Substance and Protocol: Federalist Regulation of Psychedelic-Assisted Therapy

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ABSTRACT

The psychedelic renaissance is here—after decades in darkness, two psychedelic-assisted therapies are approaching FDA approval. The therapies combine a high dose of psychedelics with psychotherapy to treat intractable mental illnesses. This modality presents a novel regulatory landscape. Traditionally, FDA regulates drugs while state governments oversee the practice of medicine. Psychedelic-assisted therapy straddles that line; one component (psychedelics) is clearly a drug, while the other (psychotherapy) falls under the practice of medicine. With approval rapidly approaching, it is imperative to delineate which level of government has jurisdiction over each component to promote availability, safety, and efficacy of these treatments.

I. INTRODUCTION

Three thousand five hundred years ago, indigenous people of Mesoamerica consumed hallucinogenic mushrooms in religious ceremonies.[1] Today, a patient with treatment-resistant depression ingests the same mushrooms, reclines on a comfortable couch, and receives psychotherapy. Humans have had a complicated relationship with psychedelic compounds for millennia—as religious sacraments, fuel for the counterculture, and now as a therapy for critical and difficult to treat mental illnesses.

Although indigenous populations have utilized a variety of psychedelic compounds for thousands of years, the western world did not "discover" these compounds until fairly recently. Albert Hoffman first synthesized Lysergic acid diethylamide (LSD) from the ergot fungus in 1938.[2] R. Gordon Wasson, a banker from New York and the first Westerner to experience psilocybin—the psychoactive chemical in "magic mushrooms"—published an account of his experience in 1957.[3] The one-of-a-kind qualities of psychedelic experiences immediately seized the attention of scientists, who saw the chemicals as a viewport into the human mind. To promote research into

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[1] F.J. Carod-Artal, *Hallucinogenic Drugs in Pre-Columbian Mesoamerican Cultures*, 30 NEUROLOGÍA 42, 45 (2015).

[2] ALBERT HOFFMAN, LSD: MY PROBLEM CHILD 44 (Randolph Hencken & Brandy Doyle eds., Jonathan Ott trans., 2009).

[3] MICHAEL POLLAN, HOW TO CHANGE YOUR MIND 103 (Penguin Press 2018).

possible uses for LSD, Sandoz—the pharmaceutical company that owned the LSD patent—gave the drug away for free to prospective researchers.[4]

By the mid-1950s, clinicians began to understand the therapeutic value of these compounds. They were using LSD therapy to treat anxiety, depression, obsessive-compulsive disorder, and addiction.[5] The research was nascent but promising, particularly surrounding addiction. An early study found that alcoholics that received a single dose of LSD "significantly reduced alcohol misuse" compared to a control group.[6] Psychedelics, however, did not remain a solely academic pursuit for long. Psychedelic substances soon left the lab and became the vice of choice for the counterculture.

The hippies of the 1960s saw psychedelics, particularly LSD, as a rite of passage. Encouraged by Timothy Leary—ex-Harvard professor turned psychedelic messiah—to "turn on, tune in, drop out," young Americans incorporated psychedelics into their rebellion against authority.[7] They burned their draft cards and protested the war in Vietnam. LSD may not have been the spark that ignited the counterculture, but it certainly added fuel to the fire.

The Nixon Administration, desperate to quell the unrest, searched for a scapegoat. They could not stop anti-war protestors from exercising their freedom of speech, but they *could* criminalize the movement's drugs of choice.[8] At Nixon's urging, Congress passed the Controlled Substances Act in 1970, which placed both LSD and psilocybin into Schedule I—the most restrictive category, reserved for drugs with a "high potential for abuse" and "no currently accepted medical use."[9]

Under mounting political and social pressure, psychedelic-based research initiatives shut their doors one-by-one. By the mid-1970s, the first wave of legitimate psychedelic research had come to a close. Some therapists continued providing "underground" psychedelic therapy, but mainstream science had all but abandoned psychedelics.[10] For several decades, the most common way to have a psychedelic experience—therapeutic or otherwise—was in the shadow of federal criminal penalties.

Today, the United States is facing a severe mental health crisis. Over 8% of adults are clinically depressed.[11] Five percent of adults have post-traumatic stress disorder

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[4] *Id.* at 143.

[5] *Id.* at 156.

[6] Albert Garcia-Romeu, Brennan Kersgaard & Peter H. Addy, *Clinical Applications of Hallucinogens: A Review*, 24 EXPERIMENTAL & CLINICAL PHARMACOLOGY 229, 232 (2016).

[7] *Summer of Love*, PBS (June 12, 2018), https://www.pbs.org/wgbh/americanexperience/films/summer-of-love/#transcript (last visited Apr. 27, 2023).

[8] Dan Baum, *Legalize It All: How to Win the War on Drugs*, HARPER'S MAG. 22, 22 (Apr. 2016) (quoting John Erlichman, the Nixon Administration "knew [they] couldn't make it illegal to be . . . against the war," so they criminalized drugs instead).

[9] 21 U.S.C. § 812(b)(1).

[10] *See* POLLAN, *supra* note 3, at 48 (describing the "knowledge about psychedelics that had been lost when formal research was halted and informal research went underground").

[11] *Major Depression*, NAT'L INST. OF MENTAL HEALTH, https://www.nimh.nih.gov/health/statistics/major-depression (Jan. 2022).

(PTSD).[12] On average, an American commits suicide every eleven minutes.[13] The gold standard of treatment, antidepressants and talk therapy, are clearly insufficient. Desperate for a solution, clinicians and patients are revisiting the science of the mid-20th century. Psychedelics have found their way aboveground once again.

As of 2023, the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to two different psychedelic-assisted therapies (PATs). Breakthrough Therapy designation is an expedited development and review process granted to drugs that "demonstrate substantial improvement over existing therapies" to treat a "serious or life-threatening disease."[14] One therapy, 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy to treat PTSD, received Breakthrough Therapy designation in 2017.[15] The other, psilocybin-assisted therapy for treatment-resistant depression (TRD), received breakthrough status in 2018.[16]

The two treatments present an innovative treatment modality—combining a psychedelic compound with psychotherapy. Most medical interventions—especially those for mental illness—are either a drug (e.g., Xanax), standalone psychotherapy or counseling, or a *suggested* combination of the two.[17] PAT *requires* the combination—in fact, many people consider the therapy as the real treatment. The psychedelic is seen as merely a key to enhance the therapy's effects.[18]

This mandatory combination creates regulatory tension between the federal and state governments. Traditionally, the federal government regulates drugs through FDA. The states, meanwhile, regulate the practice of medicine, which includes psychotherapy. PAT, therefore, combines two distinct components—one of which falls under federal jurisdiction while the other belongs to the states. This jurisdictional tension can have several possible implications on the safety and efficacy of, and access to, PAT. An overly strict framework can inhibit access to potentially lifesaving treatment. Underregulation can decrease both patient safety and treatment efficacy.

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[12] *PTSD: National Center for PTSD*, U.S. DEP'T OF VETERANS AFFS., https://www.ptsd.va.gov/understand/common/common_adults.asp (last visited Apr. 26, 2023).

[13] *Facts About Suicide*, CTRS. FOR DISEASE CONTROL & PREVENTION (Apr. 6, 2023), https://www.cdc.gov/suicide/facts/index.html (last visited Apr. 27, 2023).

[14] 21 U.S.C. § 356(a)(1).

[15] *FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Therapy for PTSD, Agrees on Special Protocol Assessment for Phase 3 Trials*, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUDS. (Aug. 26, 2017), https://maps.org/news/media/press-release-fda-grants-breakthrough-therapy-designation-for-mdma-assisted-psychotherapy-for-ptsd-agrees-on-special-protocol-assessment-for-phase-3-trials/ (last visited Apr. 27, 2023).

[16] *COMPASS Pathways Receives FDA Breakthrough Therapy Designation for Psilocybin Therapy for Treatment-resistant Depression*, PR NEWSWIRE (Oct. 23, 2018), https://www.prnewswire.com/news-releases/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment-resistant-depression-834088100.html (last visited Apr. 27, 2023).

[17] Many doctors, for example, recommend combining antidepressants with psychotherapy. Therapy is not, however, required for the antidepressants to be safe and effective. *See* Pim Cuijpers, Marit Sijbranij, Sander L. Koole, Gerhard Andersson, Aartjan T.F. Beekman & Charles F. Reynolds III, *Adding Psychotherapy to Antidepressant Medication in Depression and Anxiety Disorders: A Meta-Analysis*, 13 WORLD PSYCHIATRY 56, 56 (2014) (finding, through a meta-analysis, that combined therapy was considerably more beneficial than taking antidepressants alone, yet "only a minority [of patients] receives combined therapy").

[18] POLLAN, *supra* note 3, at 149 ("From the first . . . we considered not the chemical, but the experience as a key factor in therapy.").

Unclear regulations may dissuade healthcare professionals or investors from entering the space, thus decreasing access. It is critical, therefore, to develop a clear regulatory framework that promotes safety, efficacy, and access—people's lives depend on it.

This paper is the first of its kind to highlight the regulatory quagmire of this novel treatment modality and discusses how the federal and state governments may address the tension between their respective jurisdictions.

This paper proceeds in five parts. Part II analyzes what makes psychedelics unique and how that necessitates the use of therapy in conjunction with the substance. Part III breaks down the distinction between regulating drugs and regulating the practice of medicine. Part IV examines current mechanisms in FDA's regulatory toolkit that may grant the federal government enhanced jurisdiction over PAT. Finally, Part V proposes a federalist model for regulating PAT, drawing on currently used regulatory powers of both the state and federal governments.

II. PSYCHEDELICS AND PSYCHEDELIC-ASSISTED THERAPY

Psychedelic therapy,[19] particularly LSD therapy, rose to prominence as a treatment modality for psychiatric illnesses—and in "healthy normals"—in the 1950s.[20] Addiction recovery was one of the earliest suggested therapeutic uses of LSD therapy.[21] Bill Wilson, founder of Alcoholics Anonymous, supported psychedelic therapy as a treatment for alcoholism.[22] Early trials demonstrated great promise to treat a variety of mental illnesses, and the *Journal of Psychedelic Drugs* was founded in 1967 to catalog research in the field.[23] Psychedelics showed potential as a medical intervention, but they soon jumped over the laboratory wall and leaked into popular culture.

While most supervised psychedelic experiences are safe, unsupervised "recreational" use—particularly with unknown doses—can be quite dangerous.[24] Safety concerns, coupled with Nixon's (sometimes fraudulent)[25] war on drugs created a political atmosphere ripe for criminalization. The Controlled Substances Act effectively banned psychedelic research and drove psychedelic therapy underground.[26] People did not stop taking psychedelics—or administering them in a therapeutic manner—but they could not be as open about it. The legal status and social taboo

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[19] I use the term "psychedelic therapy" to describe the early uses of psychedelics in therapeutic settings. I differentiate "psychedelic-assisted therapy" as the (potentially) FDA-approved treatment modality combining a psychedelic and psychotherapy.

[20] *See* POLLAN, *supra* note 3, at 145–59.

[21] *Psychedelic Research in 1950s Saskatchewan*, CAN. ENCYCLOPEDIA (July 16, 2019), https://www.thecanadianencyclopedia.ca/en/article/psychedelic-research-in-1950s-saskatchewan (last visited Apr. 27, 2023).

[22] *See* POLLAN, *supra* note 3, at 153.

[23] Richard E. Doblin, Merete Christiansen, Lisa Jerome & Brad Burge, *The Past and Future of Psychedelic Science: An Introduction to This Issue*, 51 J. PSYCHOACTIVE DRUGS 93, 93 (2019). The journal has since been renamed the *Journal of Psychoactive Drugs*.

[24] *See* Sidney Cohen & Keith S. Ditman, *Complications Associated with Lysergic Acid Diethylamide (LSD-25)*, 181 JAMA 161, 162 (1962) (analyzing the "serious complications" associated with use of black-market LSD); *see also* POLLAN, *supra* note 3, at 210–11.

[25] *See* Baum, *supra* note 8, at 22 ("Did we know we were lying about the drugs? Of course we did.").

[26] 21 U.S.C. § 801.

surrounding psychedelics led to a lack of scientific rigor in psychedelic research—if one could call it "research" at all. There were no controlled studies, and one could not publish findings in *JAMA* or the *Psychological Review*, no matter how interesting. The upshot of widespread underground use is that we have plenty of conventional wisdom surrounding psychedelic compounds and psychedelic therapy, but very little scientific consensus.

A. What Are Psychedelics?

"Psychedelics" is a category that defies definition. There is no universal classification system for drug compounds. One system looks at a compound's mechanism of action and classifies drugs based on the physiological system on which they act.[27] The so-called "classic psychedelics"—LSD, psilocybin, and N,N-dimethyltryptamine (DMT)—act on the serotonergic system.[28] Mescaline and MDMA are amphetamines that act on the norepinephrine and dopamine systems.[29] Ketamine acts on the glutamate pathway.[30] All of these substances are commonly referred to as psychedelics, despite their differences. Some scholars have gone so far as to argue that cannabis should fall under the psychedelic umbrella.[31] This paper is chiefly concerned with the ongoing MDMA- and psilocybin-assisted therapy trials. It also briefly considers ketamine. I consider all three to be psychedelics.

There is also debate over the use of the word "psychedelic" to describe these compounds. Psychedelics have gone by many names before falling under their present moniker. Werner A. Stoll, one of the first LSD researchers, described the chemical as a "phantasticum."[32] When they thought psychedelic experiences mimicked psychosis, early researchers described LSD as "psychotomimetic" and "psycholytic."[33] Humphrey Osmond, a psychiatrist and early pioneer of psychedelic therapy, coined the term "psychedelic" as a combination of two Greek words meaning "mind manifesting."[34]

Some scholars have suggested different titles—such as entheogens—because many Americans attach so much negative baggage to "psychedelics."[35] Osmond himself

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[27] *See generally* Peter Imming, Tomasz Buss, Lea Ann Dailey, Achim Meyer, Helene Cæcilie Mørck, Mahmoud M. Ramadan & Tobias Rogosch, *A Classification of Drug Substances According to Their Mechanism of Action*, 59 PHARMAZIE 579 (2004).

[28] Muhammad Ishrat Hussain, Nicole Ledwos, Elise Fellows, Jenna Baer, Joshua D. Rosenblat, Daniel M. Blumberger, Benoit H. Mulsant & David J. Castle, *Serotonergic Psychedelics for Depression: What Do We Know About Neurobiological Mechanisms of Action?*, FRONTIERS PSYCHIATRY, Feb. 10, 2023, at 01, 02.

[29] ENNO FREYE & JOSEPH V. LEVY, PHARMACOLOGY AND ABUSE OF COCAINE, AMPHETAMINES, ECSTASY AND RELATED DESIGNER DRUGS 147 (2009).

[30] Panos Zanos & Todd D. Gould, *Mechanisms of Ketamine Action as an Antidepressant*, 23 MOLECULAR PSYCHIATRY 801, 803 (2018).

[31] Erin Brodwin, *Some Psychiatrists Think Cannabis Can Be Considered a Psychedelic Drug Like Shrooms—Here's Why*, BUS. INSIDER (July 5, 2017, 10:17 AM), http://www.businessinsider.com/cannabis-marijuana-psychedelic-drug-why-2017-7 (last visited Apr. 17, 2023) ("According to Julie Holland, a psychiatrist with a private practice in New York, some of cannabis' effects are psychedelic in nature.").

[32] HOFFMAN, *supra* note 2, at 63.

[33] *See* POLLAN, *supra* note 3, at 144–63.

[34] *Id.* at 163.

[35] *See generally* Carl Ruck, Jeremy Bigwood, Danny Staples & Jonathan Ott, *Entheogens*, 11 J. PSYCHEDELIC DRUGS 145 (1979).

tried to introduce a new term—"psychodelytic"—due to the negative stigma associated with "psychedelic."[36] Most modern scholars begrudgingly adopt the term "psychedelic," in part due to its perceived accuracy.[37] This paper does the same.

B. What Makes Psychedelics Unique?

Psychedelics require special oversight and therapy because they elicit a unique experience in patients. Psychedelics produce more than a simple mind-altering state; alcohol, cannabis, and other drugs alter your mind in the sense that that they inhibit or catalyze certain neural pathways. The difference between psychedelics and more "familiar drugs" is not one of degree, but one of kind. In his bestselling book *How to Change Your Mind*, Michael Pollan refers to William James' "four marks" of religious experience to describe psychedelic experiences:

> (1) Ineffability—the experience "defies expression" and cannot be described;
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> (2) Noetic—psychedelics provide deep insight and significant revelations (or, at least, the perception thereof);
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> (3) Transient—"although the mystical state cannot be sustained for long, its traces persist and recur;" and
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> (4) Passivity—the "sense of having temporarily surrendered to a superior force."[38]

All four traits relate to one's inner, subjective experience. But psychedelics don't just *act on* one's internal environment. They are also *influenced by* a patient's internal—and external—state.

This dependence on factors beyond the drug itself—so called "extrapharmacological variables"—is the trait of psychedelics most relevant to PAT.

The effectiveness of many drugs is subject to extrapharmacological variables. The placebo effect, for example, can trigger physiological changes in an individual who took nothing more than a sugar pill.[39] In fact, some scholars argue that selective serotonin reuptake inhibitors (SSRIs)—the current gold standard for depression treatment—are rarely better than active placebos themselves.[40]

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[36] POLLAN, *supra* note 3, at 199.

[37] *See, e.g.*, Mason Marks, *Psychedelic Medicine for Mental Illness and Substance Use Disorders: Overcoming Social and Legal Obstacles*, 21 N.Y.U. J. LEGIS. & PUB. POL'Y 69, 79 (2018) ("It is with some reluctance that I adopt the term 'psychedelic' . . . [h]owever, it is an appropriate term.").

[38] POLLAN, *supra* note 3, at 69–72.

[39] *See, e.g.*, Walter A. Brown, *Expectation, the Placebo Effect and the Response to Treatment*, 98 R.I. MED. J. 19 (2015).

[40] *See* Irving Kirsch, *Antidepressants and the Placebo Effect*, 222 ZEITSCHRIFT FR PSYCHOLOGIE [J. PSYCH.] 128 (2014); *see also* John Horgan, *Are Antidepressants Just Placebos with Side Effects?,* SCI. AM. (July 12, 2011), https://blogs.scientificamerican.com/cross-check/are-antidepressants-just-placebos-with-side-effects/ (last visited Apr. 27, 2023). Further probing suggested that studies showing positive effects of antidepressants were considerably more likely to be published. H. Edmund Pigott, Allen M. Leventhal, Gregory Alter & John J. Boren, *Efficacy and Effectiveness of Antidepressants: Current Status of Research*, 79 PSYCHOTHERAPY & PSYCHOSOMATICS 267, 268 (2010) ("[A]ntidepressant studies with favorable outcomes were 16 times more likely to be published as those with unfavorable ones.").

Psychedelics are unique in that they are "highly dependent on" some extrapharmacological effects.[41] The same person can have drastically different psychedelic experiences if they take a psychedelic substance at a specific time or place versus a different time or place. As journalist Jennifer M. Mitchell wrote, "I would not expect a blood thinner to have certain effects if I took it in my parents' living room versus in my neighbor's kitchen. I would not expect it to work differently depending on my mood. Psychedelics are undeniably different."[42] This enhanced influence of extrapharmacological factors requires clinicians to curate a patient's[43] environment and mindset for maximum safety and efficacy. A regulatory framework for psychedelics must understand and incorporate this principle.

Early psychedelic researchers developed the concept of "set and setting" to describe the extrapharmacological factors of psychedelic experiences.[44] Set encapsulates "anything related to the internal state of a person, including personality, preparation for the experience, [and] intention."[45] Setting is "anything related to the environment in which the experience takes place."[46] Early research developed techniques to control set and setting. To manage "set," patients were primed for predetermined therapeutic goals.[47] As for "setting," patients received psychedelic therapy in a space "decorated to feel more like a home than a hospital."[48] By managing set and setting, psychedelic therapists were able to mitigate the effects of a "bad trip" and the risk of harm.[49]

Many psychedelic therapists of the 20th century operated outside the scope of modern medicine and did not have to contend with things like peer review. Many of the pioneers pulled from the historical, shamanistic component of psychedelics in their therapy.[50] Modern medicine typically does not tolerate mysticism in treatment, but we must contend with this latent element of shamanism in the practice of psychedelic therapy. We may be able to strip some aspects of the shamanistic model from psychedelic therapy, but "it is imperative that we be conscious of the critical extrapharmacological variables that we know to be integral to the shamanic model. . . .

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41 David E. Nichols, *Psychedelics*, 68 PHARMACOLOGICAL REV. 264, 269 (2016).

42 Jennifer M. Mitchell, *A Psychedelic May Soon Go to the FDA for Approval to Treat Trauma*, SCI. AM. (Feb. 1, 2022), https://www.scientificamerican.com/article/a-psychedelic-may-soon-go-to-the-fda-for-approval-to-treat-trauma/.

43 A note on terminology: The literature on psychedelic therapy contains a variety of terms for the people giving and receiving the therapy. I adopt the word "patient" to describe the person receiving therapy, and either "therapist" or "clinician" to refer to the person facilitating the therapy.

44 Ido Hartogsohn, *Constructing Drug Effects: A History of Set and Setting*, 3 DRUG SCI., POL'Y & L., 1, 2 (2017).

45 *Id.* at 2–3.

46 *Id.* at 3.

47 *See* Charles S. Grob, *Psychiatric Research with Hallucinogens: What Have We Learned?*, *in* 1 HEFFTER REV. PSYCHEDELIC RSCH. 8, 16 (1998), https://www.heffter.org/wp-content/uploads/2020/04/chapter2.pdf; *see also* POLLAN, *supra* note 3 at 143 (describing the suggestibility of patients that take psychedelics).

48 POLLAN, *supra* note 3, at 164.

49 *See* Cohen & Ditman, *supra* note 24 (suggesting supervised psychedelic experiences are considerably safer than unsupervised).

50 *See* Grob, *supra* note 47, at 8 ("Within the context of shamanic society, [psychedelics] were utilized to facilitate healing, divine the future, protect the community from danger and enhance learning.").

The failure to adhere to any of these aspects of the shamanic paradigm would be to deny [psychedelic] research the full opportunity to test its true value."[51]

This emphasis on set and setting also clashes with modern clinical trials, where scientists prefer to remove all extrapharmacological variables using controlled studies. Timothy Leary claimed that double-blind experiments, the gold standard of pharmaceutical studies, were impossible with psychedelics. Due to the noticeable shift in perception and behavior of the experimental group, "[a]fter five minutes, no one's fooling anyone."[52]

To further complicate matters, early psychedelic researchers realized "not the chemical, but the experience [is] a key factor in therapy."[53] Most current medical interventions involve prescribing a drug, monitoring for any risk factors, and letting the drug have its effect. Psychedelic therapy is not as simple as administering a chemical to a patient and waiting for a positive outcome while they listen to soothing music and relax on a comfortable sofa. Effective psychedelic therapy must recognize that the substance is merely a tool to enhance psychotherapy—and a potential regulatory model must do the same.

The ongoing FDA trials implicitly recognize the place of psychedelics in PAT. The trial for MDMA-assisted psychotherapy contains two arms: an experimental arm where patients receive MDMA followed by talk therapy and a control arm where patients receive a placebo followed by the same therapy.[54] There is no arm where patients receive MDMA but no therapy. The trial is not testing the safety and efficacy of psychedelics in a vacuum. It is testing the safety and efficacy of using psychedelics *to enhance psychotherapy*.

C. What is Psychedelic-Assisted Therapy?

At its core, PAT combines the use of a psychedelic substance with psychotherapy. The individual components can be highly variable between treatment protocols. On the substance side, there are a handful of psychedelic compounds that could be utilized in PAT. The two most advanced FDA trials utilize MDMA and psilocybin, but studies

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[51] *Id.* ("If we are to assess optimally the true clinical efficacy and safety of the [psychedelics], it is imperative that we be conscious of the critical extrapharmacological variables that we know to be integral to the shamanic model.").

[52] POLLAN, *supra* note 3, at 192. This has posed a major problem for MAPS's MDMA-AT, with FDA demanding additional trials due to "functional unblinding" in the studies. Will Stone, *FDA Advisers Reject MDMA Therapy for PTSD, Amid Concerns Over Research*, NPR (June 4, 2024), https://www.npr.org/sections/shots-health-news/2024/06/04/nx-s1-4991112/mdma-therapy-ptsd-fda-advisors (last visited Sept. 11, 2024).

[53] *Id.* at 149.

[54] *A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1)*, U.S. NAT'L LIBR. OF MED. (Sept. 16, 2021), https://clinicaltrials.gov/ct2/show/NCT03537014 (last visited Apr. 27, 2023).

have proposed using LSD,[55] DMT,[56] and ketamine,[57] to name a few. Researchers are also racing to develop new psychedelic compounds that mitigate negative side effects or increase treatment efficacy.[58]

The type of psychotherapy is also highly variable. The MAPS training manual for MDMA therapists references over a dozen different therapy methods, elements of which may "occur spontaneously in MDMA-assisted therapy."[59] Essentially, the training manual allows for a variety of methodologies and acknowledges that each patient—and even each session for a given patient—may include any combination of methods. This wide range of allowable methods has sparked several criticisms of current PAT protocols.[60] MAPS, however, maintains that optionality is important to provide space for a patient to have their experience.[61] In its Phase 3 protocol, MAPS notes that a flexible approach allows for "facilitation of therapeutic action by providing support for approaching difficult material in a manner that does not interfere with the participant's spontaneous experience."[62]

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[55] *See generally* Juan José Fuentes, Francina Fonseca, Matilde Elices, Magí Farré & Marta Torrens, *Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials*, FRONTIERS PSYCHIATRY, Jan. 21, 2020, at 1 (providing a systematic review of trials using LSD in psychiatry).

[56] SMALL PHARMA, *Psychedelic-Assisted Therapy: A New Approach to Treating Depression*, NATURE BIOPHARMA DEALMAKERS, https://www.nature.com/articles/d43747-021-00064-4 (last visited Apr. 27, 2023) ("Small Pharma is the first company to conduct clinical trials to treat depression with the psychedelic N,N-dimethyltryptamine (DMT).").

[57] Wendy Boring-Bray, *An Introduction to Ketamine-Assisted Psychotherapy*, PSYCH. TODAY (Aug. 31, 2022), https://www.psychologytoday.com/us/blog/new-beginning/202208/introduction-ketamine-assisted-psychotherapy (last visited Apr. 27, 2023).

[58] *See, e.g.*, Shayla Love, *The Future of Psychedelic Medicine Will Be Drugs You've Never Heard Of*, VICE (Jan. 24, 2022), https://www.vice.com/en/article/m7v3dq/the-future-of-psychedelic-medicine-will-be-drugs-youve-never-heard-of (last visited Apr. 28, 2023).

[59] MICHAEL C. MITHOEFER, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUDS., A MANUAL FOR MDMA-ASSISTED PSYCHOTHERAPY IN THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER 15 (2015), https://maps.org/research-archive/mdma/MDMA-Assisted-Psychotherapy-Treatment-Manual-Version7-19Aug15-FINAL.pdf.

[60] Grace Browne, *The Therapy Part of Psychedelic Therapy Is a Mess*, WIRED (Apr. 6, 2023), https://www.wired.com/story/psychedelic-therapy-mess/ (last visited Apr. 27, 2023) ("Organizations like MAPS are conducting trials, but the sheer diversity of therapy being used undermines their results."); *see also* Allison Feduccia, Gabby Agin-Liebes, Collin M. Price, Nicole Grinsell, Summer Paradise & David M. Rabin, *The Need for Establishing Best Practices and Gold Standards in Psychedelic Medicine*, 332 J. AFFECTIVE DISORDERS 47, 52 (2022) ("One of the primary barriers the field faces for the dissemination of safe and effective psychedelic treatments is the lack of standardized training and agreed upon skills and competencies for delivering psychedelic medicines.").

[61] The MAPS approach to therapy is predicated on "non-directive" elements, designed to "create a sense of safety and communicate trust in [the] patient's ability to explore their issues." Santiago Madero & Oscar D. Alvarez, *Premise, Promise and Challenges of MDMA Assisted Therapy for PTSD*, 70 EUR. NEUROPSYCHOPHARMACOLOGY 19, 80 (2023).

[62] MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUDS., A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-SITE PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF MANUALIZED MDMA-ASSISTED PSYCHOTHERAPY FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER OF MODERATE OR GREATER SEVERITY 33 (2021), https://maps.org/wp-content/uploads/2022/05/MAPP2-Protocol-A4V1-FINAL_REDACTED_23MAR2021.pdf [hereinafter MAPS PROTOCOL].

Despite this flexibility and potential for variation, most PAT protocols contain several common characteristics: screening, preparation session, medication sessions, and integration sessions.[63]

Screening is essential to ensure that a patient can safely take psychedelics. The biggest risk factors associated with psychedelics are a personal or family history of heart conditions or psychiatric conditions.[64] Psychedelic experiences can exacerbate existing cardiac conditions and can possibly trigger long-term psychosis.[65] Like any pharmaceutical intervention, it is critical to identify traits that increase the chance of an adverse reaction and screen patients for that risk.[66] Unfortunately, if the risk associated with a trait cannot be sufficiently mitigated, then would-be patients will need to find a different medical intervention. Once patients are screened for risk factors, the real work can begin with patient preparation.

There are two important objectives during the preparation phase: getting a patient comfortable with their therapist and educating the patient on what to expect from the psychedelic experience.[67] Rapport and trust are important in any patient–therapist relationship but can be especially integral in PAT, where a patient may experience extreme fear or anxiety provoked by the psychedelic substance.[68] Multiple sober encounters prior to a medication session can build the trust and knowledge necessary to overcome such experiences. Preparing patients for what to expect during the experience can prevent patients from "being frightened by the unusual and the unfamiliar . . . . Successful use of [PAT] presupposes specific knowledge and experience."[69] Preparation sessions can equip patients with that knowledge and experience for the medication sessions.

Medication sessions are where the magic happens. A medication session typically includes a high dose of the chosen psychedelic compound plus several hours of therapy. Duration differs by compound; psilocybin and MDMA sessions typically last six to eight hours.[70] The theory and instruction of therapy differs between protocols,

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[63] *See* Feduccia et al., *supra* note 60, at 49–50.

[64] *Id.* at 49.

[65] *See* Benjamin Murrie, Julia Lappin, Matthew Large & Grant Sara, *Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-Analysis*, 46 SCHIZOPHRENIA BULL. 505, 505 (2019) ("A significant proportion of people with substance-induced psychosis later transition to a diagnosis of schizophrenia."); *but see* Zoe Cormier, *No Link Found Between Psychedelics and Psychosis*, NATURE MAG. (Mar. 4, 2015), https://www.scientificamerican.com/article/no-link-found-between-psychedelics-and-psychosis1/ (last visited Apr. 27, 2023) ("Data from population surveys in the United States challenge public fears that psychedelic drugs such as LSD can lead to psychosis.").

[66] *See, e.g.*, *1 in 5 People with High Blood Pressure Are Taking Meds That Can Make It Worse*, HEALTHLINE (May 7, 2021), https://www.healthline.com/health-news/1-in-5-people-with-high-blood-pressure-are-taking-meds-that-can-make-it-worse#Half-of-adults-take-drugs-that-elevate-their-blood-pressure (last visited Apr. 27, 2023) (listing several drugs that can exacerbate high blood pressure levels, such as "steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, or birth control").

[67] Feduccia et al., *supra* note 60, at 49.

[68] *Id.* at 50.

[69] HOFFMAN, *supra* note 2, at 76.

[70] *See* MAPS PROTOCOL, *supra* note 62, at 49 ("Experimental Sessions must be at least 8 hours long."); *see also About Psilocybin Therapy*, COMPASS PATHWAYS, https://compasspathways.com/our-work/about-psilocybin-therapy/ (last visited Apr. 27, 2023) ("The psilocybin experience typically lasts 6–8 hours. A therapist and an assisting therapist are present throughout the session.").

but the medication session(s) are the core component of all PAT.[71] Patients are generally "encouraged to focus their attention on their inner experiences" and to "trust, let go, and be open."[72] Critically, a therapist "might remind a [patient] to stay present with deeper emotions and reiterate that it is safe to face difficult feelings."[73] The overarching objective is for the psychedelic experience to help a patient harness their "innate capacities to heal and grow."[74] Patients have the potential to heal themselves; the psychedelic helps them fulfill that potential. The therapist is there to gently guide the patient's experience from start to finish, including through the post-medication session integration phase.

Integration sessions are an opportunity for therapeutic aftercare. They help resolve difficult moments from the medication session and help patients incorporate the experience into everyday life.[75] Psychedelic experiences often give patients a new insight into their condition and its symptoms. The integration session provides space for the patient to work through those insights with a therapist that is trained to understand both their condition and the psychedelic experience that evoked the insight.[76] Bringing a raw, unintegrated psychedelic experience to a therapy session with a clinician that is not trained in, or even familiar with, psychedelic therapy can decrease treatment efficacy or increase the risk of psychological disturbance.[77] It is critical to understand the psychedelic experience as a holistic process that reaches beyond the medication sessions. Psychedelic therapy is exciting because it has the capacity to affect lasting psychological changes, long after any trace of psychedelic substance remains in a patient's body.[78] Integration sessions are a crucial step in leveraging an eight-hour trip into lifelong healing.

While most, if not all, PAT protocols contain the four elements listed above, there is room for significant differences among and outside of these elements. While some flexibility can increase treatment efficacy by allowing a therapist to tailor their response to each individual patient, a lack of structure can be dangerous.

> Stated simply, psychedelics can induce a vulnerable state both during and after treatment sessions. Therefore, to assure the safe and responsible clinical administration of psychedelics, we need to develop and disseminate rigorous ethical and practice standards that are commensurate

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[71] Feduccia et al., *supra* note 60, at 50.

[72] *Id.*

[73] *Id.*

[74] *Id.*

[75] *Id.*

[76] *Id.*

[77] *See* Geoff J. Bathje, Eric Majewski & Mesphine Kudowor, *Psychedelic Integration: An Analysis of the Concept and Its Practice*, FRONTIERS PSYCH., Aug. 4, 2022, at 01, 04 ("Inadequate social/psychological support [during integration] may lead to an inability to gain insight or work through less obvious or more challenging content.").

[78] *See* Yasmin Schmid & Matthias E. Liechti, *Long-Lasting Subjective Effects of LSD in Normal Subjects*, 235 PSYCHOPHARMACOLOGY 535, 535 (2018) ("In healthy research subjects, the administration of a single dose of LSD . . . had long-lasting subjective positive effects."); *see also* Patrick C. Dolder, Yasmin Schmid, Andrea E. Steuer, Thomas Kraemer, Katharina M. Rentsch, Felix Hammann & Matthias E. Liechti, *Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects*, 56 CLINICAL PHARMACOKINETICS 1219, 1220 (2017) (finding that LSD has an elimination half-life of roughly 3.5 hours and concentrations are "very low" within twelve hours following dosing).

> with the novelty and breadth of the effects that these compounds can have on individuals.[79]

There is already evidence of psychedelic therapists acting unethically and harming their patients, both physically and mentally.[80] Some actions, such as sexually assaulting a patient, are clearly unethical and illegal.[81] But the complex nature of psychedelics and PAT pose novel concerns that requires a regulatory framework that understands the unique elements of PAT and addresses them in a clear, effective manner. The core question is not whether we should regulate or even how we should regulate—the core question is about *who* should regulate.

At the clinical trial stage, FDA has full jurisdiction and oversight by enforcing trial protocols. Any accepted Investigational New Drug Application that reaches Phase 2 must contain "detailed protocols describing all aspects of the study."[82] The Clinical Study Report compiled at the end of every trial must contain any protocol deviations, thus putting pressures on the trial sponsor to comply with the proposed protocols.[83] Both the MAPS and Compass Pathways trials had training requirements and protocols for therapists in additional to traditional elements like drug dosage and timing.

The Compass Pathways psilocybin-assisted therapy trial required a therapist training program to ensure "the shared consistency of . . . the psychological support" provided during the trial.[84] Compass Pathways offers a therapist training program consisting of "10 hours of theoretical online learning" and "three days of in-person practical skills group training."[85] They do not publish their training protocol to the public. The MAPS protocol also requires extensive psychotherapist training. The organization has published its sixty-nine-page therapist training manual for MDMA-assisted therapy on its website.[86]

As discussed above, there are several critiques of psychedelic therapy protocols, particularly surrounding the lack of strict requirements on therapy techniques.[87] Even if the training protocols required during FDA trials remain required after FDA

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[79] Brian T. Andersen, Alicia Danforth & Charles Grob, *Psychedelic Medicine: Safety and Ethical Concerns*, 7 LANCET PSYCHIATRY 829, 829 (2020).

[80] Bethany Lindsay, *Footage of Therapists Spooning and Pinning Down Patient in B.C. Trial for MDMA Therapy Prompts Review*, CBC NEWS (Apr. 9, 2022), https://www.cbc.ca/news/canada/british-columbia/bc-mdma-therapy-videos-1.6400256 (last visited Apr. 27, 2022); Will Hall, *Ending the Silence Around Psychedelic Therapy Abuse*, MAD IN AMERICA (Sept. 25, 2021), https://www.madinamerica.com/2021/09/ending-silence-psychedelic-therapy-abuse/ (last visited Apr. 28, 2023).

[81] Azza AbuDagga, Michael Carome & Sidney M. Wolfe, *Time to End Physician Sexual Abuse of Patients: Calling the U.S. Medical Community to Action*, 34 J. GEN. INTERNAL MED. 1330, 1330 (2019) ("The prohibition against physician sexual relations with their patients, which can cause lasting damage to patients, is one of the most universally agreed upon ethical principles in medicine.").

[82] 21 C.F.R. § 312.23(a)(6)(ii).

[83] U.S. FOOD & DRUG ADMIN., GUIDELINE FOR INDUSTRY: STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS 16 (1996).

[84] Sara J. Tai, Elizabeth M. Nielson, Molly Lennard-Jones, Riikka-Liisa Johanna Ajantaival, Rachel Winzer, Williams A. Richards, Frederick Reinholdt, Brian D. Richards, Peter Gasser & Ekaterina Malievskaia, *Development and Evaluation of a Therapist Training Program for Psilocybin Therapy for Treatment-Resistant Depression in Clinical Research*, FRONTIERS PSYCHIATRY, Feb. 3, 2021, at 1, 2.

[85] *Therapist Training Programme*, COMPASS PATHWAYS, https://compasspathways.com/our-work/therapist-training/ (last visited Apr. 27, 2023).

[86] MITHOEFER, *supra* note 59.

[87] *See supra* note 60 and accompanying text.

approval, there would be room for improvement. Further testing is required to determine which components of therapy are most useful and which can be improved upon.[88] There is a more pressing problem—the post-approval regulatory pathway for psychedelic therapy isn't exactly clear.[89] Historically, the federal government regulates drugs and states regulate the practice of medicine. Following that framework would lead to the federal government governing half of PAT (the substance), while states govern the other half (the therapy protocol). PAT's dual-component structure, therefore, poses a novel regulatory question. With a promising solution to the mental health crisis on the line, it is paramount that we work out a regulatory system that is strong enough to promote patient safety and treatment efficacy, and clear enough to provide fertile soil for a nascent industry to bloom.

III. DRUGS V. THE PRACTICE OF MEDICINE

The prevailing view of medical regulation is that the federal government regulates products, and the states regulate the practice of medicine.[90] PAT's novel combination of a drug and mandatory psychotherapy straddles this jurisdictional divide. A regulatory framework that maximizes patient safety, efficacy, and access must navigate the jurisdictional tension to provide clear, workable oversight of PAT.

A. FDA and Product Regulation

The federal government regulates drugs via FDA.[91] A drug may not be introduced into interstate commerce unless it has been approved by FDA and is labeled according to FDA standards.[92] Receiving FDA approval is a major milestone in a drug's life—it can now be sold to the public!

The federal government did not always exercise control over drug products. At the start of our nation's history, state governments regulated drugs.[93] FDA was established in 1906 when Congress passed the Pure Food and Drug Act of 1906.[94] The act empowered FDA to prevent the sale of adulterated or misbranded drugs.[95] The nascent FDA did not, however, require premarket safety testing of drugs—it only had authority

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[88] *See* Feduccia et al., *supra* note 60, at 50.

[89] *See id.* at 51 ("At this time, it is unclear if the FDA will require administration of specific psychological or therapeutic treatment models.").

[90] *See* Myrisha S. Lewis, *Innovating Federalism in the Life Sciences*, 92 TEMP. L. REV. 383, 398 (2020) ("States have a longstanding role as regulators for the benefit of the public health, including through the regulation of the practice of medicine."); *see also* Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 438 (2015) ("[C]ourts, medical practitioners, and Congress have not viewed the federal government—and the one-size-fits-all approach that may come with it—as a natural fit for regulating medical practice.").

[91] "Drug," for purposes of FDA regulation, is a broadly defined term. It includes all "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," "articles (other than food) intended to affect the structure or any function of the body of man or other animals," and articles intended to be used as a component for a drug. 21 U.S.C. § 321 (g)(1).

[92] 21 U.S.C. § 355(a) (stating that any new drug must be approved before it can be introduced via interstate commerce); *see generally* 21 U.S.C. § 352 (providing the requirements for branding and labelling of drugs and medical devices).

[93] *See* Patricia Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 852–53 (2017).

[94] Pure Food and Drug Act (1906); *see id.* at 855.

[95] Pure Food and Drug Act, ch. 3915, §§ 1–2, 34 Stat. 768, 768 (1906).

after drugs entered the market, where they could do real harm.[96] This proved to be a grave oversight.

"By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it."[97] An unfortunate accident would break the regulatory logjam in due time. In 1937, a Tennessee company created a version of the antibiotic sulfanilamide using, unbeknownst to them, a toxic solvent.[98] Due to the lack of premarket safety testing, over a hundred people died after ingesting the concoction.[99]

In response, Congress passed the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938.[100] The FDCA expanded FDA's oversight and authority over the pharmaceutical industry, particularly before drugs reached the market.[101] While the FDCA did not grant FDA as much authority as it has today, this was the first step toward FDA taking on its modern role as "gatekeeper" of the drug market.[102]

Even at this step in the history of medical regulation, the federal government respected state's role in governing the practice of medicine—the so-called "practice of medicine exception."[103] The legislative history of the FDCA "expresses a specific intent to prohibit FDA from regulating physicians' practice of medicine."[104] The original bill contained the qualification that "it did not apply to the regulation of the 'legalized practice of the healing art.'"[105] While that language did not make it into the bill, "the legislative history [made] clear that Congress did not want to limit a physician's ability to treat his [or her] patients."[106]

The legislative history of subsequent amendments to the FDCA provides additional support for the practice of medicine exception. With the Kefauver–Harris Drug Amendments Act of 1962—which gave FDA the authority to evaluate drugs for efficacy as well as safety—Congress reiterated its stance that the practice of medicine should not fall under FDA jurisdiction.[107] The Food and Drug Administration Modernization Act of 1997 and the Food and Drug Administration Amendments Act

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[96] *See* Zettler, *supra* note 93, at 855.

[97] Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG., June 1981, at 1, https://www.fda.gov/media/110479/download?attachment.

[98] *See id.* at 2 ("[The chemist] failed to note one characteristic of the solution. Diethyl glycol [the solvent] . . . is a deadly poison.").

[99] *See* Zettler, *supra* note 93, at 856.

[100] *See id.*

[101] *See id.*

[102] *Id.* at 857.

[103] *See* United States v. Algon Chem. Inc., 879 F.2d 1154, 1162 (3d Cir. 1989) (analyzing judicial recognition of the practice of medicine exception).

[104] Chaney v. Heckler, 718 F.2d 1174, 1190 (D.C. Cir. 1983), *rev'd on other grounds*, 470 U.S. 821 (1985).

[105] *Id.* at 1179 n.13 (quoting S. 5, 74th Cong., 1st Sess. § 201(b), 79 Cong. Rec. 8351 (1935)).

[106] *Id.*

[107] Wendy Teo, *FDA and the Practice of Medicine: Looking at Off-Label Drugs*, 41 SETON HALL LEGIS. J. 305, 308 (2017).

of 2007 again stated that "nothing in this section shall be construed to . . . limit the practice of medicine."[108]

The practice of medicine exception is not only lurking in the legislative history of amendments to the FDCA. Congress has expressed that the practice of medicine exemption applies beyond FDA. The Medicare statute, the Fertility Success Rate and Certification Act of 1992, and the Drug Addiction Treatment Act of 2000 all contain provisions that prevent the federal government from interfering with the practice of medicine.[109]

FDA itself holds the position that it does not regulate the practice of medicine. An informational page on FDA's website states that "FDA does not have the authority to: [r]egulate a physician's or nurses practice . . . [or] make recommendations for individual doctors."[110] A "Q&A" page notifies patients that "FDA does not regulate the practice of medicine."[111] Even if Congress and FDA truly mean that the federal government should never regulate the practice of medicine, that is easier said than done; drugs and the practice of medicine are inextricably linked.

The distinction between regulating drugs and the practice of medicine is sometimes a blurry line. While FDA may disclaim its ability to regulate the practice of medicine, it certainly prevents physicians from prescribing some drugs. If FDA determines that a product is a drug (or medical device, biologic, etc.) and that product has not received FDA approval, doctors are typically prohibited from administering the product to a patient.[112] While preventing doctors from prescribing unapproved drugs seems like it is regulating drug products and not the practice of medicine, not everyone agrees.

History is rife with examples of physicians proclaiming that FDA is trying to control their practice—especially in novel technologies. In 2008, FDA wrote a warning letter to Dr. Christopher Centeno—founder of Regenerative Sciences—alleging that his company's mesenchymal stem cells were unapproved "drugs" under § 201(g) of the FDCA and "biological products" under § 351(i) of the Public Health Service Act.[113] Regenerative Sciences claimed that the procedure was the practice of medicine under Colorado statute and thus not subject to FDA regulation.[114] The District Court of the District of Columbia agreed with FDA's interpretation, and the District of Columbia Circuit affirmed in *United States v. Regenerative Sciences*.[115] However, the circuit

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[108] *Id. But see* 21 U.S.C. § 360f ("A device that is banned for one or more intended uses is not a legally marketed device under section 396 of this title when intended for such use or uses."); *see also* Joel Zinberg, *The FDA Wants to Interfere in the Practice of Medicine*, WALL ST. J. (Jan. 12, 2023), https://www.wsj.com/articles/the-fda-wants-to-interfere-in-the-practice-of-medicine-physicians-patients-medical-devices-treatment-11673562165 (last visited Apr. 28, 2023) (explaining the recent update to 21 U.S.C. 360f in the 2023 omnibus bill).

[109] Teo, *supra* note 107, at 308 n.11.

[110] *FDA's Role in Regulating Medical Devices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/home-use-devices/fdas-role-regulating-medical-devices (last visited Apr. 27, 2023).

[111] U.S. FOOD & DRUG ADMIN., ABOUT FDA: PATIENT Q&A, https://www.fda.gov/media/151975/download (last visited Apr. 27, 2023).

[112] 21 U.S.C. § 355(a).

[113] *FDA Warning Letter to Christopher Centeno, M.D.*, https://quackwatch.org/cases/fdawarning/prod/fda-warning-letters-about-products-2008/regenexx/ (last visited Apr. 27, 2023).

[114] United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1319 (D.C. Cir. 2014).

[115] *Id.* at 1317.

court noted that the "focus of the FDA's regulation is the *Mixture* [of the stem cells]," but "the FDA does not claim that the procedures used to administer the Mixture are unsafe."[116] By barring the use of an unapproved drug, FDA implicitly controlled an aspect of Dr. Centeno's medical practice. Restricting what practitioners can and cannot do in their practice in this way is entirely permissible based on the FDCA.[117] FDA, therefore, does have authority to regulate some aspects of the practice of medicine, albeit in a tangential way.

FDA has occasionally taken such soft regulation a step further. In 2016, Dr. John Zhang helped create the first "three-parent baby" using mitochondrial replacement therapy (MRT).[118] MRT is an innovative form of in vitro fertilization that prevents heritable mitochondrial diseases.[119] Essentially, diseased mitochondrial DNA can be removed from an embryo and replaced with mitochondrial DNA from a healthy donor.[120] MRT allows a woman to be the biological mother of her children (the egg contains her DNA) without passing on a mitochondrial disease (the mitochondrial DNA comes from someone else).[121]

MRT is not approved in the United States. In fact, FDA is prohibited from considering MRT for approval due to a rider originally attached to an appropriations bill in 2015 and included in every such bill since.[122] In an attempt to circumvent the federal ban, Dr. Zhang flew to Mexico with a patient to perform MRT.[123] However, Dr. Zhang performed the first phase of the treatment, ovarian stimulation and oocyte manipulation, in the United States.[124] This first phase is part of FDA-approved IVF treatment.[125] Travelling to Mexico to perform the portions of therapy that are illegal in the United States created a murky regulatory area that FDA filled with a warning letter.[126]

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[116] *Id.* at 1319.

[117] *See id.* at 1326 (permanently enjoining Regenerative Sciences from violating the FDCA).

[118] Ariana Eunjung Cha, *This Fertility Doctor Is Pushing the Boundaries of Human Reproduction, with Little Regulation*, WASH. POST (May 14, 2018), https://www.washingtonpost.com/national/health-science/this-fertility-doctor-is-pushing-the-boundaries-of-human-reproduction-with-little-regulation/2018/05/11/ea9105dc-1831-11e8-8b08-027a6ccb38eb_story.html (last visited Apr. 27, 2023).

[119] Hitika Sharma, Drishtant Singh, Ankush Mahant, Satwinder Kaur Sohal, Anup Kumar Kesavan & Samiksha, *Development of Mitochondrial Replacement Therapy: A Review*, HELIYON, Sept. 1, 2020, at 1, 1.

[120] *Id.* ("[MRT is a technique] in which the embryo possessing the nuclear DNA of the parents is subjected to the IVF procedure to have mitochondrial DNA of the donor female.").

[121] *Id.* ("[MRT] provides [mothers with mitochondrial diseases] a suitable chance to have biologically related healthy offspring.").

[122] I. Glenn Cohen, *Circumvention of Medical Tourism and Cutting Edge Medicine: The Case of Mitochondrial Replacement Therapy*, 25 IND. J. GLOBAL LEGAL STUD., 439, 441–42 (2018).

[123] *Id.* at 444–45.

[124] *Id.* at 444.

[125] *See id.* at 448 (Ovarian stimulation for egg retrieval is "not a new use or indication.").

[126] Letter from Mary A. Malarkey, Dir., Off. of Compliance and Biologics Quality, Ctr. for Biologics Evaluation and Rsch., to Dr. John Zhang, Chief Exec. Officer, Darwin Life, Inc. & New Hope Fertility Clinic (Aug. 4, 2017), https://www.fdanews.com/ext/resources/files/2017/08/08-07-17-CRL.pdf?1504514387; *see also* Cohen, *supra* note 122, at 449.

The warning letter prohibited Dr. Zhang from marketing his treatment in the United States, even though he was performing the actual MRT in Mexico.[127] While in the United States, Dr. Zhang used FDA-approved drugs in an FDA-approved manner. He did not perform illegal aspects of MRT until he was in Mexico, beyond the jurisdictional reach of FDA—or so he thought. "What happens after the egg retrieval . . . is a new use or indication" that did not meet any permissible export exemptions; therefore, the human tissue is—according to FDA—subject to FDA regulation.[128]

Typically, however, once FDA approves a drug for any indication, clinicians are free to prescribe that drug for almost anything through a practice known as off-label use.

i. Off-Label Use

Nowhere is FDA's hesitancy to govern the practice of medicine more evident than with off-label prescriptions. "Off-label" refers to the practice of prescribing a drug "in a manner that has not been authorized by the FDA through its approval process for new drugs."[129] The Supreme Court has affirmed off-label use, calling it "an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine."[130]

When FDA approves a new drug, it also approves a label.[131] That label must include, among other things, the intended use of the drug.[132] That use pertains to a specific indication—the indication for which FDA approved the drug. One may think that clinicians are restricted to prescribing drugs solely for FDA-approved indications. That is not the case. In fact, a 2006 study found that over 20% of prescriptions are for off-label use.[133]

According to FDA, "[f]rom [their] perspective, 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."[134] Some examples of off-label use that FDA provides on its website are:

> (1) using a chemotherapy that is approved to treat one type of cancer to treat a different type of cancer;
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> (2) when a drug that is approved as a capsule is given instead in an oral solution; and

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[127] *See* Letter from Mary A. Malarkey to Dr. John Zhang, *supra* note 126.

[128] Cohen, *supra* note 122 at 448; *see also id.*, *supra* note 126 ("Nor is exportation [of the human cell tissue] permitted unless it meets the requirements of an applicable export exemption.").

[129] *See* Teo, *supra* note 107, at 311.

[130] Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

[131] 21 U.S.C. § 321(p)(1) (2016).

[132] 21 C.F.R. § 201.5 (2016).

[133] David C. Radley, Stan M. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006).

[134] *Understanding Unapproved Use of Approved Drugs "Off Label,"* U.S. FOOD & DRUG ADMIN. (Feb. 5, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (last visited Apr. 27, 2023).

> (3) when a drug is approved at a dose of one tablet every day, but a clinician prescribes two tablets every day.[135]

Clinicians prescribe medication off-label for a variety of reasons. There may not be an approved medication for a patient's ailment.[136] A patient may not respond to any approved treatment, leading them to search elsewhere for relief.[137] An off-label use of a drug to treat a condition may be more effective or safer than any approved use.[138] While this practice may expose a clinician to tort liability, FDA does not govern off-label use.[139]

This does not mean FDA is completely hands-off once it approves a drug. Clinicians may be free to *prescribe* drugs off-label, but FDA does regulate off-label *marketing*, which restricts what drug manufactures can say about their products. Drug manufacturers are prohibited from branding or marketing their drugs for any indication that has not received FDA approval.[140] Clinicians can choose to prescribe drugs off-label based on scholarly research that suggests a drug may work for a new indication, but they should not be influenced into off-label prescriptions by the drug manufacturer.[141]

Preventing advertisements for off-label use does not mean that manufacturers cannot capitalize on new uses after their drug receives FDA approval. New indications can be added to a label via a supplemental new drug application.[142] The process can be costly, time consuming, and fruitless, so many companies do not pursue the path of supplemental new drug applications.[143] While off-label use is not presently apposite to PAT, one psychedelic—ketamine—has already gained notoriety as a candidate for off-label use.

FDA approved ketamine for use as an anesthetic in 1970.[144] As the only psychedelic drug that has evaded Schedule I, ketamine is subject to fewer research restrictions than the other psychedelics.[145] Several studies have suggested ketamine is an effective

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[135] *Id.*

[136] *Id.*

[137] *Id.*

[138] *See infra* Section III.a.i.

[139] Shariful A. Syed, *The Law and Practice of Off-Label Prescribing and Physician Promotion*, 49 J. AM. ACAD. PSYCHIATRY & L. 49, 57 (2021).

[140] Kevin Costello & Eric Johnston, *Manufacturer Liability for Off-Label Uses of Medical Devices*, L.A. LAW., Apr. 2008, at 18 ("Nevertheless, the FDA forbids the promotion of off-label uses by manufacturers.").

[141] There is, however, tension between allowing off-label *use* but barring off-label *marketing*. *See* United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012) ("Prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information.").

[142] Randall S. Stafford, *Regulating Off-Label Drug Use - Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

[143] *Id.*

[144] Linda Li & Phillip E. Vlisides, *Ketamine: 50 Years of Modulating the Mind*, 10 FRONTIERS HUM. NEUROSCI. 612 (2016).

[145] U.S. DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET: KETAMINE (2020), https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf; *see also* U.S. DRUG ENFORCEMENT ADMIN., DIVERSION CONTROL DIV., RESEARCHER'S MANUAL: AN INFORMATIONAL OUTLINE OF THE CONTROLLED SUBSTANCES ACT 20–22 (2020), https://www.deadiversion.usdoj.gov/GDP/(DEA-DC-

treatment for mental illnesses, including major depressive disorder.[146] Based on that evidence, physicians have begun prescribing ketamine off-label for various mood disorders.[147] To improve safety and efficacy in off-label ketamine therapy, the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments published a statement in *JAMA Psychiatry* in 2017 recommending best practices for off-label ketamine use.[148]

Spravato, a branded intranasal spray containing a ketamine derivative, received FDA approval as a therapy for treatment-resistant depression in 2019.[149] Spravato's FDA approval bestowed two major benefits to the manufacturer compared with off-label ketamine use. Because Spravato has obtained FDA approval for treatment-resistant depression, the manufacture can advertise it as such, thus increasing market awareness. Spravato also contains a novel ketamine derivative, esketamine, and is protected by new patents.[150] But Spravato's approval has not brought an end to off-label ketamine use. One company, Mindbloom, has combined COVID telehealth medicine regulations with off-label ketamine prescriptions.[151] Mindbloom ships ketamine to patients' homes for at-home psychedelic experiences to treat anxiety and depression.[152] Spravato cannot be prescribed in this way due to its Risk Evaluation and Mitigation Strategy (REMS)—further restrictions imposed by FDA to balance a drug's safety and efficacy—which requires a physician to monitor patients for two hours after the Spravato dose.[153]

Off-label use may be a viable option for patients seeking to utilize PAT for a non-approved indication, such as end-of-life anxiety.[154] If the PAT in question is subject to

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057)(EO-DEA217)_Researchers_Manual_Final_signed.pdf (Schedule II–V substances are subject to fewer research restrictions than Schedule I substances.).

[146] *See, e.g.*, Cheolmin Shin & Yong-Ku Kim, *Ketamine in Major Depressive Disorder: Mechanisms and Future Perspectives*, 17 PSYCHIATRY INVESTIGATION 181 (2020).

[147] Samuel T. Wilkinson & Gerard Sanacora, *Considerations on the Off-label Use of Ketamine as a Treatment for Mood Disorders*, 318 JAMA 793, 793 (2017) ("[T]he increasing number of clinicians from a variety of medical specialties offering ketamine as an off-label treatment for psychiatric disorders has raised concern.").

[148] Gerard Sanacora, Mark A. Frye, William McDonald, Sanjay J. Matthew, Mason S. Turner, Alan F. Schatzberg, Paul Summergrad & Charles B. Nemeroff, *A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders*, 74 JAMA PSYCHIATRY 399 (2017).

[149] *See infra* Section IV.A.i.

[150] The patent for ketamine expired in 2002. *Ketamine Nomination* at 7, https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/chem_background/exsumpdf/ketamine_508.pdf (last visited Apr. 27, 2023).

[151] *See generally*, Shayla Love, *Psychedelic Telemedicine Has Arrived. What Could Possibly Go Wrong?*, VICE (Nov. 30, 2021), https://www.vice.com/en/article/pkpp3k/psychedelic-telemedicine-has-arrived-what-could-possibly-go-wrong (last visited Apr. 27, 2023).

[152] MINDBLOOM, https://www.mindbloom.com/ (last visited Apr. 27, 2023).

[153] *See FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at a Certified Doctor's Office or Clinic*, U.S. FOOD & DRUG ADMIN. (Mar. 5, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified (last visited Apr. 27, 2023) [hereinafter *FDA Spravato News Release*].

[154] *See generally* William Barone, Michiko Mitsunaga-Whitten, Lia Osunfuntáyò Blaustein, Phillip Perl, Marisa Swank & Thomas Cody Swift, *Facing Death, Returning to Life: A Qualitative Analysis of MDMA-assisted Therapy for Anxiety Associated with Life-threatening Illness*, FRONTIERS PSYCHIATRY, Sept. 27, 2022.

a REMS, however, patient access may be restricted to patients who fit a specific profile.[155]

Should FDA govern post-approval elements of psychotherapy, off-label use may also allow for added flexibility in the psychotherapy component of PAT. In the case of the MAPS/MDMA trial, therapists are trained via the MAPS Therapist Training Manual.[156] That is not the only psychedelic therapy manual available for therapists to learn from and apply in practice.[157] The practice of medicine exception may allow therapists to pull from a different manual during psychotherapy. A REMS could require therapists to be trained and/or certified in specific therapy techniques, but that may not prevent off-label use of a different technique.[158]

B. State Governments and the Practice of Medicine

The Tenth Amendment reserves unenumerated powers to the state governments.[159] One of these powers is the authority to protect the health and welfare of a state's citizens. In the early 1900s, the Supreme Court held that regulating the practice of medicine derived from the state's police power.[160] State law governs the practice of medicine via both licensing boards and tort law.

i. Licensing Boards

One mechanism states use to protect the health of their citizens is regulating the medical profession through a licensing board. The primary purpose of medical boards is to protect the public "from incompetent, unprofessional, and improperly trained physicians."[161]

Every state in the country has a medical licensing board.[162] To practice medicine, a clinician must be licensed by the board. The specific requirements vary from state to state, but typically involve evaluating a candidate's education, work history, and personal character.[163] Physicians must also pass a rigorous, three-part examination.

After a physician obtains their license, the medical board continues to oversee their work. A medical board has the "responsibility of evaluating whether a physician's

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[155] *See infra* note 203 and accompanying text; *but see infra* notes 204–205 and accompanying text.

[156] MITHOEFER, *supra* note 59.

[157] *E.g.*, D.B. BLEWETT & N. CHWELOS, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUDS., HANDBOOK FOR THE THERAPEUTIC USE OF LYSERGIC ACID DIETHYLAMIDE-25: INDIVIDUAL AND GROUP PROCEDURES (1959), https://maps.org/research-archive/ritesofpassage/lsdhandbook.pdf; Jeffrey Guss, Robert Krause & Jordan Sloshower, *Yale Manual For Psilocybin-Assisted Therapy Of Depression*, PSYARXIV (Aug 13, 2020), https://psyarxiv.com/u6v9y/ (last visited Apr. 27, 2023).

[158] *See infra* Section IV.A.

[159] U.S. CONST. amend. X.

[160] Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 159 (2004).

[161] Drew Carlson & James N. Thompson, *The Role of State Medical Boards*, 7 VIRTUAL MENTOR, Apr. 2005, at 311.

[162] In fact, there are a total of seventy medical boards in the United States. Fourteen states have a separate board to license allopathic and osteopathic doctors, and several United States territories have their own board. *Understanding Medical Regulation in the United States*, FED'N ST. MED. BDS., https://www.fsmb.org/siteassets/education/pdf/best-module-text-intro-to-medical-regulation.pdf (last visited Apr. 27, 2023).

[163] Carlson & Thompson, *supra* note 161, at 1.

professional conduct or ability to practice medicine warrants modification, suspension, or revocation of the license to practice."[164] If a patient reports a complaint about a physician, the state medical board will investigate for any professional misconduct.[165] Professional misconduct varies between states but typically includes physical or sexual abuse, not recognizing or acting on common symptoms, and overprescribing drugs.[166] If a clinician violates certain rules or regulations, the board may revoke or suspend the clinician's license.[167] Each states operates multiple licensing boards for the medical industry. States typically have, for example, one board for physicians, one for nurses, and one for psychologists or psychotherapists.

Current PAT trial protocols require several different licensed professionals at a trial site. The MAPS trial, for example, requires one person licensed to manage controlled substances, a licensed physician to perform safety screenings, and at least one person "licensed to perform therapy according to state and local requirements."[168] In California, for example, licensure to perform psychotherapy requires a masters or doctoral degree in counseling or psychotherapy and 150 hours of supervised clinical experience, among other requirements.[169] Therapists or psychologists are generally not licensed to prescribe medication, so PAT will require *another* professional that can prescribe the psychedelic substance.[170]

By requiring a license to administer various aspects of PAT, states will have ongoing control over the therapy component of PAT. While licensing can provide one jurisdictional hook over PAT, it is not the only option in the state law toolkit.

ii. Medical Malpractice

Licensing is not the only element of state law that regulates the actions of medical professionals. If a patient feels aggrieved by a clinician's conduct, they may have a cause of action against the clinician. Medical malpractice lawsuits are common—about one-third of physicians will be sued for malpractice at some point in their career.[171] Typically, medical malpractice requires proving: "(1) the applicable standard of care; (2) a deviation from that standard of care; and (3) that the deviation proximately caused the injury."[172] In theory, the threat of medical malpractice suits encourages clinicians to identify and meet this "standard of care" to avoid potential liability, thus protecting patients. In a nascent industry, however, there may not be a discernible standard of care. This uncertainty can have several effects on the power of tort law to shape PAT.

On one hand, clinicians may be wary of unintentionally deviating from a hazy standard of care. Fear of litigation may dissuade would-be psychedelic therapists from

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[164] *Id.* at 2.

[165] *Id.* at 3.

[166] *Id.* at 1–2.

[167] *Id.* at 3.

[168] MAPS PROTOCOL, *supra* note 62, at 33. Note that therapists work in pairs, but only one of the therapists needs to be licensed—the other can work under the licensed therapist's supervision.

[169] CAL. BUS. & PROF. CODE § 4999.32 (West 2016).

[170] CAL. BUS. & PROF. CODE § 2904 (West 2016).

[171] JOSÉ R. GUARDADO, AM. MED. ASS'N, POLICY RESEARCH PERSPECTIVES MEDICAL LIABILITY CLAIM FREQUENCY AMONG U.S. PHYSICIANS (2023).

[172] Gardner v. Pawliw, 696 A.2d 599, 608 (N.J. 1997).

entering the field.[173] Medical malpractice insurers may also recognize the risk of litigation and charge higher premiums to reflect that risk. The increased costs to providers may limit interest in joining the profession.[174] On the other hand, the fear of an unknown standard of care may put clinicians on their best behavior. A common refrain against issuing bright-line rules is that it allows the regulated party to go all the way up to the line with no fear of consequence. A cloudier standard doesn't allow for this kind of gamesmanship and may result in increased patient safety if therapists take it to mean they should err on the side of avoiding malpractice suits.

Finally, potential plaintiffs may find it difficult to bring a medical malpractice lawsuit. The plaintiff has the burden of proof to show a clinician breached a standard of care.[175] "As a general rule, the testimony of an expert witness is required in every professional negligence case to establish the applicable standard of care, whether that standard was met or breached by the defendant, and whether any negligence by the defendant caused the plaintiff damages."[176] As of right now, there are few, if any, people qualified to serve as an expert witness on the standard of care for PAT. Without a clear way to demonstrate the standard of care or show causality, a plaintiff's case may not survive. The subsequent lack of medical malpractice suits may, in turn, mean that some patients are not protected from clinician misconduct.[177]

IV. THE FEDERAL REGULATORY TOOLKIT

While FDA does not traditionally regulate the practice of medicine, in recent years it has gained more authority to oversee certain types of products and procedures post-approval. If a drug is potentially dangerous, FDA may require the manufacturer to develop and implement a REMS to protect patients.[178] Therapies to treat substance abuse disorders, specifically opioids, also grant enhanced post-approval authority to the federal government.[179] Both frameworks may provide precedent for the federal government to obtain some post-approval regulatory oversight of PAT.

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[173] It may specifically discourage *current medical professionals* from joining the field. Patients would likely benefit from having therapists with experience in psychotherapy.

[174] There is also a chance that increased costs will simply be passed on to consumers, limiting access for some patients.

[175] *Id.*

[176] Scott v. Rayhrer, 185 Cal. App. 4th 1535, 1542 (Cal. Ct. App. 2010).

[177] Some acts, such as sexual assault, will give rise to liability regardless of the standard of care under a theory of *res ipsa loquitur* ("[A] plaintiff in a medical malpractice case can proceed on a *res ipsa loquitur* theory where the plaintiff offers a medical expert's opinion that the injury would not have occurred in the absence of negligence by defendant."). Sides v. St. Anthony's Med. Ctr., 258 S.W.3d 811, 813 (Mo. 2008). The concern with PAT is that a therapist's negligence may spark a "bad trip" or result in psychological damage without meeting the *res ipsa loquitur* standard. If a patient cannot show that the therapist deviated from a standard of care, there will be no liability.

[178] 21 U.S.C. § 355-1.

[179] *See infra* Section IV.B.

A. Risk Evaluation and Mitigation Strategies

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA) to expand funding and authority of the FDA.[180] Under the FDAAA, if a drug poses serious safety concerns, FDA can require a REMS to "ensure that the benefits of the drug outweigh the risks of the drug."[181] The consequences of not complying with a REMS may include "product seizure, injunction or civil money penalties."[182] These sanctions can prove costly for drug manufacturers and clinicians alike, thus encouraging strict adherence to a REMS.

The implementation and requirements of a REMS are flexible depending on the safety profile of the drug. A REMS must contain a timetable for strategy submission plus one or more "additional elements" required by the Secretary of Health and Human Services.[183] The pertinent elements that a REMS may contain include Elements to Assure Safe Use (ETASU).[184] ETASU may require that:

> (1) providers that prescribe the drug have specific training, experience, or certification;
>
> (2) providers that dispense the drugs are specially certified;
>
> (3) the drug be dispensed only in certain healthcare settings;
>
> (4) the drug be dispensed only to patients who have evidence of specific safety conditions (e.g., lab results);
>
> (5) each patient is subject to certain monitoring; and
>
> (6) each patient be enrolled in a registry.[185]

There are currently sixty-one active REMS, fifty-seven of which include ETASU.[186] The two most relevant REMS for analyzing a potential PAT REMS are those for esketamine and buprenorphine.

i. Esketamine

Esketamine is the S-enantiomer of ketamine.[187] FDA approved intranasal esketamine spray for treatment-resistant depression under the brand name Spravato in 2019.[188] Spravato is subject to a REMS that requires, among other things:

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[180] *Food and Drug Administration Amendments Act (FDAAA) of 2007*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2018), https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-amendments-act-fdaaa-2007 (last visited Apr. 28, 2023).

[181] 21 U.S.C. § 355-1.

[182] *REMS Compliance Program*, U.S. FOOD & DRUG ADMIN. (Sept. 22, 2022), https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/rems-compliance-program (last visited Apr. 28, 2023).

[183] 21 U.S.C. § 355-1(c).

[184] 21 U.S.C. § 355-1(f)(3).

[185] *Id.*

[186] *FDA Risk Evaluation and Mitigation Strategy (REMS) Public Dashboard*, U.S. FOOD & DRUG ADMIN., https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last visited Apr. 27, 2023).

[187] Luke A Jelen, Allan H. Young & James M. Stone, *Ketamine: A Tale of Two Enantiomers*, 35 J. PSYCHOPHARMACOLOGY 109, 109 (2021).

[188] *FDA Spravato News Release*, *supra* note 153.

(1) healthcare settings must be certified and enrolled in the program;

(2) clinicians must counsel patients on risks and need for monitoring;

(3) clinicians must monitor patients for two hours after dosage; and

(4) patients must be enrolled in the REMS.[189]

The goal of the Spravato REMS is to mitigate the "risk of serious adverse outcomes resulting from sedation and dissociation . . . and the potential for abuse and misuse of the drug."[190]

If one considers ketamine a psychedelic, then Spravato represents the first psychedelic to receive FDA approval to treat a mental illness. While physicians have been prescribing ketamine off-label for mental conditions for some time,[191] Spravato's approval represents a milestone in psychedelic medicine. It also sets the stage for what may be in store for FDA regulation of PAT. There is a key distinction, however, between Spravato and PAT—Spravato is not used in conjunction with psychotherapy and therefore does not fall under the umbrella of PAT.

Spravato is offered as a standalone drug. It is self-administered by a patient in a certified healthcare setting under the supervision of a certified healthcare professional.[192] The supervising clinician monitors the patient for two hours to mitigate the risk of excess sedation caused by the drug, but the clinician does not provide therapy during this time.[193] There is no question regarding FDA's authority in this realm. Spravato is a drug. FDA regulates drugs. FDA has the explicit authority to require a REMS for drugs that may be unsafe.[194] The regulatory quagmire of PAT occurs when a treatment modality is not simply a drug, but a drug *plus psychotherapy* and Spravato treatment does not include a psychotherapy component. In this regard, Spravato shows us the floor for FDA regulation of PAT, but almost certainly not the ceiling.

Based on the Spravato REMS, a REMS for PAT may require that psychedelic therapy is only administered by specially trained therapists, in a certified psychedelic therapy center, to patients that have enrolled in a registry. It may require the therapist to monitor the patient throughout the duration of the psychedelic experience. All those requirements fall under ETASU and are present in the Spravato REMS.[195] Applying a REMS to the psychotherapy component of PAT goes beyond the scope of the Spravato REMS—Spravato treatment does not contain psychotherapy at all.

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[189] U.S. FOOD & DRUG ADMIN., RISK EVALUATION AND MITIGATION STRATEGY (REMS) DOCUMENT: SPRAVATO (ESKETAMINE) (2022), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Spravato_2022_01_03_REMS_Document.pdf (last visited Apr. 27, 2023) [hereinafter SPRAVATO REMS].

[190] *FDA Spravato News Release*, *supra* note 153.

[191] *See supra* Section III.a.i.

[192] *See* SPRAVATO REMS, *supra* note 189.

[193] *FDA Spravato News Release*, *supra* note 153 ("Because of the risk of sedation and dissociation, patients must be monitored by a health care provider for at least two hours after receiving their Spravato dose.").

[194] 21 U.S.C. § 355-1(a)(1).

[195] 21 U.S.C. § 355-1(f)(3); SPRAVATO REMS, *supra* note 189.

ii. Buprenorphine

Buprenorphine is a synthetic opioid that can be used to treat acute pain and opioid use disorder (OUD).[196] Several buprenorphine-containing transmucosal products used to treat OUD are subject to a REMS.[197] Buprenorphine may also be used in medication-assisted treatment as part of a specific Opioid Treatment Program (OTP)—commonly referred to as "methadone clinics"—under 42 C.F.R. Part 8.[198] When buprenorphine is part of an OTP it is not subject to the REMS "because the care of OTP patients is subject to specific requirements."[199] When used to treat OUD outside of a registered OTP, however, buprenorphine is subject to a REMS.

The two most relevant portions of the buprenorphine REMS are the "[a]ssessment of whether patient is receiving the necessary psychosocial support" and "[v]erification that the patient meets the diagnostic criteria for opioid dependence."

Like other drugs utilized in medication-assisted treatment, "[b]uprenorphine should be part of a comprehensive management program that includes psychosocial support."[200] The protocol for that psychosocial support is not strictly defined—a loose definition allows for flexible treatment of a specific patient's situation and access to resources. In fact, patients can receive buprenorphine even in the absence of such psychosocial support.[201]

While psychosocial support can drastically improve treatment outcomes, the unfortunate reality is that some Americans—particularly those living in rural areas—do not have access to the type of behavioral therapy services typically used in conjunction with buprenorphine.[202] Some of these rural areas also have the highest rates of opioid misuse.[203] To ensure that these patients are not denied treatment simply because their locality does not have specific resources, the Substance Abuse and Mental Health Services Administration (SAMSHA) recommends that doctors prescribe buprenorphine despite the lack of psychosocial support.[204] The REMS does

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[196] Rachna Kumar, Omar Viswanath & Abdolreza Saadabadi, *Buprenorphine*, STATPEARL (Apr. 29, 2023), https://www.ncbi.nlm.nih.gov/books/NBK459126/ (last visited Apr 30, 2023).

[197] *Home*, BTOD REMS, https://btodrems.com/ (last visited Apr. 27, 2023) ("BTOD" means "buprenorphine-containing transmucosal products for opioid dependence.") [hereinafter *Background on BTOD REMS*]. Other forms of buprenorphine are not subject to this REMS, but for simplicity I refer only to "buprenorphine" for the rest of the paper.

[198] See *infra* Section IV.B.i. for a discussion of medication-assisted treatment and OTPs.

[199] U.S. FOOD & DRUG ADMIN., SUBOXONE & SUBUTEX REMS 1 (2017), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Suboxone_Subutex_2017-09-19_Full.pdf.

[200] SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADMIN., FACTS ABOUT BUPRENORPHINE 1, https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf (last visited Apr. 27, 2023).

[201] *Id.* ("Treatment should not be withheld in the absence of psychosocial support.").

[202] *See* C. Holly A. Andrilla, *Barriers Rural Physicians Face Prescribing Buprenorphine for Opioid Use Disorder*, 15 ANNALS FAM. MED. 359, 361 (2017) (Rural physicians that do not prescribe buprenorphine often cite as a cause the "lack of available mental health or psychosocial support services.").

[203] Katherine M. Keyes, Magdalena Cerdá, Joanne E. Brady, Jennifer R. Havens & Sandro Galea, *Understanding the Rural–Urban Differences in Nonmedical Prescription Opioid Use and Abuse in the United States*, 104 AM. J. PUB. HEALTH e52, e52 (2014) ("[D]eath and injury from nonmedical prescription opioid misuse are concentrated in states with large rural populations, such as Kentucky, West Virginia, Alaska, and Oklahoma.").

[204] *See* FACTS ABOUT BUPRENORPHINE, *supra* note 200 ("Treatment should not be withheld in the absence of psychosocial support.").

not even explicitly require psychosocial support; it only requires prescribers to "*assess* whether the patient is receiving counseling/psychosocial support . . . and if not, *encourage* them to do so."[205]

On its face, the requirement that a patient meets specific diagnostic criteria is more restrictive than the psychosocial support requirement. The diagnosis requirement, strictly enforced, would prevent clinicians from prescribing buprenorphine for most off-label use.[206] Buprenorphine, however, is prescribed off-label. In fact, the Department of Veterans Affairs provides guidance for how often one should take Suboxone and Subutex—two products that are subject to the buprenorphine REMS—"off-label for primary pain."[207] One could make the semantic argument that the REMS eis specifically for "buprenorphine-containing transmucosal products for opioid dependence" (BTOD) and is therefore only applicable when buprenorphine is prescribed to treat OUD. BTOD has opioid dependence in the name and therefore prescribing transmucosal buprenorphine for a different indication is off-label use of the *transmucosal buprenorphine product* but does not violate the BTOD REMS. That argument is unconvincing. The standalone REMS for Suboxone does not contain any language that suggests it is specifically aimed at treatments for OUD, yet it also contains the requirement that a "patient meets the diagnostic criteria for opioid dependence."[208] It appears, then, that the REMS diagnosis requirement is also not strictly enforced. The government is aware that buprenorphine is prescribed to patients that do not meet the diagnostic criteria, and rather than prohibit such use, it provides guidance.

If either of these requirements—the psychosocial support or diagnosis—were applied to PATs and enforced to the letter, FDA would have wide jurisdiction over the treatment. If FDA required "the necessary psychosocial support" to administer PAT and defined such support as "support provided in the manner provided by a specific therapist training manual," then therapists would be required to stick to that manual. However, enforcing such a requirement may be moot. Psychedelic therapy manuals

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[205] *See Prescribers*, BTOD REMS, https://btodrems.com/prescribers (last visited Apr. 27, 2023) (emphasis added).

[206] Unless, of course, the patient met the diagnostic criteria for opioid dependence, yet the clinician was prescribing buprenorphine to treat something other than OUD.

[207] U.S. DEP'T VETERANS AFFS., BUPRENORPHINE FOR OPIOID USE DISORDER (2021), https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/IB_1498_Provider_BupforOUD.pdf; *see also* U.S. DEP'T VETERANS AFFS., BUPRENORPHINE FORMULATIONS FOR CHRONIC PAIN MANAGEMENT IN PATIENTS WITH OPIOID USE DISORDER OR ON LONG-TERM OPIOID THERAPY WITH PHYSIOLOGIC TOLERANCE 4, https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Buprenorphine_Formulations_for_Pain_Management_RFU_Rev_APR23.pdf (noting that Suboxone and Subutex are used off-label) (last visited Apr. 27, 2023); ADAM J. GORDON, PROVIDERS CLINICAL CARE SYS., THE OFF-LABEL USE OF SUBLINGUAL BUPRENORPHINE AND BUPRENORPHINE/NALOXONE FOR PAIN (2022), https://pcssnow.org/wp-content/uploads/2014/02/PCSS-MATGuidanceOff-label-bup-for-pain.Gordon.pdf (last visited Apr. 27, 2023) (laying out general principles and challenges of off-label buprenorphine); Daniel M. Strickland, *Off Label Use of Buprenorphine for Chronic Pain*, 4 MEDLIFE CLINICS 32 (2022), https://www.medtextpublications.com/open-access/off-label-use-of-buprenorphine-for-chronic-pain-1189.pdf (last visited Apr. 27, 2023) (speculating on reasons that off-label buprenorphine isn't more common; interestingly, it doesn't mention REMS as one of the challenges).

[208] *See* SUBOXONE & SUBUTEX REMS, *supra* note 199, at 2. Note: this REMS is now inactive but was last revised in September 2017, after the last revision of the BTOD REMS in January 2017. *Background on BTOD REMS*, *supra* note 197.

tend to allow for—even demand—therapist flexibility to tailor therapy to each individual patient and psychedelic experience.[209]

The requirement for specific diagnostic criteria could also limit off-label use. For example, a REMS could require that a patient have a diagnosis for PTSD to receive MDMA-assisted therapy. If a therapist wanted to administer the therapy to a patient with a different condition, such as anxiety, they would have to wait for the REMS to be updated or for FDA to approve MDMA-assisted therapy for anxiety.[210] Currently, many drugs are used off-label—despite well-supported efficacy—because it is not cost-effective to obtain FDA approval for the off-label use.[211] Applying a different standard to PAT may prevent some patients from receiving lifesaving care.

B. MATs

Medication-assisted treatment (MAT) for OUD is another example of a possible federal regulatory scheme for PAT.[212] MATs combine FDA-approved medication with counseling and behavioral therapies.[213] Administration of MATs, however, falls under the jurisdiction of SAMHSA rather than FDA.[214] There are three drugs approved for use in MATs: methadone, buprenorphine, and naltrexone.[215] Methadone and buprenorphine are Schedule II and III controlled substances, respectively, under the CSA.[216] MATs, therefore, involve a tapestry of federal regulation including FDA, SAMHSA, and DEA.

Like PAT, MAT bestows a considerably increased benefit through the conjunction of drug and therapy. While a clinician may treat a patient's OUD using medication alone, "medication treatment is most effective when it is administered as part of a cognitive behavioral approach."[217] Michael Botticelli, former Director of the Office of

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[209] *See supra* note 60 and accompanying text.

[210] MAPS is currently testing MDMA-assisted therapy for social anxiety in autistic adults. *See A Placebo-Controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA-Assisted Therapy for Social Anxiety in Autistic Adults (MAA-1)*, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUDS., https://maps.org/mdma/anxiety/autism/ (last visited Apr. 27, 2023).

[211] Christopher M. Wittich, Christopher M. Burke & William L. Lanier, *Ten Common Questions (and Their Answers) About Off-Label Drug Use*, 87 MAYO CLINIC PROC. 982, 985 (2012) ("Obtaining a new FDA approval for a medication can be costly and time-consuming . . . [and] revenues for the new indication may not offset the expense and effort of obtaining approval.").

[212] 42 C.F.R. § 8.1.

[213] *Information About Medication-Assisted Treatment (MAT)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/information-drug-class/information-about-medication-assisted-treatment-mat (last visited Apr. 27, 2023).

[214] 42 C.F.R. § 8.1 (2020). ("[A] practitioner who intends to dispense opioid drugs in the treatment of opioid use disorder must first obtain from . . . [SAMSHA] a certification that the practitioner is qualified under the Secretary's standards and will comply with such standards.").

[215] *Information about Medication-Assisted Treatment (MAT)*, *supra* note 213.

[216] U.S. DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET: METHADONE (2020), https://www.dea.gov/sites/default/files/2020-06/Methadone-2020.pdf; U.S. DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET: BUPRENORPHINE (2022), https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf.

[217] Marc A. Schuckit, *Treatment of Opioid-Use Disorders*, 375 NEW ENG. J. MED. 357, 362 (2016); *see also Drugs, Brains, and Behavior: The Science of Addiction*, NAT'L INST. ON DRUG ABUSE 24 (July 2018), https://www.camas.wednet.edu/Camas2016/wp-content/uploads/2019/01/ScienceOfAddiction.pdf (last visited Apr. 27, 2023) ("Medications are used to help people detoxify from drugs, although detoxification is not the same as treatment and is not sufficient to help a person recover. Detoxification alone without subsequent treatment generally leads to resumption of drug use.").

National Drug Control Policy, takes that claim a step further, stating "[medication-assisted treatment] should not be construed to mean that medication merely 'assists' psychosocial services, but is itself a *central element* of the MAT evidence-based practice."[218] Abram Hoffer, speaking about the early days of psychedelic therapy, had a similar comment: "[f]rom the first, we considered not the chemical, but the experience as a *key factor* in therapy."[219] While MATs improve the efficacy of treatment, their history is rooted in drug safety.

In the 1960s, physicians began using methadone as a replacement drug for patients with heroin addiction.[220] Methadone has a long half-life—the length of time a drug stays in the body—and a large accumulation can be fatal.[221] To protect patients from potentially dangerous overuse of methadone, in 1972 FDA proposed new regulations on the drug.[222] At the time, the new regulations were seen as an overreach of FDA authority into governing the practice of medicine by telling doctors how to use and prescribe a medicine.[223] Most requirements went no further than restrictions that would be permissible under a modern-day REMS, such as restricting who could take methadone at home or requiring clinics and hospitals to obtain certification in order to dispense methadone.[224]

The regulations also specified "the minimum amount of counseling to be provided."[225] The minimal counseling requirement may provide a greater precedent for FDA to assert authority over the psychotherapy component of PAT. Similar to the current buprenorphine REMS, however, the counseling requirements did not require specific types of therapy.[226] New drug compounds used in MAT don't contain the same risk profile as methadone, and subsequent research has turned the focus toward efficacy rather than simply safety.[227]

Modern MAT regulation can take a variety of forms. A technical report prepared for the Department of Health and Human Services identified twelve different

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[218] Memorandum from Michael P. Botticelli, Director, Exec. Off. of the President, Off. of Nat'l Drug Control Pol'y to Heads of Exec. Dep'ts and Agencies (Jan. 9, 2017), https://www.opioidlibrary.org/wp-content/uploads/2019/08/ONCP_Language.pdf (emphasis added).

[219] POLLAN, *supra* note 3, at 149 (emphasis added).

[220] Katherine Drabiak, *Expanding Medication Assisted Treatment is Not the Answer: Flaws in the Substance Abuse Treatment Paradigm*, 21 DEPAUL J. HEALTH CARE L. 1, 36 (2019).

[221] *Id.* at 39.

[222] Jerome H. Jaffe & Charles O'Keeffe, *From Morphine Clinics to Buprenorphine: Regulating Opioid Agonist Treatment of Addiction in the United States*, 70 DRUG & ALCOHOL DEPENDENCE S3, S5 (Supp. 2003).

[223] *Id.* ("Those conditions represented a substantial and unprecedented departure from the usual practice of allowing licensed physicians to use their own professional judgment, guided by a drug's labeling, to determine how to prescribe a medication.").

[224] *Id.*

[225] *Id.*

[226] *See supra* Section IV.A.ii.

[227] *See* Dave Marteau, Rebecca McDonald & Kamlesh Patel, *The Relative Risk of Fatal Poisoning by Methadone or Buprenorphine Within the Wider Population of England and Wales*, BMJ OPEN, May 29, 2015, at 1, 4 ("Dose for dose, methadone was found to present a significantly greater risk of fatal overdose to the wider population than buprenorphine.").

"representative models" of MAT.[228] Guidance allows for flexibility in choosing counseling and therapy techniques:

> Ideally, providers should tailor the type and intensity of psychosocial support to the patient's needs and preferences across the phases of treatment. Behavioral health services within MAT can take many forms, including individual counseling, group therapy, support groups, family therapy, and peer services. These services can also be delivered by a wide range of providers, such as social workers, counselors, peer recovery support specialists, outreach workers, physicians, nurses, and advanced practice professionals.[229]

Little to no therapy may also be an option. Some patients, particularly those in rural areas, may not have access to behavioral health services.[230] In that case, "it is important to increase access to medications to treat [OUD] even when availability of behavioral health services is limited."[231]

MAT, like the buprenorphine REMS, may serve as precedent for enabling the federal government to require a minimum amount of therapy and controlling general themes of the therapy in PAT. Importantly, guidance from several documents that allow for—even recommend—flexible therapy provide support for MAPS non-directive approach that draws from several classical psychotherapy techniques and encourages spontaneity.[232] On the other hand, unlike in the treatment of OUD, it would not be workable to provide little to no therapy—even in areas where such services are hard to come by. Unsupervised psychedelic use can be dangerous, and the therapy component of PAT is critical to its efficacy. The federal government should not suggest clinicians provide a novel psychedelic treatment method without the crucial therapy component even if that would restrict patient access to PAT.

i. Other Actors

State governments also play a role in MAT regulation. MAT is sometimes administered via a federally regulated opioid treatment program (OTP). Under federal law, OTPs must provide, at minimum, "adequate medical, *counseling*, vocational, educational, other assessment and treatment services."[233] But federal regulations only provide a floor for OTP governance. State and local governments are free to impose stricter regulations on OTPs.[234] Currently, nineteen states impose barriers to opening

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[228] PAC. NW. EVIDENCE-BASED PRAC. CTR., TECHNICAL BRIEF: MEDICATION-ASSISTED TREATMENT MODELS OF CARE FOR OPIOID USE DISORDER IN PRIMARY CARE SETTINGS 9 (2016), https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/opioid-use-disorder_technical-brief.pdf.

[229] *Understanding the Components of Medication-Assisted Treatment*, AGENCY FOR HEALTHCARE RSCH. & QUALITY, https://integrationacademy.ahrq.gov/products/playbooks/opioid-use-disorder/plan-integrate-mat-for-oud/understanding-components-of-mat (last visited Apr. 27, 2023).

[230] These are the same concerns described in buprenorphine guidance—which is one of the compounds used in MAT. *See supra* Section IV.A.ii.

[231] *Understanding the Components of Medication-Assisted Treatment*, *supra* note 229.

[232] *See supra* note 62 and accompanying text.

[233] 42 C.F.R. § 8.12(f)(1) (2016) (emphasis added).

[234] 42 C.F.R. § 8.11(f)(1) (2016) ("OTPs shall comply with all pertinent State laws and regulations. Nothing in this part is intended to limit the authority of State and, as appropriate, local governmental entities to regulate the use of opioid drugs in the treatment of opioid addiction.").

new OTPs within their state.[235] Wyoming does not have a single OTP but has almost 100 facilities that prescribe buprenorphine for use in MAT.[236]

If a similar system is applied to PAT (i.e., one that provides a federally mandated floor but allows states to impose their own restrictions), there will almost certainly be differential regulation between states.[237] If Congress decides that state overregulation of PAT is a threat to patient health or freedom, such regulation could possibly be barred via preemption.[238] In the case of OTPs, however, federal regulation specifically carves out authority for additional state regulation.[239]

OUD treatment is shaped by non-governmental actors as well. In 2015, the American Society of Addiction Medicine (ASAM) published Practice Guidelines for using methadone and other medications to treat OUD.[240] They recommended the use of "psychosocial treatment . . . with any pharmacological treatment of [OUD]."[241] The psychosocial treatment should include "a psychosocial needs assessment, supportive counseling, links to existing family supports, and referrals to community services."[242] Rather than recommend a specific type or school of psychosocial treatment, the document notes that "[f]urther research is needed to identify the comparative advantages of specific psychosocial treatments."[243]

The 2019 update to the ASAM recommendations notes that psychosocial treatment can be "provided using a variety of approaches in various milieus" and "should be individualized to each patient."[244] It also notes further research regarding comparative

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[235] *Overview of Opioid Treatment Program Regulations by State*, PEW CHARITABLE TRS. (Sept. 19, 2022), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2022/09/overview-of-opioid-treatment-program-regulations-by-state (last visited Apr. 27, 2023).

[236] *Medication-Assisted Treatment (MAT)*, WYO. PREVENTION DEPOT, https://www.wyomingpreventiondepot.org/rxtoolkit/best-practices/medication-assisted-treatment-mat/ (last visited Apr. 27, 2023).

[237] If regulation of psychedelic-assisted therapy is left to the states, even in part, we may see access inequality, particularly for less wealthy citizens of states that impose higher restrictions. Women in states where abortion is illegal or highly restricted are facing a similar problem. *See, e.g.*, *Abortion Out of Reach: The Exacerbation of Wealth Disparities After Dobbs v. Jackson Women's Health Organization*, GUTTMACHER INST. (Jan. 2023), https://www.guttmacher.org/article/2023/01/abortion-out-reach-exacerbation-wealth-disparities-after-dobbs-v-jackson-womens (last visited Apr. 27, 2023) ("[W]ealth disparities have meant that access to abortion in the United States has been bleak for millions of Americans."). No one should be surprised by this outcome; Justice Kagan predicted such disparity in her *Dobbs* dissent. Dobbs v. Jackson Women's Health Org., 142 S. Ct. 2228, 2318 (2022) (Kagan, J., dissenting) ("Above all others, women lacking financial resources will suffer from today's decision.").

[238] *See infra* notes 277–279 and accompanying text.

[239] *See supra* note 234.

[240] Kyle Kampman & Margaret Jarvis, *American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use*, 9 J. ADDICTION MED. 358 (2015).

[241] *Id.* at 363.

[242] *Id.*

[243] *Id.* at 366.

[244] WHITE ET AL., AM. SOC'Y OF ADDICTIVE MED., THE ASAM NATIONAL PRACTICE GUIDELINE FOR THE TREATMENT OF OPIOID USE DISORDER: 2020 FOCUSED UPDATE 48, https://sitefinitystorage.blob.core.windows.net/sitefinity-production-blobs/docs/default-source/guidelines/npg-jam-supplement.pdf?sfvrsn=a00a52c2_2 (last visited June 22, 2023).

advantages and recommends specific components to the psychosocial treatment but does not recommend a full treatment therapy.[245]

This guidance tracks closely with current suggestions for PAT. All therapy manuals contain a few uniform, specific recommendations—such as providing therapy in a comfortable room to manage the "setting" of the experience.[246] Beyond that, manuals and protocols encourage a flexible approach so therapy can be tailored to each individual experience.[247] While each FDA trial recommends a specific manual provided by the trial's sponsor, there are quite a few non-trial manuals to inspire a budding psychedelic therapist.[248] Finally, some people are critical of the flexible nature and the lack of rigorous testing of therapy modalities.[249] As PAT becomes more and more popular, medical societies and other professional organizations will likely start to weigh in on recommendations and best practices. Such advice will supplement the regulations enacted by the federal and state governments.

MATs and OTPs may serve as a benchmark for creating a federal system that makes space for supplemental state regulation. In any regulatory system, the primary goal should be to promote safe and effective treatment. To quote the Institute of Medicine: "Current policy, in the committee's view, puts too much emphasis on protecting society from methadone, and not enough on protecting society from the epidemics of addiction, violence, and infectious diseases that methadone can help reduce."[250] We should view psychedelics in the same light.

President Nixon's war on drugs demonized psychedelics in the eyes of many Americans. Nancy Reagan picked up the torch a decade later with her "Just Say No" campaign.[251] Political pressure coupled with shoddy science led to a moral panic against psychedelics, particularly LSD.[252] To be sure, rampant, unsupervised use of psychedelics can be dangerous to both individuals and society. So can methadone and other opioids.[253] That does not mean that they can't be helpful in the right setting.[254] It only emphasizes "the importance of finding the proper context, or container, for these powerful chemicals and experiences."[255] A regulatory framework that recognizes the great potential—and potential risk—of these substances can strike a balance between patient access and community health.

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[245] *Id.*

[246] *See, e.g.*, MITHOEFER, *supra* note 59, at 12 (describing the treatment room for MDMA therapy).

[247] *See supra* note 62 and accompanying text.

[248] *See, e.g.*, Blewett & Chwelos, *supra* note 157.

[249] *See supra* note 60 and accompanying text.

[250] INST. OF MED., FEDERAL REGULATION OF METHADONE TREATMENT 3 (Richard A. Rettig & Adam Yarmolinksy eds., 1995).

[251] *Her Causes*, RONALD REAGAN PRESIDENTIAL FOUND. & INST., https://www.reaganfoundation.org/ronald-reagan/nancy-reagan/her-causes/ (last visited Apr. 27, 2023).

[252] *See generally* Abigail M. Stanger, *"Moral Panic" in the Sixties: The Rise and Rapid Declination of LSD in American Society*, 1 CARDINAL EDGE, no. 2, 2021, at 1.

[253] Opioids, unlike psychedelics, have the added detriment of being highly addictive. David Nichols, *Psychedelics*, 68 PHARMACOLOGICAL REV. 264, 274 (2016) ("These substances do not lead to addiction or dependence and are not considered to be reinforcing.").

[254] POLLAN, *supra* note 3, at 210–11.

[255] *Id.* at 215.

V. A FEDERALIST SOLUTION

PAT, like any novel and potentially dangerous medical treatment, demands regulation. The social stigma and potential risks associated with psychedelics coupled with their vast potential as a tool to help solve America's mental health crisis raises the regulatory stakes. If PAT is underregulated and patients experience widespread adverse events, political pressures may force psychedelics back underground, preventing millions of Americans from accessing potentially lifesaving treatment. Overregulation can also impact patient access—a state government could ban PAT outright, or medical professionals may be dissuaded from becoming psychedelic therapists due to regulatory hurdles. It is necessary to find a balance of PAT regulation that promotes three key factors: safety, efficacy, and access.

Crafting a regulatory framework that balances these factors for any new product is a challenge. The case of PAT is further complicated by the hazy jurisdictional definition of federal and state authority over the substance-plus-protocol treatment model. An unclear regulatory landscape is almost certain to fail at promoting one (or more) of the factors. As FDA prepares to approve the first PAT for widespread use, we need to avoid regulatory confusion before we set an impossibly harsh precedent for PAT regulation or patients get hurt. We already have a federalist model for medical regulation—where the federal government chiefly regulates drug products and state governments regulate the application of treatment. Several recent developments have blurred that line, which has led to the federal and state governments working more cooperatively to oversee some therapies. For current treatment modalities, that model is working. OTPs provide safe and effective patient care across the country through a mix of state and federal regulation.

PAT, with its unique combination of drug and required therapy, demands a novel regulatory approach, but we are not without precedent. We can borrow from several examples of current medical regulation to craft a regulatory landscape for PAT that involves the federal government, state governments, and other stakeholders.

A. The Federal Role

As always, the federal government should govern drug products via FDA. FDA should run the approval process to ensure that treatments are safe and effective before doctors are allowed to prescribe them to patients. FDA should also continue to regulate post-approval labeling, branding, and marketing. One of the biggest dangers of taking illegal or unregulated drugs is the risk of adulteration.[256] FDA oversight will ensure the quality and purity of the psychedelic substances used in PAT. FDA oversight in this manner is standard for all drug products. Beyond run-of-the-mill drug regulation, however, FDA should require a REMS for PAT.[257]

i. REMS

A REMS for PAT should include three key requirements: certification for therapists, pharmacies, and healthcare settings; patient safety screening; and patient

[256] *See generally* Vanila M. Singh, Thom Browne & Joshua Montgomery, *The Emerging Role of Toxic Adulterants in Street Drugs in the US Illicit Opioid Crisis*, 135 PUB. HEALTH REPS. 6 (2020) (analyzing the danger of adulterants in illicit opioids).

[257] Alternatively, Congress could enact legislation creating a framework for regulating PAT or SAMHSA could craft PAT-specific regulations in the same vein as those for OTPs.

enrollment. Due to the nature of psychedelic experiences, the setting in which PAT is administered is fundamental to the safety and efficacy of the treatment.[258] Clinical trials for PAT take place in curated rooms to control the "setting" component of the psychedelic experience.[259] A REMS that requires healthcare setting certification empowers FDA to restrict the post-approval administration of PAT to similar settings, in which PAT was both safe and effective during trials.

Therapists that provide PAT should also be certified under a REMS. The MAPS/MDMA trial protocol recommends therapists be familiar with over a dozen different therapy techniques including cognitive processing, psychosynthesis, and Jungian psychology.[260] The REMS could require future therapists be trained and certified to provide the same level of care. This type of restriction would not grant FDA exclusive jurisdiction over therapist certification; the MAPS protocol requires at least one therapist be licensed by a state board.[261] If that requirement continues, states will license therapists that must comply with a federal REMS while providing PAT.[262]

A certification requirement for pharmacies that dispense the psychedelics would also be useful to mitigate psychedelic use outside of a therapeutic setting. Specifically, a potential REMS could require dispensation (and consumption) only in a certified clinic. Restrictions on drug dispensation can prevent diversion—when drug products exit the regulated path from manufacturer to consumer.[263] Taking psychedelic drugs out of context—without professional supervision—can be more dangerous than most psychedelic supporters would like to believe.[264] Preventing diversion limits the prevalence of unsupervised psychedelic experiences and thereby increases safety.[265]

Patient screening is an integral part of the general PAT model and a REMS requirement for screening could dramatically increase patient safety.[266] Patients with a family or personal history of cardiac or certain psychiatric conditions may be at extreme risk if they take psychedelics.[267] The MAPS protocol requires intensive patient screening before moving into the actual PAT. A REMS can require that screening protocols remain in place after approval.[268] A screening requirement prevents patients with high-risk profiles from receiving PAT. While this restriction

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[258] *See supra* notes 44–48 and accompanying text.

[259] *See supra* note 245 and accompanying text.

[260] *See* MITHOEFER, *supra* note 59, at 10.

[261] *See* MAPS PROTOCOL, *supra* note 62, at 33.

[262] The only alternative to this framework would require the federal government to develop a licensing program for therapists.

[263] *See generally* DEP'T OF HEALTH & HUM. SERVS., DRUG DIVERSION: WHAT IS A PRESCRIBER'S ROLE IN PREVENTING THE DIVERSION OF PRESCRIPTION DRUGS? (2016), https://www.hhs.gov/guidance/sites/default/files/hhs-guidance-documents/DrugDiversionFS022316.pdf.

[264] *See* Cohen & Ditman, *supra* note 24.

[265] Preventing dangerous, unsupervised psychedelic use has the added benefit of reducing social and political blowback of psychedelic therapies. One can imagine a "recreational trip gone wrong" headline blasted across the country leading to calls to recriminalize psychedelics.

[266] *See supra* notes 64–66 and accompanying text.

[267] *Id.*

[268] 21 U.S.C. § 355-1(f)(3)(D) (One permissible element to assure safe use is requiring "the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results.").

limits access for some patients, it does so to ensure patient safety. REMS are designed to do exactly that.[269]

The REMS should not, however, require specific diagnostic criteria as contained in the buprenorphine REMS.[270] There is an ever-growing body of evidence that PAT can be useful for a variety of mental illnesses.[271] Requiring a specific diagnosis prevents patients with other conditions from accessing PAT, even if there is evidence that PAT is an effective treatment.[272] There is even support for beneficial outcomes in "healthy normals"—people without a specific mental health diagnosis.[273] A REMS is chiefly concerned with patient safety.[274] Preventing a patient from receiving PAT because an FDA trial hasn't shown PAT to be *effective* for their condition does not necessarily comport with the spirit of a REMS.[275] If FDA is willing to update the REMS diagnosis requirement to include new diagnoses after non-FDA studies—or early-stage trials—show evidence of efficacy, then this requirement may not be entirely restrictive. Barring that level of flexibility, a diagnosis requirement will restrict patient access without improving safety, which is not in compliance with the spirit of a REMS.

Finally, the REMS should require a patient registry. Psychedelic studies have a history of downplaying—or outright omitting—the risk and prevalence of adverse events.[276] Requiring a patient registry mitigates the risk that adverse events go undetected.

There are several other roles that FDA can play beyond directly overseeing aspects of PAT regulation, including incentivizing information generation and preemption of some state restrictions. Some legal scholars suggest that FDA has become an information-generating agency rather than a consumer protection agency.[277] By

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[269] *Risk Evaluation and Mitigation Strategies: REMS*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (last visited Apr. 27, 2023) ("A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program.").

[270] *See Background on BTOD REMS*, *supra* note 197.

[271] Alan K. Davis, Frederick S. Barrett, Darrick G. May, Mary P. Cosimano, Nathan D. Sepeda, Matthew W. Johnson, Patrick H. Finan & Roland P. Griffiths, *Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial*, 78 JAMA PSYCHIATRY 481 (2021); Danilo De Gregorio, Argel Aguilar-Valles, Katrin H. Preller, Boris Dov Heifets, Meghan Hibicke, Jennifer Mitchell & Gabriella Gobbi, *Hallucinogens in Mental Health: Preclinical and Clinical Studies on LSD, Psilocybin, MDMA, and Ketamine*, 41 J. NEUROSCIENCE 891 (2021); Charles L. Raison, Rakesh Jain, Andrew D. Penn, Steven P. Cole & Saundra Jain, *Effects of Naturalistic Psychedelic Use on Depression, Anxiety, and Well-Being: Associations With Patterns of Use, Reported Harms, and Transformative Mental States*, FRONTIERS PSYCHIATRY, Mar. 15, 2022, at 1.

[272] *But see supra* notes 200–207 and accompanying text. Even if the requirement is not enforced, however, listing it on the REMS may discourage clinicians from providing off-label PAT, thus limiting patient access.

[273] *See generally* Sam Gandy, *Psychedelics and Potential Benefits in "Healthy Normals": A Review of the Literature*, 3 J. PSYCHEDELIC STUDS. 280 (2019).

[274] *See Risk Evaluation and Mitigation Strategies: REMS*, *supra* note 269.

[275] "REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication"—not to improve or ensure the efficacy of treatment. *Id.*

[276] *See, e.g.*, Rick Doblin, *Pahnke's 'Good Friday Experiment': A Long-Term Follow-Up and Methodological Critique*, 23 J. TRANSPERSONAL PSYCHOLOGY 1, 24 (1991) (discussing omitted adverse events in the reports of the famous Good Friday psilocybin experiment in Marsh Chapel). For more information on the Good Friday Experiment, see POLLAN, *supra* note 3, at 45–46.

[277] *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 370 (2007).

requiring data from extensive trials, FDA forces trial sponsors to publish information about the safety and efficacy of a therapy.

Even if FDA does not regulate the psychotherapy portion of PAT, FDA trials will have a specific psychotherapy protocol. As new drugs and therapies make their way through the trials, state licensing boards, medical associations, and other actors will get access to useful data about safety and efficacy of the chosen therapy protocols.[278]

FDA approval might also preempt excessive state regulation that may decrease—or even outright ban—patient access to PAT. While states can typically supplement federal medical regulation through a variety of mechanisms, several attempts to restrict the availability of specific FDA-approved drugs have been enjoined by federal courts.[279] This issue is currently before the courts once again following dozens of state bans on the abortion drug mifepristone in the wake of the *Dobbs*[280] decision.[281] As of this writing, two different judges have come to completely opposite conclusions, creating a tangled mess of judicial and regulatory outlooks. Future scholarship will have to apply federal preemption jurisprudence to PAT after the mifepristone litigation has been resolved. For now, this paper will address the permissive aspects of state regulation, which will hopefully increase safety and efficacy of PAT.

B. State Role

State governments can supplement federal regulation and thereby improve patient safety.[282] The most useful state government addition to PAT regulation is something they already provide for other FDA-regulated products: licensing the healthcare providers that facilitate PAT.

While FDA can mandate specific training or certification through a REMS, the federal government does not actually license healthcare professionals.[283] The MAPS/MDMA protocol explicitly acknowledges this distinction by requiring one of the therapists to be licensed by the relevant state and local authorities.[284] This distinction should be preserved following FDA approval of PAT. To provide PAT within a state, a therapist should be licensed by that state's government. The type of therapist and licensing is up to the state.

Most states grant different licenses for specific types of therapy such as educational psychology, clinical social work, and marriage and family therapy.[285] States should

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[278] Trials may adopt protocols that are already in widespread use, in which case clinicians will get more data confirming—or denying—the usefulness of that therapy protocol. The trials may choose to adopt different or slightly altered protocols which will provide even more information to the industry at large.

[279] *See, e.g.*, Zogenix, Inc. v. Patrick, No. CIV.A. 14–11,689-RWZ, 2014 WL 1454696 (D. Mass. Apr. 15, 2014) (enjoining Massachusetts' ban on Zohydro ER). For greater analysis on federal preemption of drug restrictions, see Patricia J. Zettler, Annamarie Beckmeyer, Beatrice L. Brown & Ameet Sarpatwari, *Mifepristone, Preemption, and Public Health Federalism*, 9 J.L. & BIOSCIENCES 1 (2022).

[280] Dobbs v. Jackson Women's Health Org., 142 S. Ct. 2228 (2022).

[281] All. for Hippocratic Med. v. U.S. Food & Drug Admin., No. 2:2022cv00223 (N.D. Tex. 2023); GenBioPro, Inc. v. Sorsaia, No. 3:23-cv-00058 (S.D. W. Va. 2023).

[282] We should, however, be wary of state regulation being so severe as to restrict patients from accessing PAT altogether. *See supra* note 237 and accompanying text.

[283] Even to be a physician in a Department of Veterans Affairs hospital, one must "be licensed to practice medicine, surgery, or osteopathy in a State." 38 U.S.C. § 7402(b)(1).

[284] MAPS PROTOCOL, *supra* note 62, at 33.

[285] *See, e.g.*, CAL. BUS. & PROF. CODE § 4989.13 (West 2016) (California's licensing regulations for educational psychologists); CAL. BUS. & PROF. CODE § 4991.1 (West 2016) (California's licensing

consider creating yet another licensed category—that of "psychedelic psychotherapist."[286] Of course, it may take some time to create a training and testing program for such a license, but specific training and licensure will likely promote the safety and efficacy of PAT.

Licensing requirements exist in between patient safety and access. If it is too easy to get a license, unqualified therapists may put patients at risk. If it is too difficult, there may not be enough therapists to meet demand. State licensing boards would do well to keep this balance in mind as they develop regulations for psychedelic therapists.

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These are not the only considerations for a framework to govern PAT. There are other levers for the government to pull and other stakeholders that can provide guidance. For example, medical associations will produce best practices for PAT. While nonbinding, these policies will guide therapists' decisions and may even establish a standard of care for medical malpractice claims.[287] Tort law will inevitably play a role in setting incentives for therapists.[288] While tort law is mainly derived from judge-made common law, state legislatures can shape judicial outcomes by enacting legislation that caps damages or immunizes some action from liability.[289] Insurance companies have immense power in the U.S. healthcare system and will no doubt also hold influence over the administration of PAT.[290]

These levers and stakeholders are beyond the scope of this paper, which aims to provide a general regulatory approach for PAT concerning the state and federal governments. As PAT is administered to patients outside of FDA trials, the regulatory landscape will unfold and continue to shift. Future scholarship should address the role these other stakeholders will play in the PAT regulatory framework.

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regulations for clinical social workers); CAL. BUS. & PROF. CODE § 4980.02 (West 2016) (California's licensing regulations for marriage and family therapists).

[286] Following the approval of Measure 109 in Oregon, the Oregon Health Authority (specifically, the Oregon Psilocybin Services) created a license to facilitate psilocybin experiences. The requirements for licensure are considerably lower than most psychotherapy licenses: a high school diploma, completion of a certified training program, and an examination. OR. HEALTH AUTH., PUB. HEALTH DIV., OR. PSILOCYBIN SERVS.: HOW TO BECOME A LICENSED PSILOCYBIN SERVICES FACILITATOR IN OREGON, https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/Documents/Facilitator-License-Fact-Sheet.pdf (last visited Apr. 27, 2023).

[287] *See, e.g.*, AM. MED. ASS'N, REPORT 7 OF THE COUNCIL ON MEDICAL SERVICE (A-14): COVERAGE OF AND PAYMENT FOR TELEMEDICINE, https://isb.idaho.gov/wp-content/uploads/150402_hea_materials1.pdf (last visited Apr. 28, 2023) (proclaiming to develop a policy and standard of care for telemedicine).

[288] *See supra* Section III.B.ii.

[289] *See, e.g.*, CAL. CIV. CODE § 3333.2(b)(1) (West) (California statute capping non-economic medical malpractice liability at $350,000); *see also* CAL. HEALTH & SAFETY CODE § 1799.102 (West) (California's Good Samaritan law).

[290] *See generally* Elisabeth Rosenthal, *Insurance Policy: How an Industry Shifted from Protecting Patients to Seeking Profit*, STAN. MED. MAG. (May 19, 2017), https://stanmed.stanford.edu/how-health-insurance-changed-from-protecting-patients-to-seeking-profit/ (detailing how health insurance influences the American medical system).

VI. CONCLUSION

We are at a critical moment in the story of psychedelics. After decades underground, psychedelic therapy has reentered the mainstream medical profession. PAT shows great promise in solving an intractable mental health crisis but poses novel regulatory issues. The first era of psychedelic research—and the lifesaving treatment it promised—was cut short by a society and government that didn't understand these substances.

We now have a second chance to nurture these therapies, this time armed with the knowledge of both their promise and risk. PAT's combination of substance and protocol poses a unique jurisdictional challenge for regulators, but that does not need to spell the end of the psychedelic renaissance. A federalist regulatory framework that draws on powers of FDA and state governments can enhance safety, efficacy, and access of PAT. It is imperative that authority is clearly defined and effective—to assure practitioners and investors that they are not entering a regulatory haze and to ensure patients have access to treatment while mitigating their safety risks.