EPM, which could be an indication of an anxiogenic effect, whilst it also decreased immobility on forced swim test (FST), an indication of antidepressant effect. The

Table 1. Fear and anxiety-like responses from preclinical studies

	Training	Testing	Reconsolidation	Extinction
Fear memory tests				
AYA	–	Chronic pretreatment with AYA (120 mg/kg) increased freezing at CFC and TFC (99).	AYA treatment (60 mg/kg) pretreatment before or after reconsolidation session decreases fear expression on CFC test (12).	Single AYA (0.3 mg/kg of DMT) dose reduces freezing during CFC extinction training, but not test. However, two treatment paired extinction sessions decrease freezing during test (13). Single AYA dose (60 mg/kg) before retrieval, facilitates CFC extinction learning one day after (12).
DMT	Acute treatment with DMT (10 mg/kg) increased freezing during TFC (96). Chronic treatment with DMT (1 mg/kg) did not affect behavior during CFC and TFC training (100).	Acute treatment with DMT (10 mg/kg) before training did not alter fear response during TFC test (96). Chronic treatment with DMT (1 mg/kg) did not affect behavior during CFC and TFC test (100).	–	DMT acute (10 mg/kg) or chronic (1 mg/kg) treatment facilitated TFC, but not CFC, extinction (96, 100).
β-carbolines	Pre-training harmine (10 mg/kg) treatment did not altered aversive avoidance learning during PMDAT training (102).	Pre-training treatment with harmaline (1 mg/kg) impaired fear response at the step-down passive avoidance task (101). Pre-training harmine (10 mg/kg) treatment impaired fear response at CFC, but not TFC (102). Pre-training harmine (10 mg/kg) treatment impaired aversive-avoidance during PMDAT test (102).	–	–
Anxiety test				
AYA	Acute oral AYA dose (9 mg/kg of DMT) decreased locomotion on OFT and EPM (95). Acute oral AYA treatment (0.1, 0.3 of DMT) had no effect on time in the open arms and closed arm entries, but the higher AYA dose (1.0 mg/kg of DMT) increased closed arm entries and general exploratory behavior (13). Oral single dose of AYA (60 mg/kg) did not alter open arm and closed arm entries, and did not alter locomotion (12).			
DMT	One DMT dose (10 mg/kg, i.p.) reduced exploration in the OFT and open arms time and entries on EPM (96).			
β-carbolines	Acute harmine (5, 10, 15 mg/kg, i.p.) treatment did not alter behavioral expression on the OFT (98).			

AYA: Ayahuasca; CFC: Contextual fear conditioning; DMT: N,N-dimethyltryptamine; EPM: Elevated plus-maze; OFT: Open field test; PMDAT: Plus-maze discriminative avoidance task; TFC: Tone fear conditioning; –: Unavailable data.

treatment also induced an increase in *c-fos* expressing neurons in the DRN, posterior BLA and HPP (95). Male rats treated with one dose of DMT (10 mg/kg, i.p.) also presented reduced exploratory and increased anxiety-like behaviors, while three doses were able to induce antidepressant effects on the FST (96). Psylocibin, another 5HT2A psychedelic agonist, also increases anxiety-like responses when administered 15 min prior to the OFT, but promotes anxiolytic effects when animals are tested 4 h after the administration (3 mg/kg, i.p.) (97).

Interestingly, acute treatment with harmine (10 or 15 mg/kg, i.p.) also induced the decrease in depressive-like responses on FST, without altering exploratory behaviors. Additionally, animals treated with the higher dose of harmine also presented increased hippocampal brain-derived neurotrophic factor (BDNF) expression (98).

Further comprehending how AYA can affect fear memory processing might help elucidate how this substance could be useful for treating disorders such as PTSD. Most preclinical studies on this theme focus on how AYA treatment could alter an already established fear memory, which makes sense when considered from a translational point of view. Nevertheless, the results elicited by treatment with AYA and its constituent compounds prior to fear memory formation or during reconsolidation and extinction of already established memories seem to differently affect behavioral responses.

Rats chronically treated with AYA (120 mg/kg, oral) for 30 days and later submitted to CFC and TFC presented enhanced freezing behavior during the test. On TFC test, freezing was increased even before the CS presentation. Treatment with higher doses (240 and 480 mg/kg) did not alter behavioral expression (99). DMT (10 mg/kg, i.p.) also seems to influence freezing behavior when administered 1 h prior to TFC, increasing this behavior during training, but not during test (96). Chronic treatment with smaller doses of DMT (1 mg/kg, i.p.) before the conditioning protocol, on the other hand, does not increase freezing behavior on CFC and TFC tests (100).

β-carbolines, on the other hand, seem to present an amnesic effect when administered to animals prior to fear memory tasks. Harmaline (1 mg/kg, i.p.) injected to mice 5 min before a step-down passive avoidance task training prevented increased latency to step down 24 h later during the retention test (101). Harmine administered (10 mg/kg, i.p.) to rats 1 h before CFC and TFC conditioning decreased freezing behavior when animals were tested for CFC 24 h later but did not affect freezing on the TFC test 48 h later. Rats submitted to a plus-maze discriminative avoidance task (PMDAT) also were treated with harmine (5, 10, 15 mg/kg, i.p.) before the training. In this task, a regular elevated plus maze is used, but one of the closed arms will be equipped with visual and sound aversive stimuli. Every time the animal enters the aversive arm during training, the stimuli is continuously presented until the animal lefts the arm. Although during training all animals learned to avoid the aversive arm, indicating memory acquisition, 24 h later all harmine-treated groups were not significantly avoiding the aversive arm when compared with the other nonaversive arms (102).

Rats trained in a CFC protocol that received a single dose of ayahuasca (60 mg/kg) 20 min before or 3 h after a re-exposure session to the conditioned context present less freezing behavior when tested in the same context one day later. This decrease is not observed during the re-exposure session itself nor during the test when the animals are treated without being re-exposed to conditioned context previously to testing. Interestingly, the same results are reproduced even for remote memories, when the animals are tested 22 days after the re-exposure. These results suggest that ayahuasca could be acting on memory reconsolidation, reshaping the fear response as a consequence of the memory trace becoming more labile (12).

Regarding extinction protocols, the results are conflicting. The treatment with a single dose of DMT (10 mg/kg, i.p.) 1 h prior extinction training on TFC, as well as chronic treatment with smaller DMT doses (1 mg/kg, i.p.), seem to facilitate fear extinction (96, 100). However, in the CFC protocol, even multiple treatment-paired extinction sessions were not able to extinguish the fear response (96). On mouse submitted to TFC, psilocybin administration (2.5 mg/kg, i.p.) prior to extinction training decreased fear expression during training and during extinction tests 1 and 6 days after training (103).

AYA (adjusted to contain 0.3 mg/kg of DMT) administration to rats 1 h before a CFC extinction session decreases freezing behavior during the sessions, but the reduction is not sustained one day later on the extinction test. However, when the animal is submitted to two treatment-paired extinction sessions, the extinction memory is recalled when tested one day later (13). When the AYA (60 mg/kg) treatment was administered 20 min before or 3 h after a retrieval session, one day prior to extinction training, a single dose was sufficient to facilitate the acquisition of extinction memory (12). Chronic AYA treatment (120 mg/kg, oral) before CFC altered freezing expression, but did not affect extinction learning (99).

Even after extinction, re-exposing animals to the US can promote the reinstatement of the fear response. Treatment with AYA (60 mg/kg) 20 min before or 3 h after a retrieval session can prevent reinstatement after the acquisition of the extinction memory (12). However, when the treatment (adjusted to contain 0.3 mg/kg of DMT) is carried out during the extinction session, although the extinction memory is acquired, the reinstatement is not prevented (13).

The differences between the results observed for treatment with isolated compounds of AYA suggest the β-carbolines could be more effective targeting HPP-dependent memories, as is the case of CFC, step-down passive avoidance and PMDAT tasks. These amnesic effects can be an indication that β-carbolines are promoting increased neurogenesis, once increasing HPP neurogenesis on HPP-dependent tasks can promote forgetting (104). However, all available data test these substances on memory acquisition and early consolidation, while data regarding its effects on already established memory traces are still lacking (101, 102).

DMT, on the other hand, does not affect memory acquisition and early consolidation, although its administration before TFC enhances freezing response during the training. However, during extinction protocols for TFC, treating the animal with a single dose 1 h before the extinction session or a chronic treatment with smaller DMT doses can facilitate fear extinction, but the same result does not occur on CFC trained animals (96, 100). These results suggest that, although DMT can interfere with fear processing, it is not effective for targeting HPP-dependent memories.

When AYA itself is being tested, the extinction and reconsolidation efficacy was linked to duration and frequency of exposure to the conditioned context. Extinction retention was dependent on animals being re-exposed to the conditioned context at least two times (12, 13). The current most widely accepted view on consolidation of recent into long-term memories posits that during this process the memory trace will increasingly rely more on cortical than on HPP activation (105). However, prolonged re-exposure to the conditioning context can lead to HPP activation, which then can make the already established memory once again susceptible to neurogenesis induced forgetting (104, 106). These data are reminiscent of exposure therapy protocols currently being employed to treat PTSD (31, 107). The effect of AYA on TFC reconsolidation and/or extinction protocols still needs to be tested.

Although these studies suggest that AYA and its components modulate fear memory processing, the conditioning protocols tested responses induced by nonpathological fear memories, since no protocol induced generalized fear behavior and most treatments did not increase anxiety-like responses when tested using the EPM (12, 13). The question remains whether the outcomes would be different when tested for pathological-like memories.

Trauma focused therapeutic interventions are currently widely employed and advised for treatment of PTSD (108). These interventions are based on the previously discussed premise that memory recall can facilitate the alteration of emotional and behavioral responses associated to the memory trace. However, even though data supporting trauma-focused therapies are the most robust for all currently employed therapeutic strategies, they are not always effective and, in many cases, the improvement is not sufficient to abolish PTSD diagnosis (109). Additionally, there is also reported variability in pharmacological treatment efficacy when comparing different traumatic events. For example, cannabidiol (300 mg) is effective in reducing anxiety and cognitive impairment triggered by traumatic memory recall only for nonsexual trauma (110).

Among other things, this variability can be a consequence of different symptomatology. The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) recognized a dissociative PTSD subtype, characterized by the presence of depersonalization and derealization symptoms (111). Compared with nondissociative PTSD, this subtype seems to be linked to increased cortical inhibition of limbic structures (112). In patients with borderline personality disorder, higher prevalence of dissociative experiences was a predictor for impaired acquisition and extinction of an AMY-dependent classic conditioning task (113).

Although animal models can be useful to understand different interventions outcomes on specific circuits, they lack precision to evaluate specific symptoms. Broadening the understanding of how PTSD can alter patients' brain functioning is essential to the development of better models.

Evidence for Ayahuasca' Effects on Fear and Anxiety Responses in Humans

Neuroimaging techniques used to investigate how AYA intake alters neural substrates suggest that it modulates structures and networks relevant to emotional processing.

In one study, healthy male subjects were randomized to receive AYA (adjusted to contain 1 mg/kg of DMT) or placebo and 100–110 min after intake participants were submitted to single photon emission tomography (SPECT) to assess how AYA altered regional cerebral blood flow (rCBF). Compared with placebo, AYA bilaterally increased rCBF on anterior insula and inferior frontal gyrus, increased rCBF on the right anterior cingulate and frontomedial cortex, and on the left AMY and parahippocampal gyrus (114). Another SPECT study, this time evaluating depressive patients, compared rCBF prior to and 8 h after AYA intake (2.2 mL/kg). The treatment increased rCBF on left nucleus accumbens, right insula and left subgenual anterior cingulate cortex (11).

Functional magnetic resonance imaging (fMRI) was used to assess AYA effects on the default mode network (DMN) in healthy volunteers.

Subjects were evaluated before and 40 min after AYA intake (2.2 mL/kg) when performing a verbal fluency task or during resting state. Results contrasted DMN signal during resting state and during task performing, and a decrease in signal was reported for the anterior and posterior cingulate cortices, mPFC, precuneus and inferior parietal lobules (115).

Hallucinogens effects evaluated through social cognition tasks can also be useful to better comprehend how these substances can alter emotional processing. Studies with healthy and clinical samples have been performed to evaluate how they can interfere with REFE.

A study with healthy volunteers compared how different LSD doses (100 or 200 μg) could alter REFE performance when compared with placebo. Subjects were tested 5 h after intake of the lower dose and 7 h after intake of the higher one, and both doses decreased accuracy for recognition of fearful expressions (116). Another study by the same group used fMRI to compare how healthy individuals respond when presented to fearful or neutral expressions. Each subject received 100 μg of LSD or placebo 2.5 h before the scan. Compared with placebo, LSD reduced neural response to fearful versus neutral faces on left AMY and right medial frontal gyrus. The AMY activation to fearful faces was also negatively correlated to reported subjective drug effects (117). Also, administration of psilocybin (215 μg/kg) to healthy subjects decreased the recognition of negative facial expressions when compared with placebo (90).

Regarding AYA, healthy volunteers were submitted to fMRI before and after drug intake (25–35 mL, 0.333 ± 0.056 mg/kg DMT), and asked to perform a task with implicit emotional stimuli (neutral, disgusted or fearful facial expressions). Before AYA intake, reaction time was longer when aversive stimuli were presented, but during the AYA effects, the reaction time was no longer different for neutral and aversive stimuli. Together with the behavioral alterations, AMY responsiveness to aversive stimuli was attenuated by AYA, while the anterior insula and the dorsolateral PFC responsiveness increased (118). Similarly, increases in reaction time in a REFE task were observed in healthy volunteers after a single AYA dose (1 mL/kg; ±0.72 mg/mL DMT) (119). On the other hand, a previous study evaluating the effects of a single dose of ayahuasca (1 mL/kg; ±1.58 mg/mL DMT) in healthy volunteers did not identify behavioral differences on REFE performance when compared with the placebo group (120). However, these studies did not assess parameters regarding neural activity, which could be altered even in the absence of behavioral outcomes.

Although the clinical evidence assessing the effects of AYA on fear and anxiety disorders is still scarce, a few observational and experimental studies with healthy subjects explored its effects on trauma, memory, anxiety and phobia measurements.

Long-term members of ayahuasca churches in Brazil (over 15 years), when compared with actively practicing religious individuals from catholic and protestant churches, showed lower scores on phobic anxiety availed through the Symptom Checklist 90 – Revised (SCL-30-R), a self-report inventory to assess psychopathologies (121). An observational, naturalistic study conducted with healthy participants taking part on a AYA traditional indigenous retreat in Peru used the Sentence Completion for Events from the Past Test (SCEPT) to evaluate how the hallucinogenic experience could alter their perception of autobiographical memories, and a significant reduction on scores for negative valence memories was observed when comparing the baseline with postretreatment at the 6 months follow-up. However, it is important to point out that these participants did not present a high level of traumatic childhood experiences, as assessed through the Childhood Trauma Questionnaire scores collected on baseline (14).

An experimental double-blinded study with experienced members of an AYA church assessed panic and anxiety outcomes during the substance peak effects (1 h after ingestion). AYA (3 mL) and placebo scores were compared with baseline, and only AYA was effective in reducing panic-related signs assessed through the Anxiety Sensitivity Index. Anxiety was assessed using the State-Trait Anxiety Inventory (STAI), but the placebo and AYA scores did not differ from baseline (122).

Another study investigated the subjective effects of AYA (1 mL/kg; ±0.72 mg/mL DMT) combined with placebo or cannabidiol (600 mg) on healthy subjects using the Visual Analogue Mood Scale (VAMS). During AYA effects participants reported a decrease in anxiety, independently from the pretreatment group (119).

Regarding clinical populations, a recent case series reported the use of AYA to treat PTSD in war veterans taking part in a retreat. The Post-traumatic Stress Checklist (PCL-5) was used to assess PTSD symptoms and to evaluate clinical changes through the protocol. Most participants (7 out of 8) lowered PCL-5 scores after the intervention, and 5 of them still had lower scores 3 months after the intervention when compared with baseline. More than half of the participants reported intensely experiencing intrusive memories of the traumatic event. After the intervention, the largest improvements were observed in Cluster E symptoms, concerning sleep disturbances, hypervigilance, and concentration difficulties, and although some participants reported a reduction on intrusive memories, it was not statistically significant (15).

AYA was also tested in a randomized, placebo-controlled trial with subjects diagnosed with social anxiety disorder. Participants received a single dose of ayahuasca (2 mL/kg, ±0.68 mg/mL DMT) or placebo and, after the acute effects (300 min after intake), they were submitted to the SPST. During the protocol, anxiety and self-perception of performance were assessed using the VAMS, the Beck Anxiety Inventory and the State Version of the Self-statements During Public Speaking Scale. No significant differences were found between groups on the anxiety measures, but the AYA group showed improved perception of performance when compared with placebo (7).

The observational and experimental data available imply that ayahuasca might be a potential treatment for anxiety and stress disorders; however, there is a lack of studies with clinical populations conducted on controlled settings. Since AYA is an element of traditional cultures, there is an inherent challenge on variability control of AYA studies. It cannot be manufactured with commercial purposes, and the absence of standardized procedures lead to brew batches with highly diverse alkaloid composition and concentration, which reflects on the dosage variability present in naturalistic and experimental settings.

Synthetic formulations are already being tested as a possible alternative to try improving this variability, and to try to deal with ethical problems attached to the use of traditional formulations (123).

Ayahuasca Effects on Fear and Anxiety Responses Through 5HT Signaling

The currently available data suggest that AYA and its constituent substances, that is, DMT and β-carbolines, can modulate fear and anxiety responses. However, molecular and functional data supporting the behavioral and clinical observations are still scarce.

Neuronal and synaptic plasticity mechanisms are a fundamental aspect supporting behavioral flexibility. Increasing effort has been made into elucidating psychedelic induced plasticity, and it is possible that they hold the answer for the fast-acting therapeutic properties these substances apparently have.

Similarly to other psychedelic substances, DMT can promote increased neuritogenesis and synaptogenesis on cortical neurons. This effect is possibly mediated by BDNF interaction with TrkB receptors and subsequent activation of mTOR intracellular signaling pathways (18). Mice chronically treated with harmine (20 mg/kg, i.p. for 10 days) also present increased BDNF expression on the PFC (124) (Figure 1A). In humans, healthy and depressive participants receiving a single AYA dose (1 mL/kg) expressed increased BDNF serum levels 48 h after intake when compared with placebo groups (125).

On cortical neurons, DMT plasticity increasing properties are dependent on 5HT2A receptors activation (18). However, injection of a 5HT2A antagonist into the IL did not prevent AYA facilitation of extinction learning and recall on rats previously submitted to CFC, even though it increased freezing levels during extinction sessions (13). The increased freezing expression might be due to a decrease in the inhibitory control over central AMY projections, since the IL PNs innervate the ITC which then inhibits central AMY (126) and the PNs activation might be regulated by the 5HT2A receptor.

Increased plasticity at the IL is necessary for extinction memory retention (127); however, 5HT2A antagonism did not impair extinction

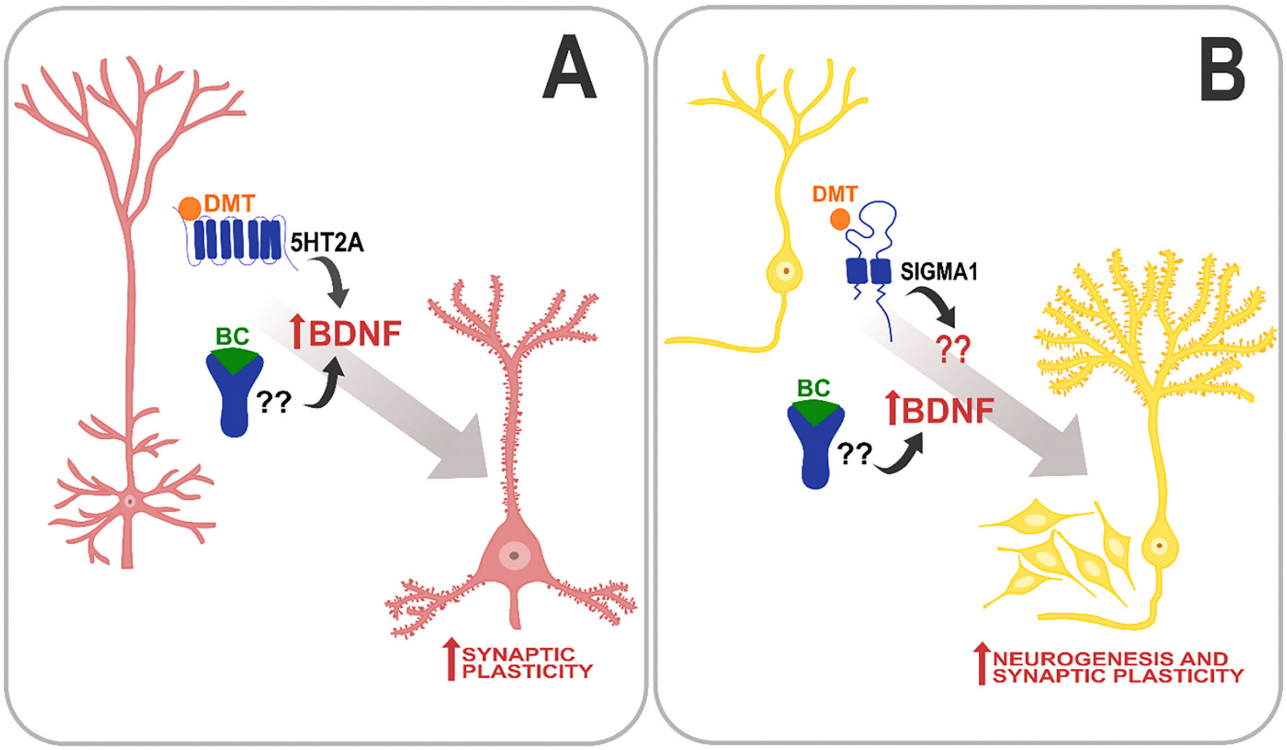

Figure 1. Plasticity-promoting mechanisms triggered by DMT and BC. (A) DMT and BC-induced increase in cortical plasticity are linked to enhanced BDNF levels, although this might result from activation of different receptors. (B) Increased hippocampal plasticity and neurogenesis induced by DMT and BC rely on different molecular pathways. 5HT2A: serotonergic receptor 2A subtype; BC: β-carboline; BDNF: brain-derived neurotrophic factor; DMT: N,N-dimethyltryptamine; SIGMA1: sigma receptor subtype 1.

learning. A possible explanation is the fact that extinction learning relies on BDNF increase on HPP inputs to the IL (128), so even though 5HT2A antagonism could prevent DMT induced plasticity at the IL, the extinction memory was not affected.

On the other hand, the same protocol testing a 5HT1A antagonist prevented AYA effects on extinction retention or recall, although it did not alter the decrease in fear expression during extinction learning (13). IL projections to BLA are necessary for extinction retention (129), and these data suggest that this effect might be mediated by 5HT1A activity. The IL projects to BLA PNs and INs, and during fear extinction synaptic efficacy of PNs innervation is reduced through a process that might resembles a long-term depression (126). Since 5HT1A receptors are relevant to modulate input-generated excitability on cortical PNs, it is possible that they are involved in the synaptic efficacy decrease. AYA and DMT acute treatments in rodents can lead to an increase in anxiety-like responses on EPM and FST, despite also inducing an antidepressant effect on the FST (95, 96). This increase in conflict anxiety responses could be a consequence of 5HT2A receptor activation by these compounds. Interestingly, different from what is observed after AYA and DMT administration, β-carbolines do not induce an increase in anxiety-like response despite their mild affinity for 5HT2A receptors (98)

Harmine chronic administration (20 mg/kg, i.p. for 10 days) can increase HPP neurogenesis in mice (124), which could also explain the behavioral outcomes of β-carbolines administration on HPP-dependent tasks (Figure 1B). Opposingly to the effects of 5HT2A activation on cortical neurons, on the HPP this receptor is not linked to plasticity increase. Rats treated with DOI, another psychedelic compound, present decreased HPP BDNF mRNA expression, whilst still having increased BDNF levels on cortical areas. This modulation was completely blocked by a 5HT2A antagonist administration. Interestingly, immobilization stress also results in a decrease in BDNF mRNAs on the HPP through 5HT2A activation (130).

Hence, 5HT2A activation on the HPP possibly does not contribute to the antidepressive and might be responsible for the anxiogenic DMT effects. Nevertheless, DMT treatment can induce neurogenesis on HPP, but the mechanism seems to result from sigma-1 receptors activation instead (131) (Figure 1B).

It is possible that the β-carbolines effect on depressive-like behaviors as well as in HPP-dependent memories could rely on its antagonism of monoamine oxidase enzymes, that could increase circulating levels of 5HT. Additionally, since they do not present affinity for 5HT1A receptors, they would not activate the raphe nuclei autoreceptors, preventing the decrease in 5HT release observed after acute administration of 5HT1A agonists (79, 132).

Possibly, β-carbolines administration could somehow predominantly activate specific raphe nuclei pathways, since the behavioral responses observed after its administration resemble the median raphe forebrain bundle tract mediated responses. This pathway directly controls HPP activity, and increased activity in this circuit is linked to antidepressant behavioral responses (133). Also, this pathway stimulation can desynchronize HPP theta oscillations, which are relevant for associative memory processing (134). This could explain why β-carbolines treatment seems to be more effective on interfering with HPP-dependent memory processing. The anxiety-like responses evoked by acute treatment with DMT suggests this substance might be acting on substrates innervated by the DRD/DRC projections and would explain the lack of effects of DMT treatment on CFC extinction, since this task is HPP-dependent. On the other hand, β-carbolines preferential effect on DRI/MnR pathway could explain the lack of treatment-induced anxiety-like behaviors, despite their mild 5HT2A affinity, besides the antidepressant properties and amnesic effects on HPP-dependent memories processing.

Future Perspectives

Although AYA has been employed in therapeutic and religious contexts for centuries, there is still a lot to be dissected on its biological and psychological effects. The complex nature of this brew, that combines different alkaloids, adds another layer of intricacy to an already challenging task.

In currently available literature, DMT is frequently mentioned as the main psychoactive constituent of AYA, however many studies discussed throughout this review highlight relevant differences on isolated DMT effects when compared with AYA or β-carbolines. Although β-carbolines lack the mind-altering properties of AYA and DMT, they seem to have therapeutic properties as well. More studies investigating the molecular pathways supporting antidepressant and memory effects elicited by them could improve comprehension on AYA, as well as indicate contexts where isolated β-carbolines could be employed as treatment. Hereof, differences on HPP plasticity and neurogenesis molecular pathways activated by DMT and β-carbolines could clarify the distinct behavioral outcomes promoted by these substances.

Regarding human studies, there is still a long way to go. The observational and experimental studies investigating healthy populations support the relevance of further investigations; however, clinical studies are still lacking, especially in controlled settings. The unknown risks that psychedelic intake can represent to specific clinical populations together with the prejudice accumulated from years of criminalization are some of the challenges faced by the researchers. On top of that, the increasing hype around psychedelic therapeutic effects can result in a positive bias. Controlling this bias is also a difficult task, since blinding is still a challenge for the field.

Final Remarks

In an attempt to associate the emerging data on hallucinogens therapeutic properties for treatment of mental disorders and the classical Deakin/Graeff theory linking fear and anxiety responses to 5HT signaling, Carhart-Harris and Nutt (2017) propose that hallucinogen-induced 5HT2A agonism, and the subsequent activation-induced plasticity, mediate active coping in a similar idea to the DRD/DRC projections. In the same review, they also propose that passive coping would be the mechanism supporting conventional antidepressants efficacy, such as SSRIs, and would be mediated by 5HT1A activity, similarly to the DRI/MnR pathway (135).

Through that perspective, AYA therapeutic properties could be a combination of active and passive coping mechanisms. The β-Carbolines apparent capacity to modulate HPP activity, in what they call passive coping, could be a relevant factor behind AYA effects on CFC extinction that could not be reproduced by DMT treatment. DMT, on the other hand, seem to behave similarly to what is proposed for other classic hallucinogens, favoring active coping strategies and mechanisms.

Author Contributions

LTLG, MSc prepared the original draft. RGDS, PhD intellectual conceptualization, review and editing the manuscript. JECH, MD, PhD intellectual conceptualization, review and editing the manuscript.

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Psychedelics

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RESEARCH REPORT

An estimate of the number of people with clinical depression eligible for psilocybin-assisted therapy in the United States

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This study aims to estimate the lower, middle, and upper bounds of potential demand for psilocybin-assisted therapy (PSIL-AT) for major depressive disorder (MDD) and treatment-resistant depression (TRD) in the United States. We calculated potential PSIL-AT demand for MDD and TRD by estimating the number of U.S. patients with MDD, identifying those in treatment, and determining who qualifies as having TRD. We established a range of estimates using the exclusion criteria from the largest trials to date on PSIL-AT for MDD or TRD. Estimates ranged from lower-bound through stringent criteria, mid-range by focusing on likely real-world scenarios, to upper-bound by accounting for double counting for patients with multiple comorbidities. A significant portion of patients with MDD and TRD is ineligible for PSIL-AT due to disqualifying conditions. Percentage of patients who are eligible are 24% (lower-bound), 56% (mid-range), and 62% (upper-bound). Variance was largely influenced by the removal of alcohol and substance use disorders as exclusion criteria, as well as removing the double counting from comorbid psychiatric and cardiovascular conditions. The analysis outlines the public health implications of providing PSIL-AT for MDD and TRD, emphasizing that the effective demand will be shaped by insurance coverage, state-level regulations, and the availability of trained providers. These findings suggest the need for careful policy planning and resource allocation to ensure equitable access and effective implementation of PSIL-AT across diverse populations and regions.

Keywords: Psilocybin, depression, exclusion criteria, psychedelic therapy.

Introduction

Psilocybin-assisted therapy (PSIL-AT) has been designated by the Food and Drug Administration (FDA) as breakthrough therapy for patients with either a diagnosis of major depressive disorder (MDD) or treatment-resistant depression (TRD) (1). TRD is defined as having at least two treatments with antidepressant medications, at adequate doses and for an adequate duration in the current depressive episode, without significant relief from symptoms related to MDD (2). Recent clinical trials have defined inclusion and exclusion criteria specifically for TRD (3) or MDD (4, 5), the latter of which may also include patients with TRD. As FDA approval and subsequent legalization for medical use of psilocybin is now being considered (6), it is important to understand the possible public health impact from the introduction of PSIL-AT in the United States. This, in turn, requires an estimation of the potential demand. We chose to define a clinical lower-bound, mid-range, and upper-bound estimates of the demand for PSIL-AT as a treatment for MDD or TRD.

Results

As shown in Table 1, of the 14.8 million people with MDD, 9 million are being treated, and 2.7 million meet criteria for TRD.

Table 2 illustrates the percentage of patients deemed eligible for PSIL-AT, accompanied by corresponding estimates for the number of individuals being treated for MDD or TRD who are eligible for this therapeutic approach.

The lower-bound estimate indicates only 24% of patients with depression would meet strict clinical trial exclusion criteria for PSIL-AT. This amounts to 2.2 million patients currently undergoing treatment for MDD or 0.6 million patients when considering only those with TRD.

In applying exclusion criteria likely to operate in real-world clinical settings (the mid-range estimate), we observe a notable increase in the proportion of included patients to 56%. Application of these more permissive criteria would expand the pool of eligible patients being treated for MDD or TRD to 5.1 million or 1.5 million, respectively. The exclusion of alcohol and substance use disorders accounts for a significant portion of this adjustment, contributing to 32% of the difference.

Finally, the upper-bound estimate, which adjusts for double counting between different medical conditions, raises the estimate to 62% of the patient population with depression being eligible for PSIL-AT. This translates to 5.6 million individuals and 1.7 million eligible for PSIL-AT when considering MDD and TRD, respectively. This adjusted increase is primarily attributed to the co-occurrence of cardiovascular and psychiatric comorbidities, with each contributing to a 3%–4% increase in eligible patients.

In addition to our base estimates, we conducted a sensitivity analysis to evaluate the impact of varying assumptions on the overall demand projections for PSIL-AT. Specifically, we assigned beta distributions with a range of plus or minus 50% of the baseline values to each of the comorbidity prevalence estimates shown in column 3 of Table 2. Using @RISK (Palisade Corporation, version 8.1.1) software, we simulated the overall uncertainty in the final estimates of the number of patients eligible for PSIL-AT among those with MDD and TRD.

The results of the sensitivity analysis are depicted in Figures 1 and 2. For patients with MDD, the analysis produced a 95% confidence interval (CI) of 4.7 million to 6.6 million eligible individuals, while for patients with TRD, the 95% CI ranged from 1.4 million to 1.9 million. These ranges highlight the potential variability in our estimates based on changes in the assumptions underlying comorbidity prevalence, emphasizing both the robustness and the uncertainty inherent in our projections.

Discussion

This analysis outlines the dimensions of the public health implications of providing PSIL-AT for the treatment of MDD and TRD. Our estimates of

Table 1. Estimates of number of people who would qualify as having MDD, those in treatment, and those who have TRD

Population	% of MDD population	Number of patients	Source
Patients with MDD in United States	–	14,800,000	(7)
Patients with MDD who received treatment in past year	61%	9,028,000	(2)
Patients with MDD who experience 2+ treatment failures (TRD)	30%	2,708,400	(2)

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Table 2. Prevalence of disqualifying comorbidities in the largest clinical trials utilizing PSIL-AT for MDD or TRD with number of patients eligible

Disqualifying comorbidities	Trials with this exclusion criterion	Prevalence of disqualifying comorbidity in patients with MDD or TRD according to: 1. Trial exclusion criteria[1] CI (Confidence Interval), OR (Odds Ratio), SE (Standard Error)	2. Real-world exclusion criteria	3. Real-world exclusion criteria adjusted for comorbid conditions[2,3]
Psychotic or manic disorder	(3–5)	19% (8)	19% (8)	23.2% (9)
Suicide attempt in the past year		8.0% [95% CI=(3–14%)] (10)	8.0% (10)	
Diabetes, uncontrolled	(5)	2.9% [OR=1.4 (1.4–1.5)] (11, 12)	2.9% (11, 12)	8.0% (13, 14)
Stroke	(3–5)	1.9% [OR=2.4 (2.0–2.8)] (11)	1.9% (11)	
Heart attack in last year	(3–5)	2.7% [OR=0.9 (0.8–1.1)] (11)	2.7% (11)	
BP 140+/90+, treatment-resistant		2.0% [OR=1.4 (1.3–1.4)] (11, 15)	2.0% (11, 15)	
Epilepsy		3.7% [OR=2.6 (2.3–3.0)] (11)	3.7% (11)	3.7% (16)
Personality disorder	(4)	2.2% [SE=.36] (16)	2.2% (17)	2.2% (11)
Hepatic impairment (Child-Pugh > 7)[4]	(5)	1.8% [SE=.10] (18)	1.8% (18)	1% (17)
Alcohol dependence	(3–5)	20.0% (19)	–	
Drug dependence		12.0% (19)	–	–
Other cardiac conditions (Long QT, cardiac hypertrophy, heart failure, tachycardia at rest, atrial fibrillation, prosthetic valve)	(5)	–	–	–
Pregnancy		–	–	–
Unwillingness to discontinue SSRIs		–	–	–
Unwilling or unable to discontinue formal psychotherapy		–	–	–
Have used psychedelics in the past 5 years; have used psychedelics 10+ times in the past		–	–	–
Have 1st degree relative with psychotic disorder or bipolar disorder		–	–	–
Received ECT or TMS in the past 90 days	(5)	–	–	–
Percentage of patients who would be ineligible for PSIL-AT	–	76%	44%	38%
Percentage and number of patients with MDD and TRD eligible for PSIL-AT				
Percentage of patients eligible for PSIL-AT	–	24%	56%	62%
Number of patients being treated for MDD who are eligible for PSIL-AT	–	2.2M	5.1M	5.6M
Number of patients being treated for TRD who are eligible for PSIL-AT	–	0.6M	1.5M	1.7M

[1]Where available, confidence intervals, odds ratios, and standard errors were reported.
[2]Double-counting calculations used prevalence estimates from the general population and are not MDD-specific.
[3]For sensitivity analysis, each comorbidity was assigned a beta distribution with alpha and beta parameters of 2 and maximum/minimum values of +/−50%
[4]Hepatic impairment estimates came from the general population and are not MDD-specific.

demand are subject to contingencies pending FDA decision around PSIL-AT. One possibility that could elevate demand beyond our projections involves off-label use of PSIL-AT for conditions other than depression. Evidence from psychiatric prescription practices suggests that psychiatric medications are used to treat a range of conditions outside their original FDA-approved indication. A retrospective analysis, for example, revealed that 91% of patients currently prescribed antidepressants would not meet randomized clinical trials eligibility based on their medical status (20). This discrepancy suggests that the eligibility for PSIL-AT might be significantly higher than our estimates if PSIL-AT is used to treat other medical conditions such as anxiety disorders, chronic pain, and other psychiatric disorders, either off-label or following eventual FDA approval for these conditions. We are aware of no reliable data that would allow us to estimate current and especially future prevalence of treatment seeking, which introduces further complexity into our demand projections.

Conversely, other psychedelics granted FDA breakthrough status such as lysergic acid diethylamide for general anxiety disorder (21) may be used off-label in the future to treat patients with MDD or TRD given high comorbidity between these conditions (22). If these other psychedelics are given FDA approval in the future, the demand estimate would need to be modified to distribute across the relative uptake of all psychedelics that have therapeutic effects on depression.

Additionally, there are countervailing practical considerations for PSIL-AT which are likely to constrain effective demand to levels lower than our estimates. These include the availability of trained providers, geographical access to therapy, and patient preferences related to cost, treatment duration, and cultural acceptability. For example, patients living in urban centers are likely to have greater access to PSIL-AT facilities and therapists, while rural areas may lack sufficient trained professionals and infrastructure for effective administration. States that have already legalized psychedelic therapies like Oregon and Colorado may asymmetrically dominate demand in the short-term while other states work through establishing their own regulatory framework for PSIL-AT.

Recent clinical trials have evaluated psilocybin's effectiveness as both monotherapy for depression (3, 4), and as an adjunct to established

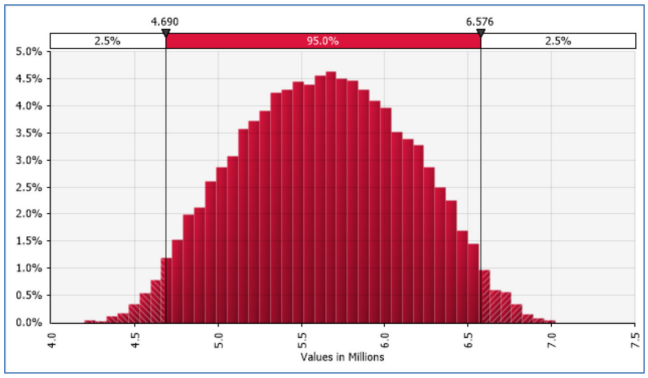

Figure 1. Patients being treated for MDD who are eligible for PSIL-AT. Multivariate sensitivity analyses, 20,0000 iterations.

antidepressant regimens (2, 23). In a 2020 article, Luo *et al.* reported that 70% of individuals with MDD utilize antidepressants (24). Therefore, if FDA approval of PSIL-AT for MDD restricts it to monotherapy, its applicability would be significantly narrowed, given evidence suggesting that nearly half of patients attempting to taper off psychotropic drugs face difficulties in completely stopping their medication (25).

Heterogeneity in the ways states choose to implement PSIL-AT will also impact effective demand. Existing legalization efforts in Colorado and Oregon may serve as a model for how PSIL-AT is rolled out nationwide post-FDA approval. Colorado's Natural Medicine Health Act, for example, mandates that licensed facilitators refrain from treating patients with many of the comorbidities discussed in this paper (26). However, patients may get clearance from a medical professional to proceed with psychedelic therapy despite exclusionary conditions (26). Whether states choose to follow Colorado or Oregon's example or implement their own regulations is unknown and makes demand estimation difficult.

Perhaps most importantly, the prospective demand will be shaped by the extent to which insurers, both public and private, include PSIL-AT in their coverage schemes. Medicaid is the largest health care payer in the United States. It covered 85 million low-income beneficiaries in 2023 (27) and 18%–20% of its beneficiaries are likely to have clinical depression (28). Thus, decisions Medicaid makes regarding the conditions under which PSIL-AT services are made available and reimbursed will be particularly important in determining effective demand. Ultimately, whether PSIL-AT has a significant impact on the mental health of the U.S. population depends on the decisions of public and private third-party payers, and Medicaid is the single most important among them.

The range of eligibility estimates (24%–62%) highlights the need for flexible healthcare planning and resource allocation strategies. Policymakers and healthcare providers must prepare for this variability by ensuring that sufficient resources—including trained therapists, facilities,

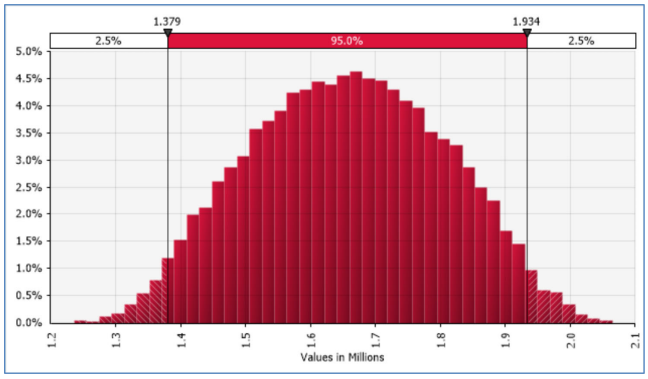

Figure 2. Patients being treated for TRD who are eligible for PSIL-AT. Multivariate sensitivity analyses, 20,0000 iterations.

and financial support—are available to meet demand under various scenarios. This flexibility will be crucial as more data becomes available post-FDA approval, allowing for adjustments in resource distribution and ensuring equitable access to PSIL-AT across diverse populations and regions.

This study serves as a basis for policymakers, healthcare payers, and pharmaceutical companies to gauge the potential public health impact of PSIL-AT pending FDA approval. As the field progresses, further research is warranted to explore psilocybin's therapeutic range, including its application to a broader array of mental health conditions and its integration into nonclinical settings. Future studies should focus on regional and demographic variations, the role of state regulations, and cultural attitudes toward psychedelic therapies. Additionally, longitudinal studies tracking the real-world implementation of PSIL-AT will be essential for assessing how initial projections align with actual demand, influencing future policy decisions and resource allocation efforts. Such analyses will refine our understanding of the potential public health impact of psychedelic therapies and help to guide policy and clinical practice.

Methods

Overview

To calculate the potential demand for PSIL-AT for TRD and MDD in the United States, we estimated the number of patients with MDD, identified how many of these patients are currently undergoing treatment, and further defined who would qualify as having TRD. We established a range of estimates: a lower-bound estimate through stringent application of exclusion criteria used in clinical trials; a mid-range estimate by considering only exclusion criteria likely to be relevant to real-world clinical scenarios; and an upper-bound estimate by refining our analysis to account for patients with two or more comorbid conditions in addition to MDD. Since each comorbidity would exclude potential patients from safely accessing PSIL-AT, we eliminate the double counting that would result from co-occurring disqualifying conditions.

We used an estimate of MDD cases in the United States based on the 2021 National Survey on Drug Use and Health (6). We then focused on the subgroup of individuals who had received treatment for their MDD in the past year and further adjusted to estimate the number of individuals who would qualify as having TRD (1).

In focusing on individuals currently undergoing treatment for depression, our approach ensures that demand estimates are grounded in real-world clinical settings, where PSIL-AT will likely be administered should they receive FDA approval. This allows us to work with a population whose treatment-seeking behaviors and clinical profiles are well documented, providing a reliable foundation for demand estimation. By choosing this baseline, we also avoid speculative assumptions about the future behavior of untreated individuals (acknowledging a potential influx post-FDA approval), ensuring that our projections remain conservative and methodologically consistent. Moreover, this approach allows for flexibility, as future research and data collection can expand upon these estimates by incorporating the potential uptake of PSIL-AT among currently untreated individuals.

A portion of this patient population fails to meet clinical eligibility for PSIL-AT due to a disqualifying medical condition. To estimate the portion of such disqualified patients, we identified the clinical exclusion criteria from the largest clinical trials to date on PSIL-AT for MDD or TRD (3–5) (see Additional Materials). Where available, we included confidence intervals and error margins from prevalence data looking at depression with different comorbidities. We constructed three different estimates of the potential demand for PSIL-AT based on three respective sets of assumptions regarding eligibility for PSIL-AT:

1. All patients with the exclusion criteria used in clinical trials, assuming no comorbid medical conditions. This represents the theoretical lower-bound of patients who would be eligible for PSIL-AT and is represented as the column labeled "1. Trial exclusion criteria" in Table 2.
2. Same as #1 but removing exclusion criteria that would be relevant in a clinical trial setting but would not apply in real-world clinical settings. This represents a mid-range estimate and is labeled "2. Real-world exclusion criteria" in Table 2.

3. Same as #2 but with further adjustment for the prevalence of comorbid medical conditions (e.g., psychosis and acute suicide risk). This represents an upper-bound estimate and is represented as "3. Real-world exclusion criteria adjusted for comorbid conditions" in Table 2.

We applied these sets of assumptions twice, to patients with MDD and to patients with TRD.

Across all estimates, we did not gather prevalence data on medical conditions that were transient (i.e., pregnancy), modifiable with a provider (i.e., tapering of a SSRI), niche with little to no reliable prevalence data available in patients with depression (i.e., diagnosed psychosis in first-degree family members or cardiac arrythmias), constructs of effective study design (i.e., discontinue existing psychotherapy or previous psychedelic use), or experimental (i.e., deep brain stimulation or vagal nerve stimulation).

In evaluating "2. Real-world exclusion criteria", we considered both the pharmacological mechanisms of psychedelic agents and the clinical insights of one of the paper's authors (Raison). Our premise is that the neurobiological effects of psilocybin will be the same in real-world clinical practice as they are in trials, thus warranting our inclusion of conditions known to be affected directly by these neurobiological mechanisms in our demand estimation. The neurological mechanism of psilocybin (29) is thought to destabilize underlying mania and psychosis (30), trigger latent epilepsy (31), and exacerbate acute suicide risk (32). PSIL-AT also exhibits underlying serotonergic effects on the body (33), which are known to cause cardiovascular stress exacerbating risk of stroke, heart attack, diabetic complication, and other sequela of hypertension (34). Additionally, severe liver dysfunction may alter the metabolism of psychotropic medications, necessitating its inclusion as a criterion for exclusion in clinical practice (35).

The benefits of PSIL-AT for the treatment of personality disorders have been discussed but are currently unsubstantiated (35) and we therefore retain it as an exclusion criteria in this analysis. We removed alcohol use disorder and substance abuse disorder from our list of exclusion criteria because evidence suggests that PSIL-AT can be beneficial for patients with these conditions (31, 36).

To avoid double counting, we then refined the resulting estimate based on the prevalence of comorbidity between the different exclusionary conditions. This is represented as "3. Real-world exclusion criteria adjusted for comorbid conditions" in Table 2. When available, we used the prevalence of comorbid conditions among people with clinical depression. Where this was not possible, we used estimates of the prevalence of comorbid conditions in the general population. For example, the 12-month incidence of suicide attempts among patients reporting psychosis and any other psychiatric condition, in this case clinical depression, was 47.4% (9). Utilizing these data, we adjusted for the potential double counting of patients ineligible due to both psychosis and acute suicide risk, resulting in a revised combined prevalence of 23.2%. Similarly, we found high comorbidity between uncontrolled diabetes (13), stroke, heart attack, and treatment-resistant hypertension (14) and formulated a total estimate of 8.0%.

Author Contributions

SFR: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Project administration.
CLR: Writing – Review & Editing, Supervision.
EM: Writing – Review & Editing, Supervision.
All authors discussed the results and contributed to the final manuscript.

Designation of Corresponding Author and Lead Contact

SFR is designated as the corresponding author and lead contact for this paper. He has taken responsibility for coordinating the effort, overseeing the data integrity, handling the submission process, and communicating with the journal pre- and post-publication. SFR ensures that all authors have approved the final version of the manuscript and adhere to all editorial and submission policies.

Conflicts of Interest

SFR confirms that he was a consultant at Sunstone Therapies. EM serves as adjunct faculty at UC Berkeley's Collaborative for the Economics of Psychedelics which has received financial support from the Usona Institute. CLR discloses that he serves as a consultant for Usona Institute, Otsuka, and Novartis. There are no other conflicts of interest among the authors, and all authors have disclosed any related work under consideration elsewhere.

All authors have agreed to the order of authorship, affirming their contributions to the work as detailed above. In case of any authorship disputes, the authors will resolve them internally without involving the journal editorial process.

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RESEARCH REPORT

What motivates spiritual health practitioners in psychedelic-assisted therapy? A qualitative study and implications for facilitator training practices

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Spiritual health practitioners (SHPs), also known as healthcare chaplains, are increasingly involved in facilitating psychedelic-assisted therapies in clinical trials and community settings. Although the motivations of therapeutic practitioners are known to impact clinical decision-making and treatment outcomes, little research has investigated what drives SHPs to pursue this work. This qualitative study examined $n = 15$ SHP's (60% female; $M_{Age} = 46.57$) who were involved in legal administration of psychedelic-assisted therapy. An inductive-deductive qualitative analysis approach yielded two major themes: (1) Initial Motivation for Practicing PAT, and (2) Ongoing Sources of Meaning and Fulfillment. The SHPs in this study often cited personal experiences as key motivations for entering this field, frequently linked to a significant personal encounter with psychedelic use. The most common Ongoing Sources of Meaning and Fulfillment included witnessing healing in others and experiencing positive personal impacts from facilitating psychedelic-assisted care. This article addresses the substantial role that personal psychedelic experiences appear to play in SHPs' motivations to pursue this area of practice. Such experiences provide valuable first-hand knowledge of the unique phenomenology of psychedelic treatment, although they can also potentially introduce biases and reduce objectivity. Training and certification guidelines set by the Association for Clinical Pastoral Education (ACPE) may help address these risks for SHPs through heavy emphasis placed on self-literacy and reflective learning components. Guided by these findings, we introduce a novel reflective learning exercise, as well as several existing ACPE learning components that may support psychedelic facilitators and facilitators-in-training from any professional background.

Keywords: Chaplaincy, psychedelic-assisted therapy, psychedelic facilitation, qualitative methods, spiritual health.

Introduction

Psychedelic-assisted therapy (PAT) involves the administration of a psychedelic compound (e.g., classic psychedelics such as psilocybin or lysergic acid diethylamide as well as MDMA and other compounds) together with therapeutic support (1–3). Evidence for the benefits of PAT for addressing several difficult-to-treat conditions (PTSD, treatment-resistant depression, demoralization among cancer patients) is mounting (4–6), and correspondingly, the utilization of PAT interventions is growing. In the United States, legal frameworks for supervised use of psilocybin have been enacted in Oregon and Colorado (7, 8), although most psychedelic compounds remain federally illegal. Recent state-level legal changes and the growing mental health crisis have sparked burgeoning research on the therapeutic use of various psychedelic compounds, as well as a rapid expansion of certification and training programs for PAT facilitation.

Among evidence-based psychosocial treatments, a distinctive feature of PAT is that it is simultaneously a pharmacological intervention *and* a clinician-facilitated therapy (9). PAT facilitators therefore play a key role in the experience that clients' have during preparation for their psychedelic dosing session, during the dosing session itself, and in integration of the experience after the acute effects of the psychedelic agents have worn off (10, 11). Several attributes of PAT make it a unique treatment to facilitate, compared with existing evidence-based therapies. These include the intense phenomenology of a psychedelic experience (which typically involves marked perceptual, affective, and cognitive changes, including hallucinations); the duration of these experiences (which can last 4–48 h); and their immediate and enduring sequelae which often involve changes in the patients' worldview (9, 12). Research characterizing the best therapeutic practices for PAT facilitation and the training components that adequately prepare facilitators to implement them is, therefore, important for the optimization of PAT. To date, very little research has characterized the attributes of PAT facilitators or investigated the role of facilitator attributes in providing effective care (2).

Spiritual health practitioners (SHPs; i.e., healthcare chaplains) have increasingly played roles in PAT facilitation in clinical trials and community practice contexts. SHPs are healthcare professionals who are employed in approximately two-thirds of all hospitals in the United States (13, 14) and trained to work on integrated care teams to recognize and respond to emotional, psychosocial, spiritual, religious, existential, and moral concerns (15, 16). SHPs training involves 1600 hours of clinical training in an accredited, year-long clinical residency, and additional professional certification requirements including published scholarship and committee appearances (17). Given the prevalence of spiritual and existential themes reported by those who have undergone PAT (18, 19), and the potential mediating role that these experiences may play in PAT benefits (19, 20), the training and professional expertise of SHPs is a natural fit for PAT. SHPs are ideally equipped to engage the spiritual dimension of biopsychosocial-spiritual models of care (21, 22) and are uniquely qualified to respond to spiritually impactful experiences that may arise for patients, including spiritual distress (19). In a prior qualitative study, these authors investigated the roles that SHPs play in PAT and the competencies they identified with as members of PAT treatment teams. Results indicated that training and formation (the ongoing internal and communally based development of the person as a spiritual care provider or clergy person) assist in SHPs being able to hold space, accompany persons in non-ordinary states of consciousness, and respond to spiritual, existential, religious and theological material that emerges in PAT. SHPs also discussed how they contribute to PAT teams by noticing and attending to power dynamics associated with identity characteristics that may confer vulnerabilities for patients (23).

The present study is motivated by recent calls to optimize the "psychotherapy" components of PAT (9, 24–26), as well as prior work indicating that clinicians' underlying motivations for practice impact therapeutic choices made during treatment and, correspondingly, treatment

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outcomes (27). This research is a novel, secondary analysis of qualitative interviews previously completed with SHPs who have worked on PAT treatment teams in legal settings (for further detail on the primary study, see ref. 23). The current secondary analysis focused on identifying the motivations that drew SHPs to this unique scope of practice and the factors that sustain their motivation to continue to provide this modality of care. Understanding the backgrounds and motivations that SHPs bring to treatment teams supplements a growing research base on the attributes of PAT facilitators and the facilitator-level factors that may contribute to effective care. Methods are detailed at the end of this article, after the *Discussion* section.

Results

Two overarching themes were identified in this analysis: "Initial Motivation for Practicing PAT," which included descriptions of what initially drew participants into this field of work, and "Ongoing Sources of Meaning and Fulfillment," which included descriptions of what provided SHPs with a sense of ongoing meaning or fulfillment that motivates their work presently. Initial Motivation for Practicing PAT was found to have five subthemes: (1) experience with trauma/adversity and healing through psychedelics, (2) psychedelic care as a component of one's spiritual-vocational path, (3) desire to alleviate suffering in others, (4) unplanned exposure to the field, and (5) multilayered motivation. Ongoing Sources of Meaning and Fulfillment had four subthemes: (1) appreciation for the patterns commonly associated with psychedelic experiences, (2) witnessing the alleviation of suffering, (3) mutuality of the facilitation experience, and (4) personal impacts of facilitating PAT.

Theme 1: Initial Motivation for Practicing PAT

Subtheme: Personal Experience of Healing Through Psychedelics

The most frequently endorsed subtheme of Initial Motivation for Practicing PAT was participants' own experiences with healing experienced through psychedelics. Some participants spoke of "healing" in broad terms (i.e., not associated with a specified ailment), while others described more specific healing from physical pain, illness, and or traumatic experience. Ten of the 15 participants spoke of this theme. As an illustrative example, one participant described experiencing physical pain from a bicycle accident, eventually leading them to seek PAT, which they found to provide surprising relief from pain that had not been responsive to physical therapy. In response to the prompt, "What led you to this work?", this individual responded:

> *"Well, in one word, pain … I had a bike accident a few years ago and multiple breaks. I was dealing with pain and doing rigorous physical therapy, with a great therapist for like a year. I was on her table, we're doing dry needling and my shoulders, which is where I seem to hold a lot … and finally, my therapist said, you know there's nothing structurally problematic about your body anymore. I think that you have trauma. And I've worked with a lot of – I mean, I've been the chaplain at a domestic violence shelter and in a trauma 1 hospital. So, I'm like, "No." Out of respect, I would say I've had hard things happen to me, but not trauma. Well, my whole definition of what that means has been completely undone. And I went to see someone who offered somatic therapy and … amplified with psychedelics, and I began a process of my own healing. And at first, I thought I was just carrying pain. I felt pain in my body. I felt pain in my heart. I felt heavy. I just felt weighted. And that was my beginning – my own healing. I started to experience the benefit of what was happening, and my whole understanding opened up to the fact that my nervous system held pain, held stories, held traumatic experiences even vicariously. And through this work, I was able to release it. I started to feel better in every way."*

Similarly, another participant described personal experience of the benefits of psychedelics in the management of their chronic illness as motivating their entry to work in the field:

> *"So I have chronic illness. Chronic Lyme disease, I also have a form of muscular dystrophy, and in my healing journey, I was just intuitively drawn. I'd heard about a therapist using specifically MDMA and psilocybin and just knew that's what I needed, and it has been an incredible healing support on all levels for me. And so, after several years of doing that work for myself and experiencing incredible benefits, I decided that I wanted to go into the field."*

Other participants spoke about psychedelic experiences that they found to be personally transformative:

> *"The bottom line is that I had my own experiences with ayahuasca, and it was deeply healing for me in ways that I just couldn't even imagine, and I kind of had a sense and a feeling that it was going to be part of my life in some way, but I didn't really know how."*

Subtheme: A Component of One's Spiritual-Vocational Path

Other participants described impactful spiritual experiences from psychedelic use that guided their vocational path. One person described how an experience with psychedelics became central to their spiritual life:

> *"Twenty-five years ago, I had the experience of working with both MDMA and psilocybin in more ceremonial and healing capacities, and one was with a native American Chicano man who studied in Mexico, who also was coming out of the Mazatec tradition in southern Mexico. And it was profound for me … It was the thing that helped me focus on my spiritual path, which has been Buddhism, for many years. I was studying and practicing Buddhism, working for many years in end-of-life care, spiritual care, and palliative care. And then kind of came back around full circle to the medicine again for my own healing."*

As illustrated by the above quote, this theme sometimes co-occurred with psychedelic experiences that were also described as "healing."

Subtheme: Desire to Alleviate Suffering in Others

Several participants expressed a desire to alleviate the suffering in others as a primary motivation for entering the field of psychedelic care. For example, one participant described the challenging emotional experience of witnessing their grandmother's cancer journey and subsequent death. Their familiarity with psychedelics helped them understand that different experiences were possible for people who were suffering. They shared:

> *"She was at home, not even talking about dying until two days before she died and then went to the hospital and died there two days later and was fully alert to the moment that her spirit left her body, eyes wide open, sitting up gripping our hand, just totally fighting this thing. And that experience really is what brought me into chaplaincy-experiencing the feeling like I know there's a better way that this can happen, and I want to find out what that is. … It doesn't need to be that way, but it still is for so many people … So for me, the tool of psychedelic care allows us to support people in their transformative process at the time in their lives that they're being called to instead of waiting for life to happen to them and, like crossing our fingers that it'll be good. So that's how I hold it- not in any way believing that it's a cure all or that magically people are transformed from just one experience, but some people are. And other people need a hand to hold for a long time. They need a particular form of care in an expanded timeline that allows them to kind of work through one piece at a time, depending on how much they're carrying."*

Subtheme: Unplanned Exposure to the Field

Some participants spoke of an unplanned encounter with the field of PAT that sparked their interest in entering this area of practice. For some, these experiences came from their personal lives; for others, they were unexpected professional experiences. One participant described working as a chaplain for an institution that initiated a clinical trial of PAT. In this context, they were invited to participate in a legal psychedelic experience to prepare for being a facilitator. They shared the following:

> *"I would consider myself a somewhat conservative evangelical Christian. And certainly those roots don't necessarily overlap well with the history of psychedelic substances, whether it be in the context of a study or just the cultural revolution that we experienced in the 50s and 60s and the drug wars in the 70s and 80s and kind of where we are today. And so I was really kind of uncomfortable, to be honest. I didn't know if I had a place in this and I didn't know if morally I could participate in such a study, so this really took me through a soul-searching process on a lot of levels, not that I'm completely done processing or completely done with the journey … Part of this journey that has drawn me is not just in the process of how do I as a chaplain create a safe space and hold space for people under medication and to prepare them and to help them integrate these processes, but I think chaplains also bring us a particular angle on the practice of medicine and the studies that we have to offer to the bigger conversation of what exactly are we doing with psychedelics and what exactly are we measuring."*

Another participant shared about a situational opportunity to participate in a clinical trial themselves. They had an impactful spiritual experience which ultimately led them into the work of facilitation:

"My introduction to this field occurred in (country elided) when I was a 23-year-old theological student. And I volunteered to help test some new drug I had never heard of … derivatives of psilocybin they were studying. And so, I lay there, open and trusting and curious. And then, this incredibly beautiful transcendental state of consciousness opened up in my mind. And I was one very starstruck young theological student. And in a way, I could say my life has never been the same since … in a positive way … This incredibly beautiful transcendental state of consciousness opened up in my mind. In Methodism, there's an emphasis on conversion experiences, especially in early adolescence – giving your life to Jesus and being saved in an experiential sense of belonging … I had always had a profound appreciation for nature. But I had never come close to experiencing what happened in that first psilocybin experience. It's beyond words- basically a unity, a state of consciousness, inner beauty, and meaning that felt more real and fundamental than the state of consciousness we're in. Like a homecoming and awakening. A remembering of what is. You know a real rediscovery of the eternal dimension of consciousness."

Several participants described exposure to PAT through educational or continuing education programs. For example, one participant spoke of hearing a researcher talk about the suitability of chaplaincy skills in PAT, which was an influence that led to their choice of making this a focus of their scope of practice.

"When I was getting my masters in psychology and religion at (seminary name elided) in (city elided), I was in the Psychology and Religion program, and we had [name elided], who's doing the psilocybin research in end of life context at (institution elided), he came in to talk to aspiring chaplains at the seminary and again that just got me really excited in the possibility of kind of utilizing my background and spiritual care … so I would see those were kind of my introductions to the field, so that when opportunities came up later through [company elided] I knew that my skills were relevant, I was excited about the field. I had a lot of just kind of intellectual knowledge about the field that's really kind of how I made the transition from chaplaincy to check it out."

Subtheme: Multilayered Motivations

Notably, for most participants, motivations to enter the field were multifaceted. Rates of co-occurrence between the above categories were high, with nearly all participants endorsing more than one of the above themes. While some participants were primarily driven by one factor, others described more blended motivations. For example, one participant succinctly described a motivation that included the promising results of recent research, the healing they had personally experienced from psychedelics, and a desire to help others experience similar healing. This participant shared:

"Having witnessed a lot of suffering from trauma in people who weren't really finding much relief and support. Then, in terms of end-of-life care … some of the psilocybin studies that have shown that people are really able to work through existential distress and other challenges of the end of life – that also connected with my vocational path. And then, on a personal note, having gone through some childhood trauma myself, I found psychedelic therapy to be really beneficial for myself. Those are the main reasons that I started to look at this. And then had some opportunities to become involved in the research, which I'm grateful for."

This participant came to PAT as an area of practice after encountering existing research on psychedelics and observing their own positive psychedelic experiences. Other participants shared different constellations of precipitating factors. For example, one participant identified challenging or difficult experiences with psychedelics:

"I then had an experience that was very, very difficult, very painful, very disorienting during a psychedelic journey … that essentially sidelined me for the next decade. It scared me very badly. I believed that I was sort of manifesting some kind of mental illness that I was going to lose my mind – that my sense of self was going to fragment. That never happened but what did happen is that one particular instance manifested what I now know to be anxiety that I had to deal with for years after that. And that I still deal with. Because of that anxiety, I was on the sidelines. My community and my friends continued to experiment, and I therefore took on more or less inadvertently the role of babysitter or a guide."

Another participant described an experience with psychedelics early in life that led to a transformative spiritual awakening, leading them into chaplaincy. Much later, an opportunity arose to train as a facilitator.

"I did a lot of psychedelics in my teenage years. I had a very powerful experience that was more spiritually based and had a very solid intention when I was 19. And that changed the course of my life and helped me experience something much deeper – a much deeper reality, if that makes sense, and I also experienced a lot around death and dying, and from that experience, I was called first, into a spiritual path that led me into meditation that then kind of took me into the calling of ordained ministry, as well as chaplaincy work, specifically with those who are dying. And then I stopped psychedelics; I didn't do psychedelics for 20 years, actually, after that really powerful experience, and I was approaching non-ordinary states of consciousness more through meditation, contemplative prayer, things like long extended retreats. But then I had an opportunity to go through the (program name elided) in the first cohort, as it was a pilot project. So, I took that opportunity, and that's kind of what then led me to begin facilitating psychedelics."

Theme 2: Ongoing Sources of Meaning and Fulfillment

Subtheme: Appreciation for the Patterns Commonly Associated with Psychedelic Experiences

Several participants described deriving ongoing appreciation and fulfillment from witnessing certain experiences or themes that commonly accompany psychedelic experience. For example, one participant described a global sense of connectedness experienced by many who have taken psychedelics:

"Seeing the similar experiences of participants in studies … creating new stories but also coming into a sense of being part of something larger … that to me is spiritual however anyone defines their spiritual journey or their religious practices … the feeling of being part of something larger than ourselves."

Similarly, in another participant's words:

"Something that just seems to consistently emerge with psychedelic therapies and that seems to be a beneficial emergence for the people that are experiencing it … to see this pattern again and again and again feels very spiritual and very affirming. I don't have to label it or know exactly what it is, or put ABC lists to it, but that there is something that connects us all, connects us to the planet, connects us … whether we call that God's spirit, the universe, humanity, earth, whatever, … it's a very spiritual experience for me to witness again and again these same patterns, these same experiences for different people."

When SHPs spoke of the patterns that emerged across facilitating psychedelic experiences, words such as "connectedness" came up frequently. SHPs described witnessing these experiences as personally meaningful, inspiring, and an important contributing factor to their motivation to continue in this field.

Subtheme: Witnessing the Alleviation of Suffering

Participants also described the satisfaction they experienced in witnessing the alleviation of suffering during PAT. This theme commonly co-occurred with the "desire to alleviate suffering" subtheme of Theme 1 (Initial Motivation for Practicing PAT), as witnessing the alleviation of suffering created ongoing motivation for persons initially drawn to PAT facilitation with this aim. Several participants described deriving satisfaction from seeing others heal and grow through psychedelic use. In one SHP's words:

"The deepest place where I access meaning is through being of service to the healing process of others. That comes through in this work because it's very client centered. It's very focused on redirecting individuals to their own inner wisdom, inner spiritual voice … It feels like that is the greater purpose … It gives me meaning – the feeling of being in alignment with life's path happens when I am holding space for others actually to sit within their relationship to their own inner guide … It's being of service. It's also assisting folks and moving into what I would call their spiritual alignment. Whether that's religious or not, or whether it's atheist … that's what gives meaning."

Other participants described the rewarding nature of witnessing improvement for clients who have had limited success with other forms of treatment:

> *"A lot of the folks that are coming to our treatment model, in particular, have been dealing with treatment-resistant depression, anxiety, or PTSD. They've been having really severe symptoms or symptoms that they just haven't been able to get a hold of for a really long time. And just really seeing this rapidly acting transformation that begins to happen in just a few sessions. I think it's just really always exciting for me … Seeing people's hard work come to fruition. … being able to use my chaplain skills and to acknowledge how difficult it is to open up at that moment. So I think that's another thing that's really fulfilling for me is that a lot of people come into treatment, maybe already having partially given up or seeing this is their last resort, so to speak. So just being able to grow that kind of breakthrough treatment for people, I think, is exciting as well."*

Similarly, another participant described hopefulness for PAT in addressing concerns typically characterized as "subclinical," such as burnout. They shared:

> *"I think there's hope in it. Other therapies haven't worked. Other things haven't spoken to people. There's too much that's unidentified living in people. That you know it's if they had access to it or knew what to do with it, they would have done it already, it would have been dealt with, you know people are not lazy or stupid, and so they can't get to it … I worked through the whole COVID in the ICU. We lost 80 nurses who have resigned from that unit over the course of the pandemic. And I'm still talking to them and hearing them say, 'I'm dead inside.' That's a quote – 'I am dead.' We're not going to talk you out of that. I don't think we're gonna bubble bath you out of that."*

Participants also discussed finding meaning in helping people experience a connection to the sacred, coupled with the capacity of PAT to treat mental health conditions:

> *"I wouldn't be doing it if it didn't give me so much meaning. Psychedelics for me are an extremely powerful tool for people to experience the sacred, the divine God, I mean whatever language … we know that's kind of ineffable … all different words to describe that. Also, from a mental health perspective, the data, the statistics that are coming out, and the results that I see in the participants that I facilitate compared to more traditional tools in the mental health world like talk therapy and pharmaceutical drugs … just such an amazing success rate with the use of psychedelics if done correctly, I really, really strongly believe that."*

Subtheme: Mutuality of the Facilitation Experience

Some participants spoke about finding meaning in the mutuality of the facilitation experience. Participants who had their own, personally impactful lived experiences with psychedelics often described an appreciation for the aspects of shared experience that accompanied facilitating psychedelic experiences for others. For example, as one participant put it:

> *"… seeing people heal – like really seeing people heal – is so satisfying. To have that and my own experience, knowing where I am in my journey because of this work, and I wouldn't be here without this work and the way that I am today, and I see that it changes people's lives."*

Another participant spoke of a similar experience of mutuality in the context of having a chronic illness:

> *"As I've worked with my chronic illness and as I've reframed my narrative, it makes me feel less isolated, less alone, part of society, part of the world. Even if I'm in pain, even if I'm still not feeling well, I can still be part of this larger fabric of the world and accept my limitations … Psychedelics have helped with symptoms, helped heal some of my chronic illnesses and helped me step more deeply into relationships with others and with this whole ecosystem that we're part of and feel more in connection with the divine. There's a plan for my life. There's a reason I came in with the challenges … But I've got ground that I can support others with now because I found this ground within myself … psychedelic therapies can support us all to recognize that we are all connected … can help us find ground and then therefore kind of be able to move from that ground. Even though I may still have symptoms, I may still not feel good some days. I still have pain, but I can still step into the world with all of myself and find a place that's meaningful for me and allows me to have joy."*

Not all participants described mutuality in terms of healing. Other participants spoke of a spiritual process that began with their own experience of taking psychedelics and is now enriched by facilitating psychedelic experiences for others. In another participant's words:

> *"Personally, sitting with the medicine requires a deep commitment to my own spiritual development, and my own inner healing work. That has been, in some ways, amplified and, in some ways, really does come to the forefront to see and to be as clear as possible for others. To offer that service working within the structures within my life has been extremely important. Encountering all my biases, healing my own stuff, and doing the inner work. The more I do that, the more clarity I have and the less of my own stuff I bring into the room with others … To hold space for folks having mystical experiences, there's also been a change within me to access those states where the opening is stabilized between sessions. And a lot of my development leans into various spiritual lineages that are not necessarily using medicine work but are encouraging and are using ancient practices to establish those same openings but maybe access them in more of a stable day-to-day expanded way. So, twofold: it's been heavy-duty spiritual practice that has amplified it in my life and our work. I think it's two sides of the same coin."*

In addition to mutuality with their clients, participants also spoke to impactful experiences of mutuality with other members of clients' care teams. For example:

> *"Personal experience with medicine working in therapeutic and ceremonial contexts and how profoundly that has impacted me, my spirituality, my healing, my sense of connection in the world … I mean, relative to other work contexts, this team has felt like I have a real sense of kinship and that we are in alignment with the model in a more holistic approach. Yeah, and just how from my own experience and from what I hear of others how, potentially, not inevitably, but potentially supportive medicine work can be for not only healing, particularly healing around trauma, but spiritual growth and self-awareness of connection in the world."*

Subtheme: Personal Impacts of Facilitating PAT

This subtheme described experiencing personal impact from engaging in PAT that sustains participants' vocational motivation. Although this sometimes included the personal impacts of the prior theme, mutuality, participants also spoke to several personal impacts independent of shared experiences. One participant described being inspired by the commonalities in psychedelic experiences that they have witnessed over years of facilitation:

> *"I've certainly been reinforced in my view of the world, in my spiritual life, in my psychological theory. I've had the great honor of being with several hundred people in their psychedelic sessions, and to me, that's a lot of evidence. People from different races, different educational levels, different careers, different physical health situations and the human mind seems to function pretty much the same with all of them. And that's inspiring …"*

Another participant spoke of the personal impact of working in a group/peer support model and the power of watching group members build trusting relationships with one another:

> *"This group model is more about peer support, and it is more about cultivating tools for presence, for grounded spacious awareness, for what it is that is emerging within us that we can accept, be with, and possibly allow for some processing simply by being present to it with compassion, and then people being witnessed by the group and feeling the sense of support and safety and trust that ideally is deepened over the weeks from the group. Seeing people who have, in this case, significant trauma histories, some of whom have been really isolated either for various reasons, socially or because of the degree of their anxiety (not comfortable leaving their house, especially in the context of the last few years) even in a short period of time, feeling a sense of bond kinship, safety. Feeling 'I'm not alone' with each other. Being able to relax and feeling a natural heartfulness, joyfulness, compassion, and inner healing wisdom emerge within that space. That to me is beautiful to witness."*

Another participant described fulfillment in the intimacy of psychedelic-assisted care:

> *"I would say things have kind of changed me about this work …. I think in some ways, like the psychiatric context, in some ways, like the hospice context, it's a very intimate setting. The medicine, in some ways, really*

helps people take their defenses down and be more engaged with the work, maybe to stay present with more difficult activating material. I think the sessions are really intimate, and I think there's some transformation just in seeing this kind of spiritual revelations that people have. I think just being able to witness that, being able to observe that, support that. I think it really just opens my eyes to the complexity of humans in our spiritual lives."

Discussion

As the evidence base for PATs continues to expand, optimizing the facilitation of these unique treatments has become increasingly important (25). In the context of the spiritual and existential experiences that often accompany psychedelic experiences, SHPs are increasingly recognized as playing vital roles on PAT care teams (19, 23). Understanding the roles that SHPs can play on PAT care teams, and how training for PAT facilitation can be optimized, requires an understanding of the motivations that draw SHPs to PAT facilitation in the first place, as well as the factors that sustain their ongoing work in this field. The major themes identified in this research highlight the deeply personal nature of PAT facilitation for the SHPs in this study, a finding which has valuable implications for PAT facilitation training.

This study found that personal psychedelic use was a strong motivator for SHPs practicing PAT—a finding consistent with a recent investigation of psychedelic use among therapists from a phase 2 clinical trial of psilocybin for major depressive disorder that found that the majority of therapists had experience with at least one psychedelic substance, most commonly psilocybin (25). Many SHPs in our study described their psychedelic experiences as "healing"; others described their experiences as spiritually "transformative," as opening new spiritual awareness, enhancing their existing sense of spirituality, or increasing their understanding of their place in the world. Notably, SHPs predominantly described personal benefits associated with their past psychedelic experiences, although psychedelic experiences are not exclusively experienced as beneficial and are sometimes experienced as challenging in the general population (28, 29).

With respect to factors that provide SHPs with ongoing sources of fulfillment and motivation for this work, witnessing others experience healing was described as particularly significant. Many participants in this study reported deriving a deep sense of meaning from the mutuality of the experience—that is, guiding someone else through an experience that they had found to be so powerful and personally impactful. Many participants also spoke to interconnectedness as a sustaining factor. Interconnectedness was sometimes described as experienced with clients, sometimes described as experienced with other members of a PAT care team, and sometimes described as drawing from repeated witnessing of themes that commonly emerge during a psychedelic experience.

These findings are aligned with prior research on the motivations that draw practitioners to psychological healing professions more broadly. Studies examining the motivations of mental health providers (including therapists, psychologists, and social workers) have found that therapists frequently describe personal experiences of adversity and healing as significant factors in their motivation for their vocation. Specifically, personal adversities, lived experiences of social and cultural marginalization, and one's own experience of receiving therapy are common motivators for vocation (27, 30, 31). The limited existing literature characterizing general vocational motivations of SHPs finds, similarly, that many come to the profession with a history of personal trauma and adversity in their families and communities (32, 33). SHPs are also likely to cite disillusionment with religious institutions as a motivator for working in chaplaincy (33). Having lived experience with symptoms and experiences reported by patients has been noted in the psychotherapeutic literature to have both advantages and drawbacks. It has been suggested that personal experiences of adversity may confer empathy and an enhanced capacity to understand human complexities (33), leading to a greater capacity for sitting with others in times of distress (24, 34). Conversely, personal experiences can increase the risk of inaccurate projection of one's own experience onto the patient (24) and may interfere with objectivity in assessment and treatment planning (35).

The question of whether personal psychedelic experience should be a prerequisite for providing psychedelic facilitation remains one of the most debated topics in the field of PAT facilitation training (24). This study adds an additional data point to an accumulating finding that, much like mental and spiritual health professionals who are motivated by their own experiences of adversity and healing, psychedelic facilitators are frequently motivated by personal experiences with psychedelic use. However, our findings also raise the possibility that firsthand psychedelic experience may not, in itself, lead to more effective care. Because personal psychedelic experiences were frequently described as key sources of motivation to provide this kind of care, it may be that motivation—rather than the experience itself—is a more immediate and influential factor in facilitating effective therapy. While no research to date has examined whether facilitators with prior psychedelic experience are more efficacious, we suggest that, even if such an association were found, it could be attributable to increased motivation rather than any inherent benefit of the psychedelic experience (or other encounters with nonordinary states of consciousness) itself. Given this, we recommend that PAT facilitation training programs acknowledge personal psychedelic use as a potential motivational factor and explicitly address this in training. Regardless of whether programs choose to offer psychedelic experiences to trainees, it is essential for trainees to recognize and thoughtfully engage with prior psychedelic experiences that are brought into training.

When the Professional is Personal: Implications for PAT Facilitation Training

Results of this research found that for most SHPs, working in the field of PAT is deeply personal. Many reported experiencing their own transformation and healing through psychedelic use and now seek to offer others support through similar methods. On one hand, this level of personal experience can be beneficial: experiential knowledge may equip SHPs to skillfully respond to the unique phenomenology associated with psychedelic agents (24, 36). A facilitator's lived experience with and belief in the effectiveness of psychedelics may also constitute common factors of treatment effectiveness. Psychotherapy research on common factors has found that therapist empathy alone exerts large effect sizes on treatment outcomes ($d > 0.8$), and expectations have smaller but still significant effects ($d > 0.2$), independent of any specific components of treatment (34).

Conversely, personal experiences can also introduce biases that hinder the ability to provide objective care. Facilitators who are strongly motivated by personal experience run the risk of "experiential encapsulation"—a term we adapt from cultural encapsulation, which is used to describe a clinicians' application of their own culture-bound experience and worldviews to those of a client without regard for important differences (37, 38). Experiential encapsulation occurs when facilitators assume that their own psychedelic experiences, the timelines of these experiences, and their frameworks for interpreting these experiences, are universally applicable. This can lead facilitators to overlook the unique and deeply personal ways in which different individuals may experience psychedelics during PAT. Just as culturally encapsulated therapists are at risk of failing to consider cultural differences between themselves and their client and imposing their own values on care (37, 38), an experientially encapsulated facilitator may fail to recognize variations in how individuals experience psychedelics and the meanings that are ascribed to these experiences. Any facilitator of PAT (whether an SHP or from another profession) whose approach is overly shaped by personal psychedelic experience runs the risk of oversights when working with someone who has a markedly different experience. Such oversights can lead to ineffectiveness, or at worst, treatment harms (9).

For SHPs, training requirements set by the Association for Clinical Pastoral Education (ACPE) may help buffer against this risk (24). The preparatory training to become an SHP through ACPE places a heavy emphasis on self-literacy. Self-literacy training occurs in the context of the Common Code of Ethics for Chaplains, Pastoral Counselors, Pastoral Educators and Students, which sets forth several standards pertaining to cultural humility and respect for autonomy in the worldview and beliefs of others in all

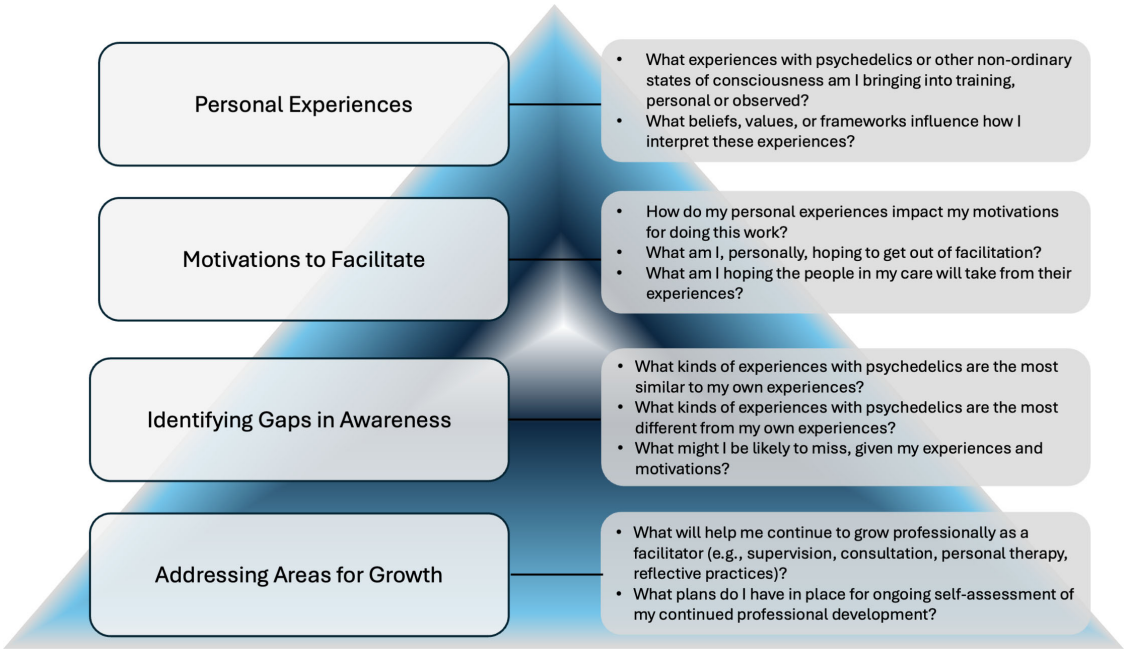

Figure 1. Self-literacy reflection exercise for psychedelic facilitators.

professional activities (e.g., Standard 1.3: "Demonstrate respect for the cultural and religious values of those they serve and refrain from imposing their our own values and beliefs on those served.") (39). ACPE training standards also include several outcomes and indicators that ask SHPs-in-training to reflect upon their motivations to engage in the work of spiritual care, the orienting system behind their spiritual care choices with clients, and their understanding of personal, social, and cultural location that impacts their way of being in the world and work (39). For example, learning outcomes include "Identify formative and transformative experiences in one's narrative history and their significance to one's spiritual journey" (IA.1) and "Demonstrate an awareness of implicit and systemic bias including cultural and value/belief-based prejudice and its impact on spiritual care" (IA.7). This reflective learning aims to aid SHPs in bringing awareness to factors that motivate their actions in spiritual care encounters. In the context of PAT, this training may also aid SHPs in sensitively approaching a participant's experience without expectations, regardless of the SHPs' relationship with psychedelics. While the personal history of transformation through psychedelics may be a significant motivator for many SHPs engaged in this work, the learning outcomes and ethical guardrails of SHPs may assist in maintaining a practice that centers the experience of the client.

Standards set forth by professional ethics codes for mental health providers (e.g., the American Psychological Association Ethics Code; the Code of Ethics for Social Work) articulate comparable practice standards with regards to respect for clients' autonomy and refraining from imposing one's own values (40, 41). However, these standards for training and practice do not explicitly address reflection on one's own narrative and psychospiritual history. In the absence of such standards, training programs for clinical mental health professions often dedicate minimal time to experiential self-literacy training as an integrated component of training. Findings from this research suggest that when it comes to PAT, training competencies associated with self-literacy of one's narrative and psychospiritual history and motivations may be particularly important. In the context of ongoing discussions about training guidelines and requirements for PAT that cut across professions, we suggest that ACPE's reflective learning model for acquiring self-literacy be considered an element of training that can benefit all PAT providers, regardless of their profession. Further, as practitioners engage in PAT, continual reflection on these learning outcomes as part of continuing education can benefit providers' work.

Guided by findings from this study and the ACPE reflective learning model, we suggest a self-literacy exercise that can be completed by PAT facilitators and facilitators-in-training coming from any professional background (Figure 1). These questions aim to balance the value of personal experience with the need for clinical objectivity and the importance of reflecting on how personal experiences and motivations can confer both strengths and gaps in awareness. The nine self-reflection questions provided in Figure 1 can be assigned as a written, narrative exercise during psychedelic facilitation training, so that trainees can practice reflectively without being required to disclose about personal experience beyond their comfort level. Practicing facilitators may be benefit from revisiting these questions annually, as motivations (and personal experience) may change over time.

Limitations and Researcher Positionality

A primary limitation of this work pertains to recruitment and the sample of participants represented. Participants in these interviews were recruited through a national professional network (Transforming Chaplaincy) that was originally co-convened by this study's principal investigator (PI). This could have led to bias such that the views of participants were similar in nature to each other and the PI. Participants in this study had a variety of chaplaincy training experiences, not all through ACPE. Relatedly, only those practicing PAT in legal settings were included. This means that our results may not generalize to the numerous practitioners working in underground settings and traditional religious/spiritual settings. Providers practicing in those settings have unique experiences facilitating PAT, and may have different motivations and sustaining factors for their work. Our results also may not generalize to legal PAT practitioners from non-SHP training backgrounds (e.g., psychiatry, clinical psychology, social work). Broadly speaking, educational pathways and practice environments impact the experiences and motivations of practitioners. Future research should reach a broader network of providers to ensure more generalizability and understand to what extent experiences may differ.

Additionally, the vast majority of participants in this study were white (80%) and North American (93%). This poses limitations on the generalizability of this work to the populations at large. Individuals from other racial, ethnic and cultural backgrounds may approach psychedelic experiences differently, leading them to have different perspectives than those represented here. For example, participants in this study expressed an orientation toward personal healing. Communal dimensions of healing are

central to many traditions of psychedelic use around the world (42) and are under-represented here.

This qualitative study should also be interpreted in light of author positionality. All authors of this study reside in the United States and work in primarily academic contexts, with settings spanning a large academic medical center, a School of Public Health, and a School of Theology. The authors include SHPs (chaplains), clinical psychologists, a clinical social worker, and a graduate student in public health. All authors have professional experience with PAT; some authors have provided PAT facilitation, while others have served research-focused roles on PAT trials (e.g., investigator, data analyst). Our training backgrounds inform the lens through which we approached these analyses and their interpretation, and individuals with other training or professional backgrounds may have generated different coding categories or drawn different conclusions than those represented here. We acknowledge that our perspectives do not represent the perspectives of all PAT facilitators or recipients of these treatments.

Conclusions and Future Directions

As the field of PAT continues to expand and the potential for FDA approval of psychedelic agent(s) appears on the horizon, it is a critical time for professional disciplines to systematically evaluate what constitutes appropriate preparation for those working in PAT. Understanding the motivating factors for SHPs who are already engaged in this work allows those within and outside the field of spiritual care to consider the complex dynamics at play within a PAT facilitation experience from a unique perspective.

A core finding from this study was that personal experiences substantially informed participants' initial and ongoing motivations for working in this field. We do not draw conclusions regarding whether experience with psychedelics is necessary to be an effective PAT facilitator. However, awareness of motivations—whether related to one's own psychedelic experiences or not—can assist the facilitator in bringing an objective approach to the work that is centered on the experience of the person seeking care. Results of this study suggest that training programs for PAT would benefit from curricula components that invite trainees to explore personal motivating factors so that insight into these can be cultivated and any resulting biases can be addressed. With a careful and self-aware approach, therapists of any discipline may be able to provide care that is sensitive to power dynamics and non-imposing of personal experience and perspective.

Methods

The present study is a secondary analysis of a qualitative study that aimed to identify the role that SHPs play on PAT teams (23). This secondary analysis was motivated by the emergence of two themes that were inductively identified during our original qualitative analyses for the primary study. These themes fell beyond the scope of that research, and therefore were not examined or reported: (1) the factors that initially brought participants to PAT facilitation, and (2) the factors that motivate their continued practice of this profession.

Participants

Participants in this research had experience facilitating PAT and also met at least one of the following criteria: (1) one or more units of Clinical Pastoral Education (ACPE), (2) ordination or status as a religious leader, (3) a Master of Divinity or other advanced theological degree, or (4) specific training in spirituality within psychedelic work, above and beyond what is offered in standard PAT certification programs. Recruitment occurred between March 2022 through June 2022. "Experience with PAT" was defined as experience facilitating PAT in settings where it was legal, including both ceremonial and/or retreat settings, as well as clinical research environments.

All participants ($n = 15$) in the parent study are represented in the present study. Participants had an average age of 46.57 (SD = 13.38), identified as 60% female (40% male), and were 20% Hispanic/Latinx and 80% White. The vast majority (93%) were North American, with 6.67% being South American. The most common context of PAT experience was within clinical trials (46.67%), with the next most common being retreat/ceremonial (40%), and private practice, clinic, and remote/virtual being the least common (6.7%). The most commonly used psychedelic in PAT interventions reported by participants was psilocybin (66.67%), followed by ketamine (46.67%), ayahuasca and MDMA (both 13.33%), and LSD, cannabis, and kambo (6.7%).

Procedures and Measures

SHPs were interviewed via the Zoom telehealth platform, except for one SHP, who was questioned via a written email exchange due to poor internet connectivity and inability to engage via Zoom. All SHPs were queried using a semistructured interview guide of 14 standard questions, reported in the originally published study (23). Interview questions included items asking SHPs to describe various aspects of their professional activities, their motivations for engaging in PAT, their view of the importance of personal experience with psychedelics, ethical concerns related to PAT, spiritual outcomes of PAT, and views of the building field of SHPs engaging in PAT.

Two previously unanalyzed questions were the analytic focus for the present investigation: a motivation question, asked to all participants ("What motivated you to work in this field?"), and a meaning and fulfillment probe (i.e., "What brings you meaning or fulfillment in this work?"). The meaning and fulfillment probe was included in the interview guide as an optional follow-up probe, and therefore not asked of all participants. Information yielded in response to this probe, when it was included, was related to the motivation theme and was therefore included in the present analysis. All interviews were video and audio recorded and transcribed using the autotranscription feature of Zoom. Transcripts were subsequently manually deidentified and corrected following the automated transcription for any errors or lack of clarity (via comparison with live recording) by two researchers.

Data Analysis

The data analytic strategy for the primary analysis is described elsewhere (23). During that process two themes emerged inductively, which did not fall within the scope of the primary analysis. These two themes were (1) participants' descriptions of their initial motivations for facilitating PAT, and (2) their current sources of ongoing motivation and fulfillment in their work. These themes were determined to be unrelated to the aims of the primary study, which were to characterize the roles and activities of SHPs on PAT treatment teams, but of sufficient scientific importance to warrant their own dedicated systematic investigation.

The present secondary analyses employed a hybrid inductive-deductive approach (43) to rapid qualitative analysis of these two themes. A rapid qualitative approach was selected because of the shifting regulatory environment of psychedelics, and ongoing discussions about the role of SHPs in psychedelic care, to which this analysis may provide directly germane, though time-sensitive, information. In the secondary analysis, our first step was to generate a codebook of subthemes, which was created by two investigators with content expertise in chaplaincy and psychedelic facilitation. The codebook was created by reviewing all transcripts, and then identifying (1) pre-existing themes that were deemed important to examine in a deductive step (e.g., the existing unexamined categories that emerged in the prior analysis that motivated the present investigation), and (2) a set of themes relevant to these two original themes, which were recognized and noted separately by the two investigators. These were discussed and consolidated into one codebook. That codebook was then refined by having the two expert coders code a subsample of transcripts independently, and then resolve disagreements by consensus, modifying and adding categories as needed. The resulting codebook was then treated as a finalized version. These codes were deductively applied by a single coder using MAXQDA version 22.2.00 qualitative analysis software. This method of rapid qualitative analysis has the advantage of taking less time than double-coded methods, and the limitation that coding may be subject to biased detection, with intercoder reliability of the full dataset not possible to establish (44). This limitation makes researcher positionality particularly important to describe and report as part of data interpretation (see *Discussion* for this reporting).

Data Availability

Data cannot be shared publicly because of concerns about identifiability, and the need to preserve privacy and confidentiality of participants. Because the topics discussed may incur legal or social sanctions the data are held on protected and encrypted university servers at Emory University. Data may be made available for researchers who meet the criteria for access to confidential data by contacting the Emory University Institutional Review Board at irb@emory.edu or the corresponding study author.

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Author Contributions

C.P. collected and analyzed reported data. D.M.K., I.P., and C.P. wrote the first draft of this manuscript, with input from R.P., J.C.S., J.M.P., and G.H.G. Revisions to this article were completed by D.M.K. and I.P., with input by C.P., R.P., J.C.S., J.M.P., and G.H.G. All authors reviewed and approved the final version of this manuscript. All authors take full responsibility for data and text and approve the content and submission of this article. No related work is under consideration elsewhere.

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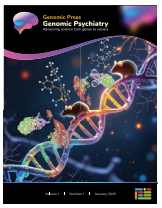

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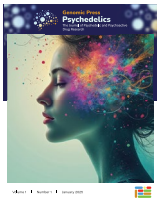

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