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# Practical and Ethical Considerations for Psychedelic Therapy and Integration Practices

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## Abstract:

While psychedelic-assisted therapies are currently being studied for several indications in clinical trials, there is legal and ethical ambiguity for mental health professionals concerning these compounds. Seventy-six mental health professionals completed an online survey asking them to rank their interest in topics related to psychedelic therapy, research, legal obstacles, barriers to incorporating psychedelics in practice, and terminology related to the field. Results showed that providers want more clearly defined terminology and operating procedures concerning business matters such as malpractice and clinic guidelines, legal and ethical clarity on administering psychedelics in private practice and integration work, and further opportunities for psychedelic therapy training. The survey responses were reflected upon through the legal and ethical lens of the current psychedelic landscape.

Key Words: psychedelic integration, psychedelic practice, ethics, harm reduction, therapy

## INTRODUCTION

From harm reduction to medical marijuana, innovative mental health treatment approaches and modalities have sometimes operated in legal and ethical "gray areas." With accumulating reports of positive outcomes from psychedelic-assisted therapy clinical trials for a range of different mental health conditions, increasing numbers of people are looking for accurate information about the safety of psychedelics and how to use these substances for therapeutic benefit. Unsurprisingly, numerous practical questions about the law, policy, and ethics of working with clients who utilize psychedelics remain today.

Alongside this growing body of science, psychedelics continue to gain attention in the media, appearing on major news outlets from CNN to FOX and The New York Times. Best-selling author Michael Pollan's book *How To Change Your Mind* <sup>[1]</sup> presented, to a largely psychedelic-naïve audience, the case for current psychedelic-assisted healing

through his experiential and research-based reporting. The changing landscape in research and public knowledge is additionally duty-bound to consider the safety of personal psychedelic use and clinical use alike.

The most recent Global Drug Survey <sup>[2]</sup> showed significant use of the most commonly studied psychedelics, such as MDMA (33%), LSD (17.5%), Psilocybin (14.8%), and Ketamine (12.8%), across its 120,000+ respondents. Interestingly, 24.6% were very likely to consider using psychedelic-assisted therapy if diagnosed with a psychiatric condition, representing a greater number than those who endorsed psychiatric medications (19.3%). This increased awareness of the potential therapeutic benefit of psychedelics may lead to greater use in naturalistic settings for intended therapeutic benefit. While psychedelic-adjacent services and training are becoming more accessible to providers, there remain ambiguities that call for

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essential, standardized, and community-  
driven frameworks in this emerging field.

The current study is the product of a collaboration between individuals from the Multidisciplinary Association for Psychedelic Studies (MAPS), MAPS Foundation Benefit Corporation (MAPS PBC), Psychedelic Support, and the California Institute for Integral Studies' (CIIS) Certificate in Psychedelic Assisted Therapies and Research (CTPR) Alumni Association to examine some of the undefined and unanswered concerns and terminology within the burgeoning field of psychedelic-assisted therapy and psychedelic-adjacent services. A survey was sent to licensed practitioners to understand what topics related to psychedelics were of most interest, what terminology was unclear or not well defined, what obstacles practitioners face in setting up clinics for psychedelic clinical trials, and what challenges they face in preparation for post-approval of psychedelic medicines.

Our intention was to compile and synthesize this information to be utilized as a starting point for the creation of resources and a dialogue between mental health providers and legal professionals to explore ethical considerations and bring consistency and clarity to this important and innovative work. We have identified some fundamental questions implicated by providing psychedelic care, like therapy and integration work within the present legal and economic status quo. These questions give rise to a few potential ethically problematic scenarios. Developing a shared lexicon related to psychedelic therapy and integration will facilitate communications amongst mental health professionals, licensing boards, policymakers, and the public. We hope that this work expands to include networks of people from a number of sectors who are positioned to support the field of psychedelic therapy, and develop the legal and ethical discourse within the field itself.

## **METHODS**

An email with an invitation to fill out an online survey was sent to providers in the Psychedelic Support Network, MAPS MDMA phase 3 trial therapists, and alumni from the California Institute for Integral Studies (CIIS) Certificate in Psychedelic-Assisted Therapies and Research (CTPR) program. Of the 290 people who were invited to complete the survey, 76 voluntarily completed it. Respondents were informed that their anonymized responses could be published. The Alder University Institutional Review Board approved using the de-identified archival dataset for research purposes in March 2019. The survey consisted of 20 questions and took approximately 15 minutes to complete. Participants selected responses from a list for most questions, while others allowed open text answers with no text limit.

The survey gathered information about the demographics of respondents, topics of interest related to psychedelic therapy and research, obstacles and barriers to incorporating legal psychedelics in their practices, and terminology used in the field that is not well defined or unclear. All available data for a given question is included in descriptive statistics.

## **RESULTS**

### **Demographics & Sample Characteristics**

Survey respondents (n=76) consisted of 40 males, 34 females, and 2 nonbinary/genderfluid persons. Nationalities of participants were largely from the USA (n=60) with a smaller representation from Canada (n=6), Czech/USA (n=1), and Scotland (n=1), while 8 did not respond. Respondents were White/NonLatino (n=60), Latino (n=3), Asian (n=3), mixed-race (n=3), and African American (n=1); 6 did not answer this question. While English was the

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primary language spoken (n=75), 27 participants were bilingual, with Spanish (n=15) and French (n=4) being the next commonly spoken languages, along with nine others. Professionally, 27.63% of respondents explicitly stated they carried a master's degree (n=21), 14.47% stated they carried a doctoral degree (n=11), and 13.16% stated they were licensed but did not specify a degree type (n=10). 50% expressed an interest in pursuing a therapy license (n=38); 21.05% expressed no interest (n=16), 9.21% responded maybe (n=7), and 15 did not respond.

### Communities and Client Demographics

Participants (n=76) served various communities in their work, with 32.90% stating they work “mostly with adults 18+”, 31.58% explicitly stated working with “racially or ethnically diverse” communities, 21.10% work with “mostly Caucasian” communities, and 5.26% work with “communities of color,” and 17.11% work with “LGBTQ+” communities. Participants also described the populations they served economically and geographically as “middle or upper class” (n=12), “low SES” (n=7), “rural” (n=3), and “urban/suburban” (n=6). 25% of respondents described the communities they serve as “diverse” or “all” (n=19).

Over half of respondents planned on serving their current client population with psychedelic-assisted therapies (n=43), while 26 responded ‘maybe.’ There were 7.90% not planning on using psychedelic-assisted therapies in their current communities (n=6). One participant’s reasoning was “while my population does very often involve those with trauma, PTSD, addiction, and anxiety (which have seen benefit from MDMA-assisted psychotherapy), my clients with severe and persistent mental illness, such as psychotic disorders, would likely not be recommended to psychedelic therapy.” Other reasons for

not serving, or maybe serving, their current communities with these therapies ranged from “illegality” to “inappropriate client base” (e.g., minors). Table 3 displays the type of substances clinicians would be interested in incorporating into their practices if legal.

Participant responses highlighted research and clinical terms related to psychedelics as being unclear and needing further definition from practitioners and the psychedelic community (Appendix 1). 53.95% asked for clarity concerning the term ‘psychedelic-assisted therapy,’ and 51.33% desired a better understanding of the term ‘psychedelic integration.’ While the terms ‘guide’ (n=1), ‘participant’ (n=1), and ‘ceremony’ (n=1) were seen as needing less clarity, many respondents wanted clarity for the terms ‘psychedelic practitioner’ (n=36), ‘psychedelic medicine’ (n=26), and ‘medicine session’ (n=19). ‘Psychedelic harm reduction’ (n=31) and ‘psychedelic intention setting/preparatory support’ (n=29) were additionally seen as being unclear, while ‘psychoactive-assisted therapy’ (n=1) and ‘ethical off-label use’ (n=1) were not. Respondents were also given the opportunity to define these terms in an open response format (Appendix 1).

Additionally, participants showed interest in learning more about business, legal/ethical, and professional development items as they relate to psychedelic-assisted therapy (Table 1). Respondents also foresaw obstacles in running a psychedelic practice, setting up a psychedelic clinic, and setting the cost for services (Table 2).

Facilities; facility regulations	5 (6.58%)
Cost of services for low income access	2 (2.63%)

† Scheduling, record keeping, office management

Table 1. Topics of Most Interest for Having More Information

Topics	Respondents (N=76)
<b>Business</b>	
Malpractice insurance coverage for providers of psychedelic therapies	54 (71.05%)
Setting up a clinic	46 (60.53%)
Getting involved in clinical trials	31 (53.95%)
Insurance coverage for clients	34 (44.74%)
Obtaining Schedule 1 DEA License	30 (39.47%)
<b>Legal</b>	
Legal/ethical questions related to using cannabis or psychedelics in a private practice	55 (72.37%)
Legal/ethical questions related to offering preparation/integrations services	50 (65.79%)
<b>Professional Development</b>	
Psychedelic therapy training opportunities	56 (73.86%)
Professional Networking	51 (67.11%)
Supervision and mentorship	47 (61.84%)

Table 2. Topics Perceived as Obstacles

Obstacles	Respondents (N=76)
Client, and practice, insurance coverage	50 (65.79%)
Administrative and business tasks †	44 (57.89%)
Setting fees for services	34 (44.74%)
Obtaining a Schedule 1 license	32 (42.11%)
Payment processing	21 (27.63%)
Finding a co-therapist	13 (17.11%)

Table 3. Substances (if legally approved) of Interest for Use in Professional Practices

Substance	Respondents (N=76)
MDMA	63 (82.89%)
Psilocybin	62 (81.58%)
Ketamine	43 (56.58%)
Cannabis	36 (47.37%)
LSD	8 (10.53%)
Ayahuasca/DMT	7 (9.21%)
San Pedro/Mescaline	3 (3.95%)
5-MEO-DMT	2 (2.63%)
Ibogaine	1 (1.32%)

**LIMITATIONS**

The survey was only sent to mental health providers who were already affiliated with a psychedelic organization. Thus the sample does not represent the general population of mental health care professionals. Still, there was significant uncertainty even among this group of practitioners who are reasonably knowledgeable about psychedelics. It can be expected that as new practitioners become interested in these novel modalities, there will be additional questions. There are many unknown factors related to the regulation of psychedelic therapies, and new information is constantly emerging. For this reason, speculations around legal and ethical oversight discussed here will likely change as the field moves forward.

The information in this article is not intended to be taken as legal advice. Practitioners seeking answers about these issues as it relates to their practice should consult legal counsel within their jurisdiction.

## DISCUSSION

The responses from this survey offered a comprehensive view of questions and challenges currently facing practitioners who work with clients that use psychedelics or plan to include psychedelics in their practices after projected regulatory approval. The use of Spravato (esketamine) and off-racemic ketamine in treating depression and other psychiatric conditions is quickly growing and requires practitioners to follow specific guidelines to safely and legally administer it. By offering interpretations of commonly used terminology in this field, we have begun to establish a means to communicate more effectively between mental health care providers, clients, and policymakers. Many practitioners expressed the need for more information around several topics of interest and perceived obstacles, and more opportunities for professional networking and sharing of informational resources. Questions around legality and standards of care will need to be addressed for both public safety and provider liabilities.

Psychedelic-assisted therapy practices will bring logistical challenges not currently faced by many providers we surveyed in traditional therapy or healthcare practices. Private practices will require several adaptations to meet the unique needs of delivering psychedelics in medicalized settings. To establish long-lasting, successful treatment practices, psychedelic providers will need to receive appropriate training and find competent professional partnerships while juggling higher regulatory requirements for Psychedelic integration & practice survey: Report & analysis of results 8 dispensing scheduled substances, business management, administrative duties and oversight, and client care.

Professional networking opportunities specifically on therapeutic applications of

psychedelics are very limited at this time, but large psychiatric and psychological conferences are beginning to feature symposiums and discussions of psychedelic research. Information in this field is mostly amassed by groups conducting research trials or small grassroots efforts to share educational content online and at community gatherings. Recently, a few professional associations specific to psychedelic medicine have begun to appear. More general harm reduction conferences and organizations tend to be open to discussions and topics of all drugs, including psychedelics. More in-person events, online discussion forums, and video conference meetings would facilitate networking between professionals and cross-pollination of information across disciplines.

Most survey respondents (73.86%) wanted more details around training opportunities and supervision/mentorship (61.84%). A greater number of training programs for psychedelic-assisted therapy are becoming available from clinical trials sponsors, such as MAPS PBC, and other academic or private institutions. However, the training requirements for delivering approved psychedelic treatments remain unknown until final negotiations with FDA and other regulatory agencies. Ketamine use, on the other hand, is rapidly expanding for mental health indications, but since it is prescribed off-label, there are no formal training requirements for providers. There are a growing number of training and continuing education courses on ketamine therapy being offered by clinicians, but again there are no agreed-upon competencies and certifications available.

The criteria for drug delivery and overnight stays will likely be stipulated in the drug safety program of the FDA for MDMA and psilocybin, known as the Risk Evaluation and Mitigation Strategy (REMS), which will be specific to each approved drug. Survey participants anticipated incorporating several

psychedelics in their practices if approved, which could present currently unknown challenges.

For many reasons, MDMA and psilocybin trials have two therapists or guides for each study participant. The individual undergoing treatment is not left alone and having a team of two is practical for lunch and bathroom breaks during all-day sessions. Therapeutically, working with two providers enhances feelings of safety and support, provides opportunities to more effectively manage transference, countertransference and attachment issues in treatment, and can balance the dynamics between the patient and therapy team [3]. In addition, therapists working together can help each other manage the more intense countertransference that can come up in psychedelic sessions. Only a small number of respondents (17.11%) thought that finding a co-therapist would be an obstacle. Nonetheless, having to work on a team presents challenges of finding a compatible person to work with, both in terms of personality fit, scheduling, billing, and often business partnerships. Practices may benefit from having providers with complementary yet different therapeutic modality proficiencies and professional experiences.

### **Insurance Coverage**

Currently, health insurers do not reimburse for co-therapists working concurrently with a single client, which will provide a challenge in implementing a co-therapist model in practice. The qualifications of providers may also affect fees for services. The amount of time a patient spends in a clinic for psychedelic-assisted therapy is substantially more than the typical 60-90 minute office visit. Ketamine infusions without therapy are often scheduled for 60-90 minutes, but when integrated with therapy, a minimum of two hours appears needed. In clinical trials, sessions of MDMA and psilocybin last for 6-

8 hours, and some studies require participants to stay overnight with a night attendant. Many survey respondents (60.53%) endorsed the need for more information in regards to clinic setup. However, finding a suitable space to accommodate a comfortable overnight visit where zoning regulations allow for such can be difficult in many locations. Although overnight stays may not be required post-FDA approval, the option to stay overnight has advantages for safety and a more immersive therapeutic process. Arranging for meals, cleaning of bedding and facilities, and night attendants are necessary details that are not needed in traditional therapy practices. While some insurers allow practitioners to bill for extended psychotherapy sessions using specific billing codes as add-ons (CPT codes 99354 and 99355), it is unknown how insurers would respond to billing for 6-8 hours long sessions or overnight stays at this time. Perhaps “partial hospitalization” or “day program” billing codes could be utilized, but this remains uncertain.

The specific needs of offering psychoactive pharmacotherapies that carry requirements for greater patient supervision, time in a clinic, regulatory compliance, training requirements, and administrative tasks will inevitably result in higher costs. Barriers to access are created for low income clients because fees for services escalate to cover the additional criteria. Survey respondents highly endorsed and expressed interest in related topics like setting fees for services and offering insurance coverage for psychedelic therapies.

Based on the data submitted for FDA review and drug approval, insurance companies may end up covering an entire therapy-drug treatment package, only the drug, only the therapy, or in the worst-case scenario, nothing at all. It is currently unknown how providers will bill insurance companies for psychedelic-assisted

therapies. Given the anticipated high price of psychedelic-assisted therapy <sup>[4]</sup>, insurance companies may require robust health outcomes from widespread population data outside of clinical trials to justify reimbursement of the high price of treatment packages. Compared to the standard of care treatments, preliminary cost-effectiveness of MDMA phase 2 trials of MDMA-assisted psychotherapy for chronic PTSD suggests the treatment would generate a net savings of \$103.2 million for 1,000 patients over 30 years <sup>[5]</sup>.

Although generic ketamine has been prescribed off-label for mental health disorders for years, the lack of FDA clinical trials has limited insurance companies from covering off-label ketamine even with demonstrated efficacy outside of FDA-approved trials. The nasal spray Spravato (esketamine) received marketing approval by FDA for treatment-resistant depression in 2019 after the drug manufacturer, Janssen, demonstrated safety and efficacy in phase 3 trials when esketamine was administered with an antidepressant <sup>[6]</sup>. However, there are key differences between Spravato and generic ketamine and between ketamine treatment providers. Spravato must be used in a clinic, can be covered by insurance, and aims for a sub-dissociative/ sub-psychedelic experience. In contrast, generic ketamine may be prescribed for home use at lower doses and may or may not incorporate psychotherapy at higher doses, where the dissociative and psychedelic effects of ketamine are viewed as central to the healing process. Ketamine also has relatively few drug interactions as compared to other psychedelics, which should help it remain an important treatment option even as other serotonin-targeting psychedelics become available.

## **Ethical and Legal Implications of Harm Reduction, Psychedelic-assisted Therapy, and Integration**

As described in the appendix, psychedelic harm reduction “refers to the peer to peer or practitioner to participant practices and protocols that are intended to reduce the risk of mental, physical, spiritual or social/legal harm associated with the use of psychedelics.” These practices are drawn from the broader theory of harm reduction, which may refer simultaneously to a set of public health practices, an approach to psychotherapy, or a social justice movement focused on the rights and wellbeing of people who use drugs <sup>[7]</sup>. Licensed practitioners may engage at one or all of these levels.

To engage in harm reduction work, practitioners need to gain comprehensive and accurate knowledge about a range of different substances and how they are used. This includes understanding risks and safety measures. Harm reduction generally also requires a philosophical stance of radical acceptance, respect for client autonomy, willingness to meet the client “where they are at” and work at their pace, an empowerment/strengths focus, acceptance of non-abstinence goals, and a willingness to explore one’s own biases and conditioning about “drugs <sup>[7]</sup>.”

The lack of even-handed mass education, paired with biased messaging, perpetuates the stigmatization of drugs and people who use drugs. In addition to stigma and lack of information, prohibition on substances can exacerbate potential harm by forcing markets and use underground. Use of any substances may indeed come with risks of harm, which can be influenced by the set (attributes and current state of the person), setting (factors outside the person including physical, social, or cultural environment), substance, or dose. However, the lack of accurate, evidence-based information about drugs and prohibition amplifies these risks. Without

accurate information about the benefits and risks of a given substance from a trusted source, a potential user cannot make an evidence-based decision about whether and how to use that substance. In the context of psychedelics, as with other substances, there is a recognition that the risks and harms of any drug are not just a natural consequence of the drug itself. Factors like prohibition, social stigma, and drug purity/consistency can create more harm than the drugs themselves. Drug prohibition and abstinence-focused policy choices have given rise to a dearth of evidence-based education; programs like D.A.R.E. focused on and exaggerated the risks of using controlled substances and failed to acknowledge benefits or provide information about how to use them in ways that reduce risks. Education and knowledge about drugs are also distorted by media and commercial motives. Marketing of legal substances like alcohol and tobacco minimizes perceived risks associated with those substances, while depictions of illicit drug use overemphasize or misrepresents associated risks. When a practitioner or other professional discusses the harm associated with any currently illegal drug, they should acknowledge that they are generally talking about the harm of that drug when handled, produced, and sold without liability, quality control, or safety checks. By definition, a substance can only be regulated (for quality control, recommended use and dosage, monitoring for side effects, etc.) when it is legal.

Legality can take different forms - from federal medical approval to unscheduled but commercially distributable supplements - and varies from country to country and state to state. A substance intended for human ingestion may be unscheduled under the US Controlled Substances Act (CSA) and commercially produced and obtained on a small scale, giving rise to virtually no regulation beyond standard product liability.

For widely marketed products like supplements and food, a substance may be subject to FDA regulation and any relevant state and local regulations covering labeling and restricting false or misleading claims about health benefits. Over-the-counter and unscheduled prescription drugs must nonetheless be shown to be safe and effective (through the FDA) and have stricter marketing rules. Prescription status of some substances marks a drug as “safer” in the minds of many consumers, and doctors may be incentivized to offer branded drug products--thereby needing to minimize risks while selling patients on benefits. Finally, drugs in Schedules II-V of the CSA and analogous state laws must meet the FDA requirements, be prescribed, and control their production and distribution. Schedule I substances are entirely prohibited except for in scientific research settings with high barriers to entry.

For example, in 2019, the U.S. experienced a record 49,860 overdose deaths involving opiates <sup>[8]</sup>, yet numerous drug administrations at over 100 sites worldwide have occurred in Safe Consumption Spaces (SCS) around the world with apparently zero fatal overdoses <sup>[9]</sup>. When discussing harm reduction in relation to psychedelics, we can assume there are contexts in which psychedelic use is more dangerous (e.g., consuming illicitly-produced MDMA, potentially adulterated with unknown other drugs, with inaccurate drug knowledge, alone or in an unfamiliar setting) and situations in which it is safer (e.g., pharmaceutical quality MDMA, taken by someone with accurate drug knowledge, in the presence of trusted others who have accurate drug and harm reduction knowledge). Licensed practitioners can help people who are using drugs do so more safely by utilizing harm reduction practices.

### **General Scope of Legal Needs**

## Practical and Ethical Considerations for Psychedelic Therapy and Integration Practices

The survey also sought input from current or potential practitioners about their legal concerns and ethical considerations. Practitioners' legal concerns span interactions with presently illegal therapeutic contexts, the legal landscape related to preparation and integration services, and the logistics of clinical management and regulatory compliance. Ethical questions focused primarily on referrals, underground culture, training and oversight, and management of adverse or unexpected outcomes. In general, survey respondents reported challenges to retaining sufficient and competent legal counsel to address their questions. It would be advantageous to the field if practitioners in different states who seek answers from subject matter experts on this myriad of legal questions share them in the spirit of "open access." Doing so would help protect both clients and providers, and over time would provide a consistent body of knowledge regarding the legal landscape of psychedelic care practice.

Practitioner licensing boards have never overseen psychedelics in mental health, and they have not defined what falls within and outside of accepted and ethical practices for many years. Thus, they are of limited utility in answering inquiries about the best practices for offering harm reduction or integration services, despite being responsible for governing these practices. Nevertheless, psychedelic use in the public has been steadily trending upwards for over a decade, and new medications are gaining FDA approval. Legal and ethics professionals may provide nimble legal guidance for practitioners working in this space and to future entities charged with regulating it.

In general, licensed practitioners avoid most legal risks by completely avoiding engagement with clearly illegal behavior, including underground psychedelic therapy. However, many questions about emergent

frameworks for legal psychedelic-assisted psychotherapy also still fall into legal gray areas.

Many licensed practitioners, including prescribers, have questions about the extent to which they can discuss psychedelic modalities with their clients. In *Conant v Walters* <sup>[10]</sup>, the Ninth Circuit Court of Appeals held that the federal government could not punish a doctor merely for telling a patient that their use of marijuana for medical use is proper, which lends support to licensed practitioners interested in similarly "recommending" psychedelic-assisted therapy. Referrals to legal clinical trials or licensed practitioners utilizing psychedelic-assisted therapy as the off-label use of an approved drug (i.e., ketamine) should not pose legal or licensure threats so long as the referring practitioner believes in their professional opinion that the treatment offered meets the standard of care required for the referred client. Furthermore, licensed practitioners can safely discuss their knowledge of or professional opinions about psychedelic care or underground practices as part of their free speech rights outside of a patient-provider setting. However, can licensed providers discuss or recommend illegal psychedelic therapy?

Based on the logic in *Conant* and other First Amendment law, licensed practitioners may also be able to safely discuss currently illegal psychedelic-assisted therapy with clients in the way marijuana was discussed as a modality in *Conant*--including the pros and cons, details of modalities, and theoretical applicability of the therapy to the client and their circumstances or condition. However, recommendations for medical treatment with controlled substances as protected free speech by practitioners is not completely settled. Even in *Conant*, the court stated that if a recommendation was being used to obtain federally illegal substances with enough requisite knowledge and intent on behalf of

the recommending physician, the physician, Lourido, Bathje, Hallisey, Booher, Novick, Feduccia could be subject to charges of aiding and abetting in federal drug crimes [1].

A district court case in Washington D.C. challenging the same policy challenged in *Conant* found that medical marijuana recommendations were effectively prescriptions because they operated as the means to receive cannabis under state laws. See *Pearson v. McCaffrey* [11] (analogizing recommendations to prescriptions under the California Compassionate Use Act). Prescriptions of controlled substances were not found to be protected speech. See *id.* at 121 (stating that speech that is part of the practice of medicine is subject to reasonable licensing and regulation and that speech in the commission of a crime is not subject to First Amendment protection). However, speech about “potential medical benefits of marijuana use” short of these prescriptions or recommendations was not interfered with under the government’s policy. *Id.* No appeal was taken in this case, but analogous litigation (about First Amendment rights to recommend or refer patients to treat with Schedule I substances) that could give rise to a circuit split in the future. Of course, all of these rulings are limited to their jurisdictions.

In addition to asking about the legal limits of what practitioners can say and do with respect to recommendations, a number of survey respondents also asked about whether or not practitioners can directly refer a patient or client to underground therapists. A referral to an underground practitioner may expose a licensed practitioner to higher legal risk based on the aforementioned law. Doing so could be seen as an action meant to aid and abet or conspire in criminal activity, rather than merely discuss or recommend a potential modality. However, one of the most complex and potentially nuanced issues that emerged in survey responses was the ethical obligations of practitioners as they relate to

referrals because the desire to avoid legal risk comes into tension with the desire to provide the best care for their participant or client (which some practitioners believe may be through psychedelic-assisted therapy).

One survey respondent noted that “One of the fundamentals in good therapy is not requiring clients to bear secrets - that can be deeply damaging to clients. So, when we are discussing these options, what does that look like ethically if a client is asking for underground referrals?” Going one step further, another practitioner questioned whether or not it is “ethical to withhold referrals when it's clear someone could greatly benefit from working with psychedelics/entheogens and don't have the time/means to travel to a country where it's legal?” These are the types of conundrums that practitioners face, but referring clients to anything other than legally available options such as ketamine, research trials, and international ayahuasca and psilocybin retreats would likely be interpreted as a violation of their license.

Practitioners also had questions about prescribing psychedelic substances off-label to patients with and without a diagnosed mental health condition. According to the FDA itself, “once the FDA approves a drug, healthcare providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient [12].” Specifically, within the context of mental health treatment, ketamine has set this precedent—the development of ketamine as a modality for treating chronic depression was established by years of off-label use by providers using generic, racemic ketamine, prior to FDA’s recent approval of Spravato. Although Spravato is now approved for the treatment of treatment-resistant depression (TRD), racemic/generic ketamine remains available and legal to use in off-label contexts for the same treatment. There have been a small number of licensing board

investigations into ketamine practitioners, but the authors are not aware of any that have resulted in direct disciplinary action. So, while MDMA and psilocybin are on track to be approved by FDA based on their ability to treat specific indications, it is plausible that a body of research develops to support the off-label use of MDMA or psilocybin as a treatment for other indications as well.

Another question that emerged was the legal status of incorporating experiential training as part of the education of psychedelic therapists, where the trainee undergoes a psychedelic session as part of their instruction. Experiential training has a long history in the training of psychotherapists, where it was once required and remains encouraged that students receive their own therapy, to experience the client role and resolve their own issues. MAPS PBC has permission from FDA to offer an optional experiential MDMA session through a study protocol as part of its training for therapists learning the MDMA-assisted psychotherapy modality. Although the use of scheduled substances for experiential training outside of FDA-approved cor 10 not clearly established, these factors t suggest that permitting practitioners to be taught through experiential methods may result in improved outcomes. While schedule II through IV medications can be used off-label as described above, a clinical rationale is generally required to prescribe them.

Another category of questions concerned screening, liability, and release forms. Specifically, practitioners seek appropriate templates for forms regarding informed consent, including potential side effects of psychedelic substances. The field would benefit from creating norms and boilerplate language to ensure that people unfamiliar with psychedelic therapy are fully briefed on how it is similar or different from other forms of therapy. In this vein, and related in part to the issues of off-label use referenced above,

there are also questions about what screening methods are most appropriate for different patients. This is a question that we anticipate the field collectively answering over time, as more modalities emerge and different types of patients begin to engage with psychedelic therapy.

Practitioners are unclear about the extent to which informed consent/release forms provide protection from civil or criminal liability. There is currently a misperception that signing release forms in underground contexts provide protection from civil or criminal penalties; however, in the United States, contracts formed on the basis of currently illegal behavior are not enforceable, so release forms used in underground therapy contexts may not carry legal weight. However, they may still provide useful information to clients and have value as one way to put potential underground clients on notice and receive informed consent about the risks, legal and otherwise, in engaging with underground work.

Given this context, questions remain about which liabilities are incurred regarding the risk of mental injuries or negative experiences, including therapy abuse in which a therapist takes inappropriate advantage of or otherwise harms a client.

- Novel Issues in Compliance & Logistics
  - Over the last years, a number of practitioners have expanded their practice to include teleconferencing. During the coronavirus pandemic, this became more common as more physicians began prescribing take-home doses of ketamine. However, this is a novel phenomenon, and many practitioners are undereducated about the nuances of the legality regarding teleconferencing, particularly in how it can be utilized in psychedelic

contexts. One survey respondent even asked whether or not there is “a case to be made for accompanying a client virtually (via video) who is under the influence of a psychedelic?”

- In addition to novel approaches including telemedicine, a number of questions about the logistics of clinical practice and regulatory compliance remain, including questions about the storage, tracking, and dosing of medicines; and questions about screening, disclosure, and liability. Other practitioners are concerned about the technical aspects of how medicines will be stored, tracked, dispensed, disposed of, and dosed. Practitioners will need to work with the DEA office in their jurisdiction to maintain compliance. It should be noted that these requirements are stringent for all scheduled drugs, but particularly for schedule I drugs. These questions and more will be answered as more information about psychedelic medicine REMS is published.
- Elective Use and Social Care
  - For clients without any diagnosed mental health condition, the path toward legal access is less clear. Elective cosmetic medicine (cosmetic surgery, injectables, prescription eyelash growth serums, dermatological laser treatments, etc.) has become normalized in medical culture <sup>[13]</sup>. There are examples of providing prescription medications to individuals who are healthy but want to chemically alter some system of their body (e.g., FDA approved giving human growth hormone to children who are

healthy but may end up in the lowest percentiles of height (shorter than 97% of their peers)). Outside of talk therapy modalities, however, the mental healthcare profession and our other mainstream institutions have not conceived of a care paradigm that includes chemical intervention for the mentally “well” in addition to the full spectrum of individuals, including those with diagnoses of varying degrees and severities.

- Concepts of psychedelic therapy or healthcare for the general population align well with modern concepts of well-being and individual determination but can clash with drug stigma and may not as easily fit into the standardized lifestyle of our society (i.e., the productivity-focused, 40-hour workweek). Because governing institutions like FDA have legislative mandates based on treating diagnoses, practitioners looking to extend psychedelic-assisted therapies to “well” patients may need to be activists in support of this far-from-inevitable expansion in their field. As in the case of cannabis, legal changes at the state and local level could provide some opportunities for practitioners; however, practitioners will still need to be mindful of licensing and ethics-monitoring bodies, as well as federal enforcement bodies like the DEA. Finding and developing a body of evidence that supports the gradual expansion into this “betterment” model of care could allow practitioners to maintain their ethical and professional standing and obligations, while cleverly

innovating at the edges of their fields.

- Other Ethical Issues

- Survey respondents also identified a number of critically important ethical questions that are beyond the scope of this article. Numerous practitioners have questions about how transference and countertransference are impacted by other power dynamics, including racial, socio-economic, and cultural ones. This is further complicated by how boundaries - i.e., with touch - are different in psychedelic-assisted therapy. MAPS PBC has recently published a second edition of the MDMA-Assisted Psychotherapy Code of Ethics<sup>[14]</sup> which touches on some of these topics, and the Journal of Psychedelic Psychiatry published Practical and Ethical Considerations for Psychedelic Therapy and Integration Practices

Practical and Ethical Considerations for Psychedelic Therapy and Integration Practices

- However, at least one survey respondent recognized the ethical expectations of clients themselves, something rarely discussed in traditional therapy contexts. A number of questions also remain about the legality of psychedelic preparation and integration 12

- services. Specifically, practitioners are interested in providing “auxiliary” services (that is, services that “don’t touch the drug”) but obviously wish to do so without jeopardizing their license or risking getting sued or arrested.

- On a more conceptual level, numerous practitioners brought up questions about the ethics of medicalization of psychedelic experiences in general. Working with psychedelic substances

becomes complicated when practitioners work with medicines - traditional plant-based ones in particular - that are being used outside of or beyond their cultural context. There is an open question about how to appropriately train practitioners working with these substances, unlike MDMA, ketamine, and LSD - which clearly emerged from a primarily scientific, “Western” paradigm - mushrooms, ayahuasca, iboga, and other substances have a historical context which should be considered by practitioners seeking to work with these medicines.

- In addition, there seemed to be a general concern among respondents with a paradigm which necessitates finding and defining mental health as having local causes (uniquely within a single person), places primary control in the hands of experts instead of democratizing knowledge and emergent experience, and frames that control within the influence of profit-oriented motivations for research, use, and treatment. The authors look forward to continued engagement with this issue even as we continue to operate within the present regulatory paradigm and the reality of its limitations.

## CONCLUSION

Psychedelic clinical trials are advancing through the FDA development pipeline, and ketamine and esketamine have already seen a rapid adoption by many clinics and therapists. The emergence of psychedelics in healthcare practices brings forth the need to modify current operational procedures and structures to accommodate the specific

criteria necessary for treatments and safety. With the uptake of these medicinal technologies, practitioners must be educated on well-defined terminology, safety, and effects, harm reduction practices, and receive legal and ethical guidelines for establishing clinics and administering psychedelics. The very nature of psychedelic medicine will require the intersection of many disciplines, including health care providers, legal counsel, federal and state regulatory agencies, healthcare boards, insurance companies, and other payers. If psychedelic treatments prove to be safe and effective for the growing list of indications under study, the coming decades could represent a major evolution in mental health care.

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Lourido, Bathje, Hallisey, Booher, Novick, Feduccia

#### FOOTNOTES

1. It may be important to note that the federal policy challenged in both court cases discussed is a distinction with the current situation around psychedelic-assisted psychotherapy. After a handful of states passed medical marijuana legislation, the federal government announced, via the Office of National Drug Control Policy, that the DOJ's position was that recommendation or prescription of Schedule I controlled substances was considered inconsistent with the "public interest" as used in the Controlled Substances Act. As of this writing, the government's intentions and position toward practices adjacent to psychedelic-assisted psychotherapy is unclear. Open questions exist about the comparative nature of public support for psychedelics relative to public support for cannabis, about the intentions of law enforcement and other political bodies around enforcement priority for psychedelics in therapeutic contexts, and about legislative and rulemaking intentions around these topics that could move the conversation away from first amendment conversations.

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## APPENDIX

### Supplemental Material

#### Terms and Interpretations of Phrases

The survey asked respondents what terms in the psychedelic field were unclear and how they would interpret the meaning of specific phrases. Table 1 displays the percentage of participants reporting the term could use more precise definitions and their response on how to define the term or phrase. Following the survey participants' responses, the authors have attempted to provide concise interpretations of the terms, based on survey responses and language used in clinical research and cultural settings, as a means of facilitating further discussion around a shared

terminology. However, the field of psychedelics is multidisciplinary and rapidly evolving, therefore the interpretations of these phrases are fluid and dependent on the context of use.

Table 1. Survey Response to Terms and Interpretation of Meaning

Terms	Respondent Interpretation of Meaning
Psychedelic-assisted therapy (53.95%)	<p>A. "Using psychedelics to explore the experience of non-dual awareness under the guidance of a therapist who can contribute to a safe drug, set and setting; and can assist in setting intentions and integrating the experience in terms of making sense of/ figuring out how to talk about a space that is outside of typical, normal daily reality."</p> <p>B. "Psychedelic-assisted therapy is a treatment utilizing psychedelic medicine as a catalyst for opening up the capacity of the participant to the treatment during the medicine session. The medicine itself is not the treatment, as preparatory and integration sessions are the major components."</p> <p>C. "Psychedelic assisted therapy is any type of therapy that is performed with the client under the influence of a short-acting psychoactive mind-altering substance to potentiate the effects of the therapy."</p>
Psychedelic integration (51.33%)	<p>A. "The integration of externally-sourced psychotropic medications into the practice of internal, emotional and psychological self-exploration and healing."</p> <p>B. "Integration involves 'meaning making' that brings the psychedelic experience into everyday consciousness..."</p>
Psychedelic practitioner (47.37%)	<p>A. "I understand there have been many underground practitioners of psychedelic 'therapies' that are not traditionally trained and have done great work with people. However, as this work is everything in the legitimate therapy world, I believe it is important that a psychedelic practitioner be someone with extensive training in clinical practice, as well as in psychedelic-assisted therapy. It is important that this field embodies legitimacy."</p> <p>B. "A psychedelic practitioner is someone who uses expanded states of mind to resolve psychological issues."</p> <p>C. "I wonder if that could mean anyone who practices aspects of that process - ie, until it is legal, I would call myself this in terms of prep and integration work and knowledge base, with clear discernment I don't provide the medicine session."</p>
Psychedelic harm reduction (40.79%)	<p>A. "Some objections have been raised to the term 'psychedelic harm reduction,' and I can understand the concern. I have heard some talk of changing language to 'optimization' or something else that does not suggest that psychedelics are inherently harmful or dangerous. Though I do recognize that 'harm reduction' is a term that has familiarity and traction."</p> <p>B. "Psychedelic integration and Psychedelic harm reduction: Includes having a presence that is easily accessible for persons who have had psychedelic experiences that are outside of the realm of a controlled setting and need help making sense of what they have experienced."</p>

Psychedelic intention-setting/preparatory support (38.16%)	A. "What I envision psychedelic intention setting and prep support to be is: an opportunity to assist the client in defining why they want to have an experience and preparing them with tools to use during the session, especially if you will not be there as a practitioner. This may change as we are allowed to be with people during sessions."
Psychedelic medicine (34.21%)	<p>A. "Psychedelic medicine is the medicine used in psychedelic-assisted therapy, and other spiritual and cultural contexts with the intention for healing."</p> <p>B. "Soul-manifesting substances."</p>
Medicine session (25%)	A. "Sessions that use or refer to psychedelics"
Psychoactive-assisted therapy (1.32%)	A. "Either psychedelic or psychoactive terms are fine with me. They both represent an altered state of consciousness that is going to be supported by a clinician."
Ceremony (1.32%)	Respondents: N/A
Participant (1.32%)	Respondents: N/A
Guide (1.32%)	Respondents: N/A
Ethical Off-label use (1.32%)	Respondents: N/A

'Psychedelic-assisted therapy' is the process of using a psychedelic substance alongside a therapeutic approach to support a person's mental healing or well-being; hallmarks of the process include supportive and non-directive psychotherapy during prior preparatory sessions with the participant, the sessions themselves, and post-session integration. This term can be applied broadly to a range of substances, dosage levels, and theoretical orientations. Current clinical teams, such as MAPS, have standardized their definition of psychedelic-assisted therapy in trials to also include "client safety and wellbeing," "provider training and experience," "nondirective therapeutic approach based on empathetic rapport," the use of "inner healing intelligence," by the client, the therapeutic team's ability to "guide or redirect" the client, as well as "enable the processing of trauma" by "maximizing the inner experience" with caution placed on "client safety and the avoidance of being retraumatized"; "addressing somatic manifestations", creating a therapeutic environment that "evokes and supports emotional experiences [3]." However, therapeutic approaches are varied across

trials, substances, and indications under study.

‘Psychedelic medicine’ is defined here as a class of naturally occurring or derived compounds or substances known to produce strong phenomenological experiences, in either clinical and research settings. These substances have also often been used in indigenous cultures and naturalistically throughout time. Often categorized into entactogenic, serotonin enhancing substances (such as MDMA) and ‘classical psychedelics’, such as LSD and psilocybin, which act as agonists to the 5-HT<sub>2A</sub> receptors, the latter is often found in naturally occurring fungi or plants and has been used by traditional cultures for thousands of years [16]. Clinical trials in recent years are now showing efficacy for psychedelics used more commonly in cultural settings, like psilocybin, in modern medical practice to treat a variety of mental health disorders such as depression, end-of-life distress, and addiction [17, 18, 19, 20]. The Food and Drug Administration (FDA) describes only substances that have been approved through the federal drug development pathway as ‘medicines’.

The word ‘participant’ is used to describe one who intentionally, and knowledgeably, consents to a psychedelic experience or psychedelic-assisted therapy in either naturalistic, culturally specific, or clinical settings. In clinical research, a person can also be referred to as a ‘subject’, whereas a person who pays a practitioner for mental health services is called a ‘client’ or ‘patient’. Clinical trials, therapeutic settings, and many culturally focused psychedelic ceremonies have unique inclusionary/exclusionary criteria that require participants to be in good health, or to be specifically suffering from an ailment before psychedelic-assisted treatment is allowed.

The word ‘medicine sessions’ specifically references the active time under the influence of a psychedelic substance as a means of mental, physical, or spiritual healing. A medicine session may refer to the administering of psychedelics in naturalistic settings by users, clinically administered patients in research, or experiential with practitioners. In many studies, double-blind experimental designs may mean a medicine session is conducted with an active dose of a psychedelic or with a placebo. In ceremonial contexts, medicine sessions may be seen as the specific rituals, traditions, and language that different cultures employ when using psychedelics in a ceremonial or spiritual setting.

Prior to a medicine session, ‘psychedelic intention setting’ or ‘preparatory support’ occurs, where participants are offered supported discussion and reflection as a means of examining the user’s goals and intentions for the psychedelic-assisted sessions. Intention setting can act as a priming effect in therapy. Clinically, preparatory and intention setting is defined as meeting with clinical therapists in which the therapeutic alliance is solidified, the participant is given information of what they can expect to experience, and there is ample opportunity to discuss the participants’ intentions and concerns prior to psychedelic-assisted session [3]. Explanations of possible sensations, challenges, fears, and procedures are also addressed. Historically, psychedelic literature has pointed to appropriate preparation activities, such as in Dr. James Fadiman’s 2011 book, *The Psychedelic Explorer’s Guide: Safe, Therapeutic, and Sacred Journeys*, which offers readers preparation insight that is based on both historical and clinical uses of psychedelics [21]. Further, there are a myriad of intention-setting protocols that vary from culture to culture prior to the use of psychedelic substances in ritualistic or spiritual contexts.

Some therapists offer preparatory services in which drugs are not administered, but a person using in naturalistic settings is offered support and a chance to ask questions or set intentions.

After a medicine session, psychedelic-assisted therapy is paired with ‘integration’, the intentional supported discussion, writing, or reflection that occurs after a psychedelic experience as a means of allowing the patient to examine their phenomenological experience, as well as to reflect upon their preexperience intentions, make meaning of their interpretations, and explore ways to incorporate them postexperience. In clinical trials, integration sessions occur after a dosing session to allow the client to further explore the experience of their psychedelic-assisted session and receive continued support for their therapist as they discuss ways to incorporate that experience into the client’s life moving forward<sup>[3]</sup>. Techniques and number of integration sessions vary between trials. Outside of clinical trials, psychedelic integration further expands to individuals seeking this same type of processing with a health professional who was not involved in the administration of the psychedelic or oversight of the experience<sup>[22]</sup>.

A ‘psychedelic practitioner’ is a person who supports this experience through a variety of protocols or practices. We use a general term because practitioners may employ or be trained in shamanistic or traditional healing modalities, or in a variety of scientific fields such as psychiatry or psychology. There is variance among psychedelic practitioners, even in clinical trials. Johns Hopkins has used session monitors, from graduate students to psychiatrists and clinical psychologists, while MAPS, under their expanded access program, expresses that practitioners encompass a team from the medical doctor who obtains the DEA schedule 1 license to

the ‘therapy pair’ in which one must be fully licensed to administer therapy according to state mandated regulations all while following a strict code of ethics<sup>[19, 23]</sup>. Beyond professionals pursuing research, practitioners like those found through the provider network Psychedelic.Support (www.psychedelic.support), are licensed, may or may not have worked in psychedelic research, and are empathetic to the naturalistic use of psychedelics by clients. They may be considered practitioners by way of integration or intention-setting services, but administer no psychedelic substances. The word ‘guide’ is frequently used to encompass shamans, clinical trial therapists, underground therapists, or any person who is psychedelic-informed, trusted, and competent person who assists consenting participants through preparation, integration, the psychedelic experience, and is responsible for the participant’s safety and well-being while they are under the influence of a psychedelic. This may include licensed or unlicensed practitioners, or may refer to the numerous cultures that continue to provide healing, ceremony, and spiritual guidance through a psychedelic ritual, such as the use of ayahuasca by Amazonian shamans or the use of the mescaline containing peyote cacti by indigenous tribes of the American southwest<sup>[24]</sup>. However, it does not necessitate that the guide be the giver of a psychedelic medicine or therapy. For example, Zendo Project’s ethical guidelines for peer support training require that one does not ‘guide’ a peer having a psychedelic experience at all<sup>[25]</sup>, whereas clinical trial therapists are trained to specifically guide participants using a non-directive approach, and shamans pull from their cultures’ ritual and traditions to facilitate the psychedelic experience<sup>[3, 26]</sup>.

‘Psychedelic harm reduction’ (sometimes referred to as ‘psychedelic risk reduction’ or ‘harm reduction and healing’) refers to the

peer-to-peer or practitioner-to-participant practices and protocols that are intended to reduce the risk of mental, physical, spiritual, or social/legal harm during a psychedelic experience, and is a hallmark of safety across the field. Classically, harm reduction refers to the consideration of human rights in practice, theory, and policy meant to reduce harm to people who use drugs [27]. When considering psychedelic harm reduction, Zendo Project's training manual regards "creating safe spaces," "sitting, not guiding," "talking through, not down," and "difficult is not the same as bad" as the key components for reducing harm in psychedelic users [25]. The approach is attentive to set and setting, and relies on human relationships to navigate challenging experiences and support open or positive experiences, while also attending to medical needs that may occur, such as those due to preexisting health issues, drug interactions, or overdose.

'Ceremony', in relation to psychedelic use, can describe a variety of ancient traditions that allow participants to experience facilitated psychedelic experiences, such as ayahuasca ceremonies in Peru to the use of peyote by Native American tribes of the southwest [26]. Covering a wide array of traditions, rituals and psychedelic substances, the wider purpose of a ceremony is to facilitate spiritual, and often mental and physical healing. Practitioners and guides may employ a ceremony that encompasses preparation, medicine sessions, appropriate rituals, and integration of the experience. Recent clinical trials draw on these historical traditions to help guide the development of psychedelic-assisted therapy protocols, such as MAPS' use of therapeutic teams and integration [3].

Today, traditional psychedelic ceremonies are legally available in countries throughout the world [26].

The broader class of 'psychoactive-assisted therapy' is where a psychoactive substance is given as an adjunct to a modality of therapy, such as psychotherapy. Currently, psychedelic-assisted therapy falls under the larger umbrella of psychoactive-assisted therapy. The World Health Organization defines psychoactive substances as any substance that affects a person's cognition to include not only psychedelics but also pain medications, caffeine, and nicotine [28]. Not exclusive to psychedelic-assisted therapy, psychoactive-assisted therapy may encompass practices such as pain management and off-label use. 18

In clinical settings, 'off-label use' to a doctor prescribing an FDA-approved medication for an indication that was not investigated in the full battery clinical trials necessary to gain marketing approval from the FDA. Because 'off-label prescriptions' employ a medication outside of its primary intended use, health providers must consider the available published evidence, safety risks, and potential risk/benefit ratio and assume legal risks in prescribing medications off-label. Ethical off-label use is intrinsically intertwined with legal frameworks and is an attempt to use medicines to promote healing outside of their intended use while still considering patient safety, legal restrictions and provider responsibility, where these considerations vary from one country to the next [29].

# Newspaper Coverage of Psilocybin – Sentiment and Frequency (1989-2020)

Dax Oliver, M.A.

## Abstract:

A growing body of medical research has focused on the chemical compound psilocybin in recent years <sup>[1,2]</sup>. However, this research is not merely a scientific issue but also a social and political one. In the 1960s, psilocybin and other psychedelics were often ingested outside of research settings <sup>[3]</sup>. This alarmed many people, resulting in severe legal restrictions on psilocybin research <sup>[4]</sup>. Today, many advocates hope that it will avoid the negative public sentiment of the 1960s <sup>[5]</sup>. To help gauge public sentiment about other psychoactive compounds, some studies have examined newspaper coverage <sup>[6,7]</sup>. The present study hoped to build a similar gauge with newspaper coverage of psilocybin. The author hypothesized that general sentiment about psilocybin has become more positive among American newspapers in recent years and that the annual number of newspaper articles mentioning psilocybin has increased. To test these hypotheses, all mentions of psilocybin were examined in four regional American newspapers from January 1, 1989, to December 31, 2020. Contrary to the hypotheses, a significant rise in positive sentiment was seen in only one of these newspapers, and the annual number of articles mentioning psilocybin significantly increased in only one newspaper. These results could be a warning to psilocybin advocates about the risk of negative social and political sentiment growing again.

## INTRODUCTION

Psilocybin is a chemical compound (molecular formula:  $C_{12}H_{17}N_2O_4P$ ) <sup>[8]</sup> found in several species of fungus. Many people consider it to be a member of a class of compounds called "psychedelics," which in humans cause "effects on the mind, such as feelings of deep understanding or unusually strong experiences of color, sound, taste, and touch <sup>[9]</sup>." After ingestion, psilocybin and some of its metabolites (such as psilocin) <sup>[10]</sup> cross the blood-brain barrier and bind to neuron receptors for serotonin (a neurotransmitter) <sup>[8]</sup>. There are several types of receptors for serotonin on human neurons <sup>[11]</sup>. Many researchers believe there is a correlation between psychedelic experiences and the binding of psilocybin and some of its metabolites to the 2A serotonin receptors (also known as 5-HT<sub>2A</sub> receptors) <sup>[12]</sup>.

However, there does not seem to be a consensus as to why psilocybin's agonism with serotonin receptors might be correlated with psychedelic experiences.

In the 1950s and 1960s, a number of research studies were conducted about psilocybin, such as examining its effects on color perception,<sup>[13]</sup> the spiritual emotions of divinity students,<sup>[14]</sup> and criminal recidivism <sup>[15]</sup>. One prominent researcher, Timothy Leary, began actively promoting the use of psychedelics like psilocybin for the general public, saying that Americans should "tune in, turn on, and drop out <sup>[16]</sup>." Although Leary often became the public face of psychedelics in the United States, their use was also advocated by many other well-known people such as musicians and actors. As psychedelic use rose among Americans, a social backlash developed. Some mainstream media described psychedelic users as committing

suicide [17] and having permanent genetic damage [18]. Amendments to the U.S. Food Drug and Cosmetic Act in 1962 and 1965 "imposed severe restrictions on distribution, possession, use, and research"<sup>3</sup> of psilocybin. In 1970, President Richard Nixon signed the Controlled Substances Act, which listed psilocybin as a "Schedule 1" drug that had "no currently accepted medical use in treatment in the United States [19]." Psilocybin remains a Schedule 1 drug today.

However, even after these numerous legal restrictions, the American government still occasionally approved tightly controlled research of psilocybin [3]. From the late 1980s until today, this research has accelerated. For example, Johns Hopkins Medicine has conducted studies about psilocybin's potential to help treat anorexia nervosa, nicotine addiction, and Alzheimer's Disease [2]. In 2018, the U.S. Food and Drug Administration stated that psilocybin was a "breakthrough therapy [21]."

Within the psychedelic research community, there seems to be a growing sense of optimism that psilocybin could become an accepted part of American life. However, as scientists in the 1960s discovered, the legal scheduling of a chemical compound by the U.S. Drug Enforcement Administration is not merely a matter of scientific research – it is also a matter of politics and public perception. If a new social backlash develops against psilocybin and other psychedelics, it could overwhelm the positive impact of recent scientific research. Therefore, finding ways to determine public sentiment about psilocybin might be beneficial.

McGinty et al. [6] and Zhang et al. [7] have explored newspaper coverage as a method to gauge public opinion about opioids and ketamine, respectively. Building on their studies, the author read and analyzed every article mentioning psilocybin in four regional

American newspapers over the period from January 1, 1989, to December 31, 2020.

The present study had two hypotheses about these newspaper articles:

- 1) General sentiment about psilocybin had become more positive between the beginning and end of the studied period.
- 2) The annual number of articles mentioning psilocybin had increased between the beginning and end of the studied period.

The author recognizes the risk that newspapers might be a less accurate gauge of media opinion in 2020 than they were in 1989, considering the growth of other media outlets such as cable news and podcasts. However, an analysis of newspapers might still provide at least some type of gauge, even if it is far from a perfect one.

## METHODS

The imperfections of methods for examining sentiment must be considered when reading the results of studies about sentiment. Due to current flaws in machine assessment of sentiment, a human assessment was determined to be better for the present study (although this might change in the not-distant future). A more detailed explanation is given below.

Similar to McGinty et al., [6] the present study divided the United States into four geographical regions (Northeast, Southeast, Midwest/Plains, and West) and chose one newspaper from each region: *New York Times* (Northeast), *Tampa Bay Times* (Southeast), *St. Louis Post-Dispatch* (Midwest/Plains), and *San Diego Union-Tribune* (West). It was hoped that examining all of these newspapers could mitigate potential regional differences in sentiment toward psilocybin. Some of these newspapers purchased and/or absorbed other newspapers over the time period being examined (January 1, 1989, to December 31, 2020).

Following the example of McGinty et al.,<sup>[6]</sup> the archives of those absorbed newspapers were included under the titles of their current publishers.

To avoid any variations in the quality of databases administered by the newspapers themselves, all article sets were created from the online media database Nexis Uni (the academic research portal of the LexisNexis database). When creating sets of articles, it was necessary to search for a variety of terms in addition to "psilocybin" because, unlike many psychoactive substances, psilocybin is frequently referenced by its delivery container (mushrooms) even in journalistic contexts. After extensive reading of psilocybin journalism, the present study chose four search terms for psilocybin: "psilocybin," "magic mushroom," "hallucinogenic mushroom," and "psychedelic mushroom." Searches were made for both singular and plural forms. There are also many slang terms for psilocybin, such as "shrooms" or "boomers." However, many of these slang terms also have other meanings and seemed rarely used by the newspapers in this study, so they were omitted. Also not included were articles about mushroom species containing hallucinogenic compounds other than psilocybin (such as muscimol, which is found in some *Amanita* species).

Duplicate articles were removed from the sets both using Nexis Uni filters and manually, even if articles had different datelines. However, multiple articles about the same news event were included as long as the articles seemed independently written (for example, following new developments in the event or approaching the event from a different perspective). It might also be important to note that many newspaper articles mentioning psilocybin do not feature psilocybin as their central topic.

After the searches and data cleaning described above, the final article set consisted

of 578 articles for all four newspapers. Of these, 335 articles were from the *New York Times*, 95 articles from the *San Diego Union-Tribune*, 78 articles from the *Tampa Bay Times*, and 70 articles from the *St. Louis Post-Dispatch*.

Determining the sentiment of each particular article presented challenges. For example, the same article might mention both positive and negative opinions of psilocybin. In addition, some articles might have stronger positivity or negativity than others. To address these challenges, the author found inspiration in previous studies about media portrayals of psychoactive substances. McGinty et al.<sup>[6]</sup> and Zhang et al.<sup>[7]</sup> created different thematic categories in which each article could be assessed. For the present study, the author identified five thematic categories to rate sentiment about psilocybin. For each category, each article was given a score of -1 (negative), 0 (neutral), or +1 (positive). The total scores in each thematic category were then calculated for each year for each newspaper. The scores in each category were also then added together to provide a single sentiment score for each year.

The five thematic categories in the present study were:

- 1) **Legality:** Is psilocybin seen merely as an illicit substance (negative) or as a substance that should be legal (positive)?
- 2) **Mode of Action:** Is psilocybin seen as physically damaging (negative) or physically beneficial (positive) to the user?
- 3) **Personal Impact:** Is psilocybin seen as psychologically detrimental (negative) or psychologically beneficial (positive) to the user?
- 4) **Scientific Integrity:** Is psilocybin research seen as pseudoscience (negative) or rigorous and serious (positive)?

5) **Social Impact:** Is psilocybin seen as detrimental (negative) or beneficial (positive) to society beyond the user?

The decision to use machine or human judgment for rating the sentiment of articles was a difficult one. Nexis Uni, for example, has a feature called "Negative News," which attempts to algorithmically choose 22 negative articles for a particular search. Unfortunately, the Negative News results for psilocybin were sometimes highly inaccurate and similar problems seemed to arise with other algorithms. A full discussion of the debate between machine and human judgment is beyond the scope of the present study, touching on the fields of computer science, philosophy, and logic. To avoid the current problems of using algorithms to determine sentiment, for the purposes of this study, the author decided that human judgment was a better option. If machine judgment of sentiment eventually matches or surpasses human judgment, the present study might benefit from being conducted again by machines.

Efforts were made to mitigate the risks of using human judgment of sentiment. In addition to the categorical and regional distinctions above, the author read and rated all 578 articles during two separate periods of time, separated by roughly two months, to allow for variation in mood or focus. The mean sentiment scores of the separate analyses were then calculated for each year. A data table with sentiment scores for each period is available upon request. This was still far from a perfect method, but the author believes the results might still provide at least some insights.

Trend lines in the Discussion section were calculated using ordinary least squares. The calculations were performed by Tableau, a widely-used data visualization software, and p-values were also calculated by Tableau.

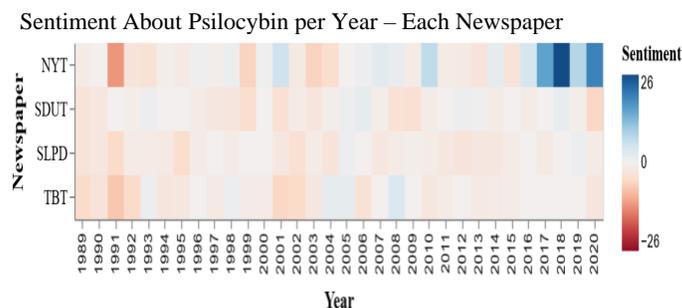
Future studies might also consider the political leanings of newspapers, assess how coverage of psilocybin changes in regions where it has been decriminalized, expand analyses to psychedelics besides psilocybin, and/or include media other than newspapers.

## RESULTS

### Sentiment of Articles

Annual sentiment about psilocybin from January 1, 1989, to December 31, 2020 in articles (N=578) from the *New York Times* (NYT) (n=335), *San Diego Union-Tribune* (SDUT) (n=95), *St. Louis Post-Dispatch* (SLPD) (n=70), and *Tampa Bay Times* (TBT) (n=78):

Figure 1



The annual sentiment scores for each newspaper ranged from 26 in 2018 for the *New York Times* to -12.5 in 1991, also for the *New York Times*. The *San Diego Union-Tribune* ranged from 2 in 2006 to -5.5 in 2020. The *St. Louis Post-Dispatch* ranged from 1 in 2005 and 2019 to -5 in 1991. The *Tampa Bay Times* ranged from 3.5 in 2008 to -7.5 in 1991.

There were also a number of variations when comparing annual sentiment scores within the parameters of each individual newspaper, comparing newspapers by their sentiment scores in each thematic category, and comparing thematic categories within

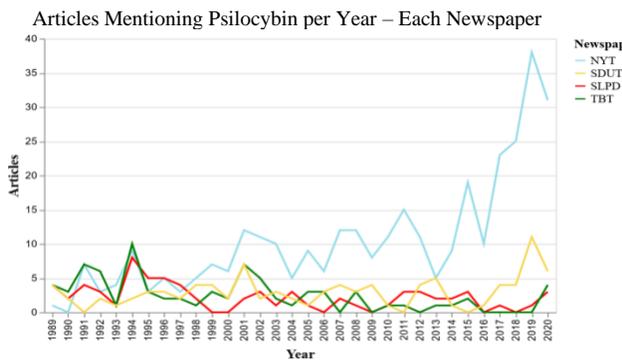
Newspaper Coverage of Psilocybin – Sentiment and Frequency (1989-2020) each individual newspaper. Charts of these variations are available upon request.

The mean sentiment per article for each year (perhaps calculated by dividing the total sentiment score each year by the number of psilocybin articles that year) did not seem a useful statistic because many mean article scores did not accurately reflect the sentiment of the year. For example, in the *Tampa Bay Times*, 2011 would have had a high negativity (-1) than 2001 (-0.786), <sup>1 23</sup> was only because 2011 had a single psilocybin article (which happened to be negative), as opposed to 7 psilocybin articles in 2001 with a total negativity of -5.5.

### Number of Articles

The final article set for the present study contained 578 total articles for all four newspapers. Of these, 335 articles were from the *New York Times*, 95 articles from the *San Diego Union-Tribune*, 78 articles from the *Tampa Bay Times*, and 70 articles from the *St. Louis Post-Dispatch*. The annual number of articles mentioning psilocybin ranged from 38 in 2019 for the *New York Times* to 0 in several years for all four newspapers.

Figure 2

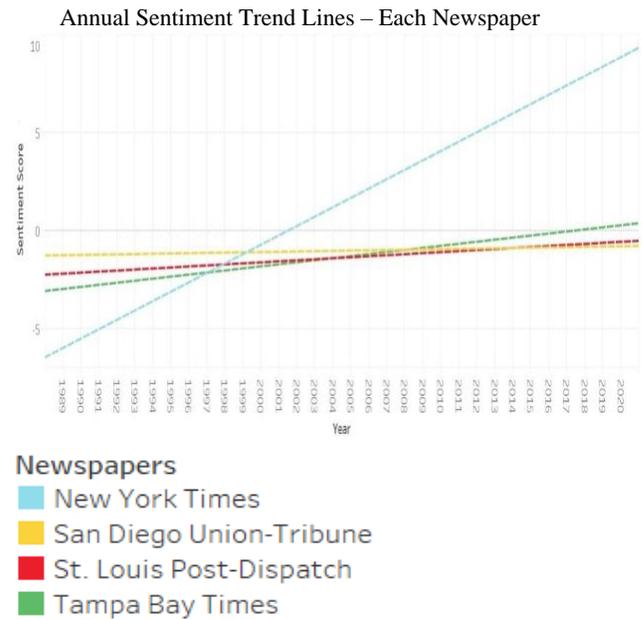


## DISCUSSION

### Sentiment of Articles

The first hypothesis was that general sentiment toward psilocybin in the studied articles had become more positive between the beginning and end of the 32-year period. This hypothesis was mostly false. Only one of the four newspapers (*New York Times*) showed a significant increase in positive sentiment [Figure 1]. The trend lines of annual sentiment in the four newspapers can be seen in the chart below:

Figure 3



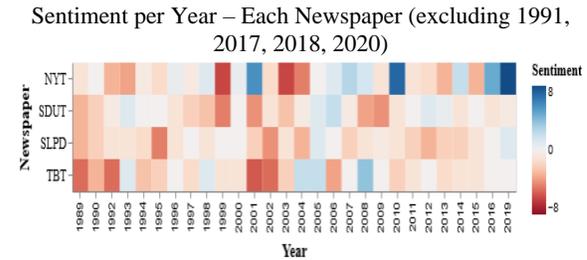
The *New York Times* (n=335, p=0.0002) showed a much stronger trend toward greater positive sentiment than the other newspapers. In fact, although the other newspapers also showed slight trends toward more positive coverage, there are potential flaws in those trend lines. The trend line of the *San Diego Union-Tribune* (n=95, p=0.682) can be discarded, since it had such a high p-value that we cannot reject the null hypothesis. Trend lines for the *St. Louis Post-Dispatch* (n=70, p=0.057), and *Tampa Bay Times* (n=78, p=0.0198) had higher chances of being statistical anomalies than the *New York Times*. The *Tampa Bay Times* did not publish any articles mentioning psilocybin between 2016-2019, which means that its zero

sentiment scores for those years were closer to being null values than zero values. In addition, the *San Diego Union-Tribune* had its lowest sentiment score (-5.5) in 2020 [Figure 1].

When viewing the annual sentiment scores of all the newspapers [Figure 1], the dark blue positive scores from 2016-2020 for the *New York Times* are so strong that they drown out almost all the other scores. The positive scores reached by the *New York Times* during the 2016-2020 period, much as 743% higher than the highest recorded by any of the other three newspapers in any year. It might be asked whether this was because the *New York Times* simply published more articles on all topics compared to the other newspapers (i.e., it was a larger newspaper in general). Unfortunately, it is difficult to find information about how many articles were published each year in each newspaper, especially when factoring reprints, briefs, and online content. However, a high number of psilocybin articles did not always mean that a sentiment score would be extreme. For example, the highest yearly number of articles for any of the four newspapers was 38 articles by the *New York Times* in 2019 [Figure 4], but the *New York Times*'s sentiment score that year was only 8 [Figure 1]. This was because many of those 38 articles had negative sentiments about psilocybin, which mitigated the many articles with positive sentiments. This might indicate that psilocybin coverage by the *New York Times* in 2017, 2018, and 2020 was genuinely more positive in comparison to other years, rather than its high positive scores simply being a reflection of high numbers of articles.

It should also be noted that when the outlier years of 1991, 2017, 2018, and 2020 are removed, the *New York Times* appears much less different from the other newspapers in terms of sentiment intensity:

Figure 4



In addition, until 2001, the number of psilocybin articles in the *New York Times* was not particularly different from the other three newspapers [Figure 2]. (The *New York Times* published more psilocybin articles than the other newspapers from 1998-2000, but those numbers were not higher than some previous years for the other newspapers.) In fact, other newspapers often had more psilocybin coverage until 2001.

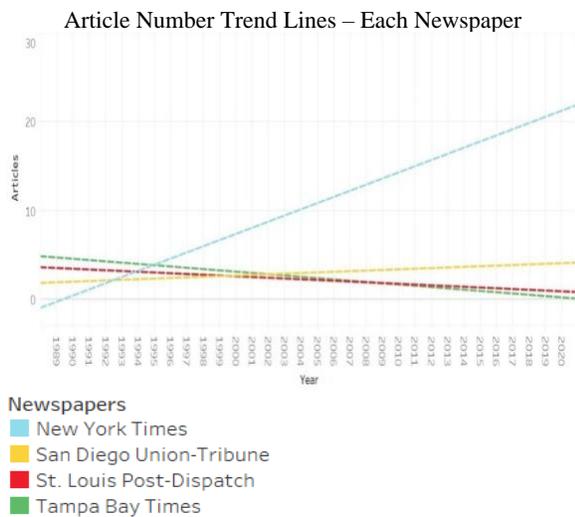
Comparisons among the different thematic categories also revealed some interesting patterns. For example, legality was rarely positive. In all four newspapers, over the entire 32-year time span, whenever the legality of psilocybin was mentioned, the connotation was usually negative. This should probably not be surprising, though, since the illegality of psilocybin meant that articles sometimes mentioned people being arrested and/or imprisoned for psilocybin-related crimes. Therefore, a good question might be whether psilocybin legalization would make newspaper coverage more positive overall simply by reducing articles about psilocybin-related crimes. Psilocybin possession was decriminalized in Denver and Oakland in 2019, [20,21] and after a few years, it might be fruitful to examine whether newspaper coverage has become more positive in those cities. Some studies have shown that mainstream news often has a tendency toward negativity [22,23]. The recent surge in positive reporting by the *New York Times* [Figure 1] could possibly indicate an even more significant shift toward positivity

if it swam against a tide of general journalistic negativity.

### Newspaper Coverage of Psilocybin – Sentiment and Frequency (1989-2020)

The second hypothesis was that the annual number of articles mentioning psilocybin (N=578) in the studied newspapers had increased between the beginning and end of the 32-year period. This hypothesis was mostly false. Only the *New York Times* (n=335,  $p < 0.0001$ ) had a significant increase in psilocybin coverage. The *Tampa Bay Times* (n=78,  $p = 0.0008$ ) and *St. Louis Post-Dispatch* (n=70,  $p = 0.013$ ) had decreases. The *San Diego Union-Trib* (n=95,  $p = 0.106$ ) had an extremely slight upward trend in coverage, but its trend line had such a high p-value compared to the other newspapers that this cannot be taken at face value.

Figure 5



The increase in coverage by the *New York Times* between 2015-2020 [Figure 2] was particularly striking (although the number of articles went down in 2016, that year was still as high as the second-highest number of yearly articles recorded for any of the other three newspapers). After setting a new high

in psilocybin coverage with 19 articles in 2015, the *New York Times* had already doubled that number by 2019 with 38 articles.

It was difficult to determine the reasons for the increase in the *New York Times* simply by examining its articles. Although a regional news focus sometimes affected psilocybin coverage, such as with the *Tampa Bay Times* from 1989-1994 (when there was a jump in stories about psilocybin mushroom pickers in local cow pastures), the articles in the *New York Times* from 2015-2020 rarely had a regional quality. The *New York Times*'s articles about psilocybin's therapeutic potential often featured studies conducted outside the New York area, meaning that any other newspaper could have covered them just as easily. It might be suspected that the *New York Times* simply published more articles in general, which thereby created a larger number of articles mentioning psilocybin. Unfortunately, it was difficult to determine the number of articles that a newspaper published in general each year, especially when factoring reprints, briefs, and online content. However, even if true, this did not seem enough to explain the entire increase in psilocybin coverage since the number of psilocybin articles in the *New York Times* did not differ greatly from the other newspapers for several years. Compared to the increase in the *New York Times* in recent years, there was not much variation among any of the newspapers between 1989 and 2000. (Even though the *New York Times* had more psilocybin articles than the other three newspapers in 1998-2000, its totals for those years were still less than the *St. Louis Post-Dispatch* and *Tampa Bay Times* had in some previous years.)

The change in coverage by the *Tampa Bay Times* was interesting because of how much it decreased. For example, from 1989-1994, the *Tampa Bay Times*'s 31 psilocybin articles were more than any of the other

newspapers. Yet for 2015-2019 (when mentions in the *New York Times* had greatly increased), the *Tampa Bay Times* had zero articles mentioning psilocybin. This was not merely due to a lack of interest by the *Tampa Bay Times* for articles about psychoactive substances, since Nexis Uni returned 28 articles in that newspaper about LSD and 648 articles about cocaine during that period.

## CONCLUSION

The above results might be a warning to psilocybin advocates that their optimism about public perception could be premature. Although the *New York Times* showed a significant trend upward in both positive sentiment [Figure 3] and mentions [Figure 2] of psilocybin, this did not occur in the three newspapers. In fact, the *San Diego Union-Tribune* had its lowest sentiment score (-5.5) in 2020. In addition, even the *New York Times* showed a sharp drop in positive sentiment between 2018 and 2019 [Figure 1]. If psilocybin advocates are mostly discussing psilocybin with each other, rather than discussing it with people outside of their communities, they might have developed a mistaken impression of how many people have accepted its use. However, more research is recommended, especially considering the methodological challenges of the present study.

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#### Newspaper Coverage of Psilocybin – Sentiment and Frequency (1989-2020)

## Psychedelics and Response Duration

Gregory Jones, M.D.; Hunter Hinman M.D.; Elizabeth Mays M.D.; Daniel Liaou M.D.

### INTRODUCTION

Over the last century, diseases of despair (DoD) have become alarmingly prevalent. Suicide, addiction, and related illnesses represent some of the most significant contributors to increasing morbidity and mortality worldwide <sup>[1]</sup>. Indeed, depressive symptoms form a core amalgamation across these tragedies. Unfortunately, conventional (mostly monoaminergic) treatments have historically failed to provide relief for many, with delayed responses, high rates of relapse, and undesirable side effects <sup>[2]</sup>.

The discovery of ketamine's rapid antidepressant effects (even in treatment-resistant patients) represented a paradigm shift in both our therapeutic and mechanistic understanding of DoDs <sup>[3,4]</sup>. Likewise, the recent revival of psychedelic-assisted psychotherapy with psilocybin, lysergic acid diethylamide (LSD), ayahuasca, N,N-Dimethyltryptamine (DMT), and others holds significant potential. Though far more validation is needed, the rapid onset of action and large effect sizes seen with these compounds represents arguably the most promising advance in mental healthcare in over a half-century.

Common to all the rapid-acting antidepressants appears to be variable effects on glutamatergic modulation, which in turn enhances "neuroplasticity"-broadly interpreted to be a prominent underpinning of most depressive phenotypes and treatments <sup>[5]</sup>.

Unlike ketamine's short duration of response, serotonergic hallucinogens (SHs) appear to produce positive effects lasting months (and possibly years) after only a few doses <sup>[6-10]</sup>. Adjunctive psychotherapy with SHs would seem a likely answer—albeit

incomplete. Though data regarding ketamine-assisted psychotherapy (KAP) is sparse, unlike with SHs, it appears that repeated ketamine infusions do not enhance the antidepressant or anxiolytic effects of KAP at long-term follow-up <sup>[11]</sup>.

As follows, understanding the neurobiological underpinnings which differentiate the response duration of these psychedelic therapies holds significant potential for patients and practitioners alike. Herein, we will outline some of the most prominent mechanisms of action for these compounds that may explain this difference, highlighting areas for future research, with a specific focus on the roles of inflammation, epigenetics, opioid receptor mechanics, and neuroplasticity.

### GLUTAMATE, NEUROPLASTICITY, AND CONNECTIVITY

Ketamine and SHs espouse several similarities regarding their immediate mechanisms of action. Ketamine, psilocybin, and LSD appear to similarly enhance spontaneous signal complexity ("entropy") directly following administration <sup>[12]</sup>. Both classical and dissociative psychedelics appear to temporarily reduce functional connectivity within the default mode network (DMN) and increase interconnectivity with other resting-state networks related to depression <sup>[13-16]</sup>. Measures of signal transmission and connectivity are thought to reflect underlying neurochemical homeostasis, particularly with regards to glutamate—the brain's predominant excitatory neurotransmitter <sup>[17]</sup>.

In that regard, both ketamine and SHs trigger a rapid increase in excitatory

signaling (“glutamate surge”) in layer V pyramidal neurons throughout the different cortico-limbic regions [18,19]. This is widely believed to upregulate the protein synthesis necessary for neuro-synaptogenesis via increased expression of brain-derived neurotrophic factor (BDNF) and its downstream effector molecules (TrkB and mechanistic target of rapamycin complex 1 (mTORC1)—a specialized protein complex that powerfully regulates cellular proliferation, inflammation, and energy metabolism) [2,20].

SHs accomplish this process via direct pyramidal serotonin (5HT)-2A receptor stimulation, whereas ketamine is suggested to have more pleiotropic and indirect effects [2,21]. Briefly, ketamine inhibits NMDA receptors on neighboring inhibitory interneurons, increasing glutamate release within relevant synapses. Following disinhibition, glutamate is shunted towards neighboring AMPA receptors—the expression of which ketamine also upregulates. This is classically known as the “NMDA to AMPA throughput” model, which is thought to facilitate calcium influx into the dendritic compartment, modulating excitability and plasticity [22].

Importantly, numerous other mechanisms have been proposed for the immediate antidepressant effects of ketamine (and its metabolites), many of which are independent of NMDA receptor inhibition [2]. Notwithstanding, compelling preclinical and human evidence suggests that AMPA-receptor-dependent increases in BDNF-TrkB-mTORC1 signaling are required for the behavioral, antidepressant, and neuroplastic effects seen with ketamine and most SHs [2,19,23–25]. Notably, differential dendritic excitation patterns based on the location of 5-HT vs. NMDA/AMPA receptors along synapses have been suggested to contribute to differences in neuroplasticity realized by

these compounds (see the following review for a more detailed explanation) [18].

*In vitro*, SHs (particularly LSD) appear to more potently upregulate BDNF-TrkB-mTORC1 signaling than ketamine [26]. However, blockade of either TrkB or mTORC1 appears to completely prevent the neuroplastic effects of both ketamine and SHs [26], suggesting a limiting reagent in this pathway that is independent of initial stimulus potency. Moreover, enhanced neuroplastic signaling realized through repeated acute-phase administration of ketamine still confers relapse in the vast majority of patients within the first month following their final infusion [27]. As follows, evidence for the correlation between increased BDNF levels and treatment response appears somewhat inconsistent across studies with ketamine and SHs [19]. Thus, we suggest that alternative mechanisms may also contribute significantly to discrepancies in response duration.

### **MTORC1 SIGNALING**

Rapamycin is an mTORC1 inhibitor that confers potent immunosuppressive and anti-aging properties [28]. In line with aforementioned *in vitro* studies, when administered directly into the prefrontal cortex (PFC) of rodents, rapamycin appears to block the immediate neuroplastic and antidepressant effects of ketamine completely [29,30]. Indeed, it is known that low-physiologic levels of neuroinflammation are necessary to promote synaptic plasticity and neurotransmission [31]. Conversely, despite being quite brain-penetrant, systemically administered rapamycin has failed to block antidepressant effects of ketamine in rodents [32]. Importantly, in a recent first-in-class randomized trial, Abdallah et al. found that pre-administration with a single dose of rapamycin might

significantly prolong ketamine's antidepressant effects in humans [33]. Though these findings require further validation, they warrant attention for our purposes.

Independently, rapamycin itself has equivocal antidepressant effects [34]. However, systemic alterations in metabolic and inflammatory activity have been observed in humans and animals, lasting months after a single dose [35,36]. Mechanistically, mTORC1 acts as a rheostat, creating a “set-point” for inflammatory and growth activity based on the availability of nutrients and environmental conditions [28]. Inhibition of mTORC1 “lowers” that set point, promoting sustained reductions in both central and peripheral inflammation, improved blood-brain barrier integrity, and increased cellular autophagy [37]—a mechanism that has been proposed for many conventional antidepressants [38].

The acute antidepressant effects of ketamine have been observed through both mTORC1-dependent and (to some degree) independent mechanisms [2]. As discussed in the following section, we suggest that ketamine's acute therapeutic effects may be rapidly degraded when patients regress into a baseline state of chronic inflammation underlying their depression. Systemic administration of rapamycin may temporarily lower their inflammatory “set-point” without completely inhibiting initial neuroplastic signals. Indeed, in Abdallah et al., response rates were identical between groups at 24 hours but were more than three-fold higher in the rapamycin group at two weeks [33]. Taken together, this may explain why rapamycin-induced immunosuppression could enhance (or at least fail to inhibit) ketamine's antidepressant effects in humans.

## **INFLAMMATION**

Peripheral and central inflammation appear to be reliable, highly correlative findings in depression, associated with aberrant glutamate signaling and compromised neuroplasticity [39]. Meta-analyses suggest that over half of depressed patients show elevations in inflammatory markers, which are reflected in the serum [40]. Moreover, nuanced, proinflammatory behaviors also occur at the single-cell level, which are just starting to be investigated in neuropsychiatric conditions [41]. It is thus likely that most (if not all) patients with depression have some degree of inflammatory aberrancy.

With few exceptions (ECT and targeted anti-inflammatory drugs), elevated baseline inflammation is associated with treatment resistance to most antidepressants [42,43]. Conversely, ketamine's inflammatory profile in depression remains elusive. Conflicting results exist when attempting to correlate treatment response (or resistance) with baseline inflammation and post-treatment suppression across trials [42,44–48]. As previously suggested, the effects of chronic inflammation may act to subvert the rapid antidepressant effects of ketamine. We further suggest that the sustained effects of SHs may be partially related to their superior efficacy in suppressing chronic inflammation—a property that ketamine lacks.

Ketamine's complex immunomodulatory characteristics are best described through research into its analgesic efficacy—where doses are comparable to those used in depression. Much like its antidepressant effects, analgesic relief appears to be short-lived, and its utility in chronic pain management remains controversial [49]. Interestingly, it appears best suited for pain types that espouse a tonic-inflammatory component (i.e., neuropathic, cancer, etc.) [49].

Unlike many neuropsychiatric conditions (where broad suppression of

chronic neuroinflammation appears to be therapeutic), full elaboration of systemic, pro-inflammatory signaling is often necessary to promote successful tissue repair in pain treatment [50]. Pain experts describe ketamine as a “homeostatic immune regulator” as opposed to a purely anti-inflammatory agent [50]. This moniker is derived from the fact that it appears to prevent exacerbation of local inflammation without interfering with broader immune signaling cascades. This unique property has been suggested to contribute to ketamine’s high clinical utility in perioperative and critical care settings [49,50].

The balance between pro- and anti-inflammatory effects in this setting is believed to be largely mediated by T-helper cell populations [50]. Indeed, while ketamine and morphine both reduce T-helper cell activity in response to inflammatory stimuli, morphine favors anti-inflammatory Th2 differentiation, while ketamine promotes a relative increase in pro-inflammatory Th1 populations [51]. These findings agree with broader themes of *in vitro* ketamine research, where it appears to have little impact on cytokine expression unless administered in the presence of an inflammatory stimulus. As well, in such cases, it appears to exclusively modulate pro-inflammatory cytokine activity [50].

Conversely, SHs consistently appear to exert potent anti-inflammatory effects across many different disease models and cell lines [52–55]. 2,5-dimethoxy-4-iodoamphetamine (DOI), a synthetic derivative of mescaline, is perhaps the most-studied SH with regards to inflammation. It has been shown to profoundly suppress TNF- $\alpha$  mediated inflammation *ex vivo*, even at picomolar concentrations. With the exception of a few naturally occurring substances (i.e., botulinum toxin), no commercially available compound has demonstrated comparable immunosuppressive potency [55]. Likewise,

due to its potent immunosuppressive capacity, DMT was recently granted orphan drug designation by the FDA for the treatment of ischemia-reperfusion injury in solid organ transplant [56] and is garnering significant attention from pharma for other neuroinflammatory conditions [57,58].

One recent clinical trial has demonstrated CRP reductions which correlate with an initial response to ayahuasca [59]. To our knowledge, no clinical trial to date has published negative results regarding cytokine changes with SHs. However, biomarker reporting in psychedelic studies is infrequent, and none have provided longitudinal tracking of inflammatory markers after SH administration. We suggest that longitudinal inflammatory monitoring and single-cell secretome analysis should be a priority in future trials with these compounds.

## **OPIOID RECEPTOR MECHANICS**

Opioid receptor signaling has been deeply implicated in depression [60] and appears to be important for psychedelics in general. Mu-opioid activation appears to attenuate 5HT-2A downstream activity in layer V pyramidal neurons [61], a key site of action for all SHs. Conversely, LSD specifically appears to attenuate kappa-opioid receptor-mediated depressive effects in rats [62].

In obsessive-compulsive disorder, single-dose morphine and ketamine appear to have almost identical, short-lived response timelines [63]. Furthermore, nonspecific opioid receptor blockade with naloxone appears to attenuate ketamine’s antidepressant (but not dissociative) effects [64,65], though these results should be interpreted carefully [66]. Indeed, dissociative effects do not appear to correlate with antidepressant response in most ketamine trials, whereas mystical experiences seem to be some of the strongest predictors of short-

term therapeutic outcomes with SHs [67]. Whether or not these observations are related to opioid signaling is a possible area of future consideration.

One relevant compound in that regard is salvinorin A. It has been reported to produce mystical/hallucinogenic effects similar to LSD, which appear to be mediated exclusively through kappa opioid receptors, with no appreciable activity at mu, 5HT-2A, or other canonical psychedelic receptors [68]. Speculation notwithstanding, the contrasting opioid signaling activity between SHs and ketamine appears to be a plausible candidate to investigate differences in both treatment duration and addictive profiles [69].

The atypical psychedelic Ibogaine also appears to be relevant to this discussion. It espouses highly pleiotropic effects but appears to act in part via 5HT-2A and 32 receptors, possibly contributing to its applicability in addiction treatment [69].

Notably, Ibogaine also interacts with the sigma receptor family, the first of which was conceptualized as a *sigma-opioid receptor* [70]. Initially, this family was proposed to engender the psychotomimetic properties of opioids [70]. However, further investigation led not only to their independent reclassification but also uncovered profound modulation of metabolic, inflammatory, and epigenetic processes which will be discussed below.

## **SIGMA AND EPIGENETICS**

*Sigma receptors* (sigma-1 and sigma-2) are considered highly unique. Though they possess a binding pocket and some structure-activity relationships, there are no specific endogenous ligands for either receptor and no formal transduction system [71]. Purification studies have revealed that their amino acid sequence is structurally unrelated to any known mammalian proteins, instead primarily having a shared homology with

fungal proteins involved in ergosterol synthesis. Interestingly, ergosterol was first discovered as a membrane component of *Claviceps Purpra* (a fungus that produces lysergic acid--the precursor of LSD) [72]. They have recently become a focus across a wide range of pathologies from cardiometabolic to oncologic and particularly neuropsychiatric [73]. They have been implicated in pathophysiologic processes related to depression, addiction, anxiety, stress responses, learning, and memory [74]. Indeed, many neuroleptics, antipsychotics, antidepressants, and neurosteroids have sigma-receptor activity [73].

As a molecular chaperone, the sigma-1 receptor plays many roles. It modulates cell survival and oxidative metabolism (via calcium signaling between mitochondria and endoplasmic reticula). It mediates inflammatory signaling in microglia and astrocytes across various neuropsychiatric disease models [75]. It also participates in the elaboration of proBDNF into its mature end-product [76] and potentiates nerve growth factor (NGF) secretion [77].

More importantly, sigma-1 forms heterodimer complexes with both 5HT-2A and D2 receptors to facilitate neurotransmission and dopamine/norepinephrine release, also potentiating NMDA antagonism [72]. Recently, sigma-1 has also been discovered to translocate to the nuclear envelope, acting as an epigenetic regulator. It has a dose-dependent interaction with histone deacetylase (HDAC) complexes, which regulate chromatin compaction and gene expression—a mechanism that appears to be particularly relevant to sigma-1's role in addiction [69,72]. Notably, like HDAC, mTORC1 is also believed to exert epigenetic regulation by modifying chromatin structure (via H3K36) and gene expression [78].

Long-lasting effects realized with only a few doses of any compound evokes the

notion of epigenetic modulation more than any other mechanism discussed in this review. Only a handful of psychedelics have been investigated for their sigma-receptor activity. DMT is a highly potent ligand for the sigma-1 receptor <sup>[79]</sup>, having an order of magnitude greater affinity than ketamine <sup>[77]</sup>. Ibogaine's affinity for sigma-1 is roughly equivalent to ketamine's. However, it appears to have a much higher affinity for sigma-2 than 5HT-2A or any other endogenous receptor studied <sup>[80]</sup>. The specific functions of sigma-2 are enigmatic; however, they appear to be tangentially related to some of those discussed for sigma-1. The recent cloning of the receptor should engender significant discoveries in the coming decade <sup>[71]</sup>. Overall, the differential sigma receptor activity of ketamine and other hallucinogens may present another explanation for the duration of response.

## **CONCLUSION**

Psychedelic drugs appear to hold significant promise in ameliorating a myriad of neuropsychiatric conditions. Achieving rapid and sustained responses without daily dosing of medication should be the benchmark for mental healthcare going forward. As Jung envisioned, for durable responses, pharmacology should be used as an adjunct to psychotherapy rather than a unitary measure. In this regard, psychedelics can already be viewed as a success. However, uncovering the mechanisms responsible for prolonging the response to rapid-acting antidepressants may be as important as the initial discoveries themselves. Though the answer is almost certainly multifactorial, inflammation, epigenetic regulation, opiate signaling, and neuroplasticity all appear to be promising avenues for investigation.

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