

PSYCHEDELIC MEDICINE FOR MENTAL ILLNESS AND SUBSTANCE USE DISORDERS: OVERCOMING SOCIAL AND LEGAL OBSTACLES

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Mental illness is a public health crisis. Millions of Americans suffer through their days crippled by symptoms of mood, anxiety, and substance use disorders. These conditions take large social and economic tolls on our communities. However, the medicines used to treat them have remained largely unchanged for over fifty years. Though helpful to many people, traditional psychiatric drugs are often ineffective, prompting patients and physicians to seek alternatives including psychedelic compounds such as ketamine, psilocybin, MDMA, and DMT. These drugs showed therapeutic potential in the mid-twentieth century until the U.S. War on Drugs halted all research. Now, having few alternatives, scientists are revisiting psychedelics as treatments for mental illness.

This article is the first comprehensive review of the social and legal obstacles to developing psychedelic medicines. It argues that the current mental health and opioid crises demand scientific exploration of the therapeutic potential of these drugs. With subtle modifications to state and federal drug law, psychedelics could be thoroughly studied and made available to patients under carefully controlled conditions. Possible pathways include working within the existing federal regulatory framework to gain Food and Drug Administration (FDA) approval for psychedelics; removing psychedelics from the Drug Enforcement Administration (DEA) list of Schedule I controlled substances; reducing federal restrictions on psychedelics research without changing their Schedule I status; decriminalizing psychedelics at the state level; creating state-governed systems for regulating psychedelics; and implementing state-sponsored psychedelics research programs. Some approaches may be counterproductive or have counterintuitive results. Recent state level marijuana reform efforts could serve as a roadmap for amending the laws governing psychedelics. Ultimately, creative solutions that promote collaboration between state and federal government may be most likely to succeed.

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INTRODUCTION

Catherine is a healthy looking eighteen-year-old high school student. She lies on a padded pink recliner in a doctor’s office. A needle protrudes from a vein in Catherine’s left arm. Plastic tubing connects her to a small pump on an adjacent table. The doctor flips a switch and a clear fluid, the powerful psychedelic drug ketamine, is infused into Catherine’s bloodstream. Within minutes, the dark cloud of severe depression that followed her for years begins to lift. She feels calm, relaxed, and at peace. A smile creeps across her face as she becomes aware of emotions she thought she was incapable of feeling. Love, gratitude, and compassion well up within her. She cries. But unlike the tears she cried for years while depressed, these are tears of joy.

Stories like Catherine’s are becoming common in the United States. With the recognition that mental illness is a public health crisis, physicians and patients are becoming frustrated with traditional therapies. Some are turning to psychedelic compounds to help patients with major depression, anxiety, post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and substance use disorders. In the United States, nearly one in five adults will experience some form of mental illness each year.¹ Of these disorders, major depression is among the most prevalent, affecting over six percent of American adults.² OCD is another common illness that afflicts at least one per-

1. *Mental Illness*, NAT’L INST. MENTAL HEALTH, <https://www.nimh.nih.gov/health/statistics/mental-illness.shtml> (last updated Nov. 2017) (reporting that, in 2015, 17.9% of U.S. adults age eighteen years or older experienced some form of mental illness).

2. *Major Depression*, NAT’L INST. MENTAL HEALTH, <https://www.nimh.nih.gov/health/statistics/major-depression.shtml> (last updated Nov. 2017) (reporting that, in 2016, 6.7% of American adults experienced at least one major depressive episode).

cent of Americans.³ The economic impact of these disorders is staggering. According to Thomas Insel, former Director of the National Institute of Mental Health, the overall cost of mental illness to the U.S. economy may exceed \$57.5 billion per year, which could be greater than the economic impact of cancer.⁴ The World Health Organization estimates the global cost of mental illness in 2010 was nearly \$2.5 trillion, and it could exceed \$6 trillion by 2030.⁵

The financial impact of these disorders reflects the fact that current treatments are inadequate and that alternatives are urgently needed. Though television commercials for psychiatric drugs are abundant in the United States, these drugs are not as effective as one might think. For example, up to two-thirds of patients who seek medical treatment for depression may fail to respond adequately to the first medication prescribed, typically a selective serotonin reuptake inhibitor (SSRI) such as Celexa, and over thirty percent may fail to respond to multiple medications.⁶ In other words, of the U.S. patients treated with multiple trials of antidepressants, one-third may receive no benefit. The statistics are comparable for OCD, in which forty to sixty percent of patients fail to respond adequately to antidepressants.⁷

Instead of getting relief from their symptoms, millions of patients struggle through their daily routines encumbered by feelings of worthlessness, guilt, anxiety, and sadness. Their conditions also affect their

Major depressive episodes were more common for women (8.5%) than men (4.8%), and the prevalence was highest in young adults aged eighteen to twenty-five (10.9%).

3. *Obsessive-Compulsive Disorder (OCD)*, NAT'L INST. MENTAL HEALTH, <https://www.nimh.nih.gov/health/statistics/obsessive-compulsive-disorder-ocd.shtml> (last updated Nov. 2017); see also *About ADAA: Facts and Statistics*, ANXIETY & DEPRESSION ASS'N AM., <http://www.adaa.org/about-adaa/press-room/facts-statistics> (last visited Aug. 12, 2017).

4. See Thomas Insel, *The Global Cost of Mental Illness*, NAT'L INST. MENTAL HEALTH (Sept. 28, 2011), <https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2011/the-global-cost-of-mental-illness.shtml>.

5. *Id.*

6. Alison Little, *Treatment-Resistant Depression*, 80 AM. FAM. PHYSICIAN 167, 167, 170 (2009); see also George I. Papakostas et al., *Treatment of SSRI-Resistant Depression: A Meta-Analysis Comparing Within- Versus Across-Class Switches*, 63 BIOLOGICAL PSYCHIATRY 699 (2008) (explaining that many patients fail to respond to antidepressants despite increasing availability of these drugs, and describing the STAR*D trial in which less than one-third of patients achieved remission following twelve weeks of therapy with the SSRI citalopram); *Questions and Answers About the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study—All Medication Levels*, NAT'L INST. MENTAL HEALTH (Nov. 2006), <https://www.nimh.nih.gov/funding/clinical-research/practical/stard/allmedicationlevels.shtml>.

7. Stefano Pallanti et al., *Treatment Non-Response in OCD: Methodological Issues and Operational Definitions*, 5 INT'L J. NEUROPSYCHOPHARMACOLOGY 181 (2002).

family members, friends, and employers. Some sufferers become incapacitated and reclusive, and many end their lives with suicide.⁸

Mood and anxiety disorders often coexist with substance use problems such as alcohol use disorder and opioid use disorder, which are subcategories of mental illness according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).⁹ The rates of alcohol and opioid use are rising, and deaths from opioid overdose nearly tripled between 2002 and 2015.¹⁰ In total, over 20 million American adults are affected by substance use disorder and about 8 million suffer from drug dependence and another mental illness such as depression or PTSD.¹¹ The U.S. opioid epidemic has become so severe that President Trump and six U.S. states have declared it a public health emergency.¹²

This article discusses several promising psychedelic medicines for treating mental illness and the barriers to their widespread use. It argues that the mental health crisis demands further evaluation and

8. Isidoor O. Bergfeld et al., *Treatment-resistant Depression and Suicidality*, J. AFFECTIVE DISORDERS (2018) (explaining that thirty percent of people with treatment-resistant depression attempt suicide at least once in their lives); see also William O. Cooper et al., *Antidepressants and Suicide Attempts in Children*, 133 PEDIATRICS (2014) (reporting that pediatric patients who use multiple antidepressants simultaneously are at increased risk for suicide); Peter C. Gotzsche, *Antidepressants Increase the Risk of Suicide, Violence and Homicide at All Ages*, 358 BMJ 3697 (2017); Fabian Termorshuizen et al., *Suicide Behavior Before and After the Start with Antidepressants: A High Persistent Risk in the First Month of Treatment Among the Young*, 19 INT'L J. NEUROPHARMACOLOGY (2016) (concluding that suicide risk persisted following the start of treatment with antidepressants in patients under twenty-five).

9. Deborah S. Hasin et al., *DSM-5 Criteria for Substance Use Disorders: Recommendations and Rationale*, 170 AM. J. PSYCHIATRY 834, 834 (2013) (“DSM is the standard classification of mental disorders used for clinical, research, policy, and reimbursement purposes in the United States and elsewhere. It therefore has widespread importance and influence on how disorders are diagnosed, treated, and investigated.”); see also Harry Man Xiong Lai et al., *Prevalence of Comorbid Substance Use, Anxiety, and Mood Disorders in Epidemiological Surveys, 1990–2014: A Systematic Review and Meta-Analysis*, 154 DRUG & ALCOHOL DEPENDENCE 1 (2015) (reporting that substance use disorders are more common in people with severe mental illness).

10. *Overdose Death Rates*, NAT'L INST. ON DRUG ABUSE, <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> (last updated Sept. 2017) (providing data reflecting how national deaths from opioids nearly tripled from 11,917 in 2002 to 33,091 in 2015).

11. *Substance Use and Mental Health*, NAT'L INST. MENTAL HEALTH, <https://www.nimh.nih.gov/health/topics/substance-use-and-mental-health/index.shtml> (last updated May 2016).

12. Greg Allen, *From Alaska to Florida, States Respond to Opioid Crisis with Emergency Declarations*, NAT'L PUB. RADIO: Health Shots (Aug. 11, 2017, 4:43 PM), <http://www.npr.org/sections/health-shots/2017/08/11/542836709/from-alaska-to-florida-states-respond-to-opioid-crisis-with-emergency-declaration>; Julie Hirschfeld Davis, *In Declaration, No New Funds For Drug Crisis*, N.Y. TIMES, Oct. 27, 2017, at A1.

development of these drugs and presents several pathways for overcoming the regulatory hurdles. Some of the substances described here, such as ayahuasca and ibogaine, have been used by indigenous societies for centuries.¹³ Others, such as lysergic acid diethylamide (LSD) and ketamine, were first synthesized only a half century ago, yet for reasons discussed below, they have largely been ignored by Western medicine.

The thought of prescribing psychedelic or hallucinogenic compounds to mentally ill patients could make many physicians cringe. It brings to mind concerns of substance use disorders, overdose, crime, and medical malpractice. Nevertheless, to improve clinical care and the general welfare of society, the medical community should move beyond these concerns, which are often based on stereotypes and cultural biases. Physicians and policy makers should instead attempt to understand where these biases come from and examine whether they are rooted in fact or fiction.

Despite the growing promise of psychedelics, investigations into their therapeutic effects are often too slow, expensive, and infrequent. Legitimate medical research is hindered by the Schedule I status of these drugs. Updating current regulations could reduce barriers to research and open up new alternatives to millions of patients who are nonresponsive to traditional therapies.

Part I of this article describes current medical treatments for psychiatric illness and their shortcomings. It concludes with a detailed definition of psychedelics and a brief introduction to the clinical applications of six psychedelic drugs. Part II discusses hurdles to psychedelics research and the clinical use of psychedelics including federal regulation, social stigma, safety concerns, and the lack of incentives for pharmaceutical companies to engage in research and development. Part III introduces potential paths through the hurdles to psychedelics research and development. The options discussed include conducting Food and Drug Administration (FDA) sanctioned clinical trials, rescheduling psychedelic compounds at the Drug Enforcement Agency (DEA), and decriminalizing or regulating psychedelics at the state level. With respect to state-level regulation, the recent wide-

13. Thomas Kingsley Brown, *Ibogaine in the Treatment of Substance Dependence*, 6 CURRENT DRUG ABUSE REV. 3, 3 (2013); Ariel Levy, *The Drug of Choice for the Age of Kale: How Ayahuasca, an Ancient Amazonian Hallucinogenic Brew, Became the Latest Trend in Brooklyn and Silicon Valley*, NEW YORKER (Sept. 12, 2016), <https://www.newyorker.com/magazine/2016/09/12/the-ayahuasca-boom-in-the-u-s.>; Alex Hannaford, *Dying to Get Clean: Is Ibogaine the Answer to Heroin Addiction?*, GUARDIAN (Dec. 10, 2017, 3:00 PM), <https://www.theguardian.com/society/2017/dec/10/ibogaine-heroin-addiction-treatment-gabon-withdrawal-danger-death>.

spread efforts at marijuana reform could serve as a roadmap for amending the laws governing psychedelics.

I.

MENTAL ILLNESS IS A PUBLIC HEALTH CRISIS AND PSYCHEDELIC MEDICINES COULD BE PART OF THE SOLUTION

This section introduces current medical and surgical interventions for psychiatric illness, all of which have significant limitations. Psychedelics could create a true paradigm shift in the treatment of mental illness. Specifically, six psychedelic substances and their clinical applications are discussed. Non-pharmacologic interventions such as psychotherapy are also available and can be provided in conjunction with psychiatric drugs. Although these therapies can be helpful, they are not discussed further in this article outside the context of psychedelic-assisted psychotherapy.

A. *The State of the Art in Psychiatry*

The gold standard for treating anxiety, depression, OCD, and PTSD is to prescribe one of the many SSRIs available to the modern psychiatrist.¹⁴ Prozac was the first SSRI to be introduced. It was released in Belgium in 1986, approved by the FDA in 1987, and hit the U.S. market in 1988.¹⁵ SSRIs function by preventing reuptake of serotonin in the synaptic cleft, the junction between communicating neurons.¹⁶ They are an improvement over previous treatments such as tricyclic antidepressants and monoamine oxidase inhibitors because they produce fewer side effects and carry a lower risk of overdose. However, their overall effectiveness may be comparable to these older medications.¹⁷ Since the introduction of Prozac, six additional SSRIs

14. See David S. Baldwin et al., *Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: A Revision of the 2005 Guidelines from the British Association for Psychopharmacology*, 28 J. PSYCHOPHARMACOLOGY 403, 411 (2014) (explaining that SSRIs are generally accepted as first-line treatments for anxiety disorders or OCD); Frederick Rohan Walker, *A Critical Review of the Mechanism of Action for the Selective Serotonin Reuptake Inhibitors: Do These Drugs Possess Anti-Inflammatory Properties and How Relevant Is This in the Treatment of Depression?*, 67 NEUROPHARMACOLOGY 304, 305 (2013) (“The prescription of selective serotonin reuptake inhibitors (SSRIs) is a major component in the medical treatment of mood related psychopathology.”).

15. Edward Shorter, *The 25th Anniversary of the Launch of Prozac Gives Pause for Thought: Where Did We Go Wrong?*, 204 BRITISH J. PSYCHIATRY 331 (2014).

16. Walker, *supra* note 14, at 305.

17. *Id.* at 306.

have been marketed.¹⁸ Though they have proven helpful to millions of people, they are far from perfect. Oftentimes, it takes weeks for the blood concentration of SSRIs to reach therapeutic levels. Patients and their doctors cannot be sure whether the drugs are working until they have been taken regularly for up to six weeks.¹⁹

Patients often discontinue SSRIs due to unpleasant side effects, and up to two-thirds of patients fail to benefit from the first SSRI that is prescribed.²⁰ To reduce the likelihood of side effects, physicians often increase the dose gradually, which could further delay the onset of therapeutic effects. It is common for several SSRIs to be tried sequentially before adding a second agent such as an atypical antipsychotic like aripiprazole.²¹ Like many psychiatric drugs, SSRIs are blunt instruments: they raise serotonin levels globally in the central nervous system, and it is unknown why increased serotonin leads to clinical improvement in some patients with mental illness while leaving others with no benefit.²²

Patients who fail to respond to treatment with antidepressants have few options remaining, and none are very appealing or effective.²³ For example, electroconvulsive shock treatment (ECT), transcranial magnetic stimulation (TMS), psychosurgery, and deep brain stimulation (DBS) have been used to treat anxiety and mood disorders.²⁴ However, with the exception of ECT, there is limited evidence to support the clinical efficacy of these treatments.²⁵ These treatments can be expensive, dangerous, and ineffective, and the mechanisms through which they exert their effects are poorly understood.²⁶ Meanwhile, despite the need for effective treatments for many mental ill-

18. *Selective Serotonin Reuptake Inhibitors (SSRIs) Information*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm283587.htm> (last updated Dec. 23, 2014).

19. Walker, *supra* note 14, at 307.

20. *Id.*

21. See Papakostas, *supra* note 6, at 699.

22. See generally Walker, *supra* note 14, at 307 (discussing criticism of the monoamine theory of depression, which links the disorder to a deficit of serotonin).

23. See, e.g., Little, *supra* note 6, at 171.

24. E.g., Sarah H. Lisanby, *Electroconvulsive Therapy for Depression*, 357 NEW ENG. J. MED. 1939, 1940 (2007); see also Sarah H. Lisanby, *Noninvasive Brain Stimulation for Depression—The Devil Is in the Dosing*, 376 NEW ENG. J. MED. 2593 (2017); Luc Mallet et al., *Subthalamic Nucleus Stimulation in Severe Obsessive-Compulsive Disorder*, 359 NEW ENG. J. MED. 2121, 2128–29 (2008).

25. Little, *supra* note 6, at 171.

26. See *id.* (explaining that there is limited evidence for the use of TMS and DBS in treatment-resistant depression); cf. Lisanby, *supra* note 24, at 2593–94 (explaining that the effective dose of current TMS is not known, and though TMS may be more effective than placebo, it is unclear whether the treatment is as effective as medication).

nesses, pharmaceutical companies have decreased their investment in the development of psychiatric drugs, and some have halted it altogether.²⁷

Frustrated with the limited effectiveness of traditional drugs and more invasive procedures like ECT and DBS, some doctors are turning to psychedelic medicines to relieve their patients' suffering. Catherine, whose story opened this article, was administered a very small dose of the anesthetic drug ketamine, which is routinely administered in hospitals worldwide. Long thought of in popular culture as a horse tranquilizer or a club drug, ketamine has recently been found to have significant antidepressant and anxiolytic properties. In clinical trials and countless case reports, up to seventy percent of participants have experienced significant benefits after intravenous administration of ketamine.²⁸ A seventy percent response rate may not seem impressive, but it is a significant advancement considering that most patients treated with ketamine have failed to respond to multiple antidepressants. It is also notable that ketamine exerts its effects almost immediately, whereas SSRIs may take weeks or months to produce a benefit.

Other psychedelics such as LSD and psilocybin are currently being studied in mentally ill populations. Specifically, they have been found to improve symptoms of depression, PTSD, OCD, and alcoholism.²⁹ Psychedelics have also been used to treat chronic pain, anxiety, and depression in patients with terminal illnesses.³⁰

B. What Are Psychedelics?

There is currently no universally agreed upon definition of "psychedelics." Oxford Dictionaries defines them as drugs that "produce hallucinations and apparent expansion of consciousness."³¹ Encyclopedia Britannica describes them as "mind-expanding drugs that

27. Sheldon H. Preskorn, *Ketamine: The Hopes and the Hurdles*, 72 *BIOLOGICAL PSYCHIATRY* 522, 523 (2012).

28. See Marije Aan Het Rot et al., *Ketamine for Depression: Where Do We Go from Here?*, 72 *BIOLOGICAL PSYCHIATRY* 537, 539 (2012) (reporting antidepressant response rates between fourteen and seventy percent in seventy-two hours following ketamine administration); Franz X. Vollenweider & Michael Kometer, *The Neurobiology of Psychedelic Drugs: Implications for the Treatment of Mood Disorders*, 11 *NATURE REV.* 642, 643 (2010) (reporting a response rate of seventy-one percent within twenty-four hours).

29. *E.g.*, Vollenweider & Kometer, *supra* note 28, at 642.

30. *See id.*

31. *Psychedelic*, OXFORD DICTIONARIES, http://www.oxforddictionaries.com/us/definition/american_english/psychedelic (last visited Aug. 14, 2017).

are able to induce states of altered perception and thought.”³² The term psychedelics traditionally includes agents that act on the serotonergic system, such as LSD, psilocybin, and N,N-dimethyltryptamine (DMT).³³ Other drugs like marijuana and ketamine are sometimes included despite having different mechanisms of action.

For the purposes of this article, marijuana will not be included among the psychedelic drugs. Though it may have some psychedelic properties, it is not typically categorized with drugs like LSD and psilocybin, which are referred to as classic hallucinogens.³⁴ However, the regulation of marijuana will be discussed because, like the psychedelics, it is a stigmatized Schedule I controlled substance, and a growing body of evidence supports its medical use. Furthermore, recent changes to federal and state regulation of marijuana may serve as useful case studies for the legalization of psychedelic medicines. Groups that hope to study or legalize psychedelic medicines can learn many lessons from the triumphs and failures of efforts to regulate medical marijuana.

Ketamine will be included among the psychedelics. At relatively low doses, it has been shown to produce altered states of consciousness similar to those induced by the classic hallucinogens LSD and psilocybin.³⁵ However, unlike marijuana and the classic hallucinogens, ketamine is an FDA-approved drug that can be prescribed legally by any licensed physician. Ketamine clinics, in which physicians administer the drug in single doses, are a new phenomenon that is growing in popularity throughout the United States. They can serve as

32. John Philip Jenkins, *Psychedelic Drug*, ENCYCLOPÆDIA BRITANNICA, <http://www.britannica.com/EBchecked/topic/481540/psychedelic-drug> (last visited Aug. 14, 2017).

33. See Vollenweider & Kometer, *supra* note 28, at 646 (presenting an illustration of the mechanism of action of psychedelics in the prefrontal cortex mediated by post-synaptic 5-HT_{2A} receptors).

34. See generally 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>.

35. See Vollenweider & Kometer, *supra* note 28, at 644 (explaining that ketamine and psilocybin produce overlapping subjective experiences as measured by validated instruments such as the five-dimensional altered states of consciousness (“5D-ASC”)); see also MICHAEL M. SCHATNER ET AL., INCREASED SPONTANEOUS MEG SIGNAL DIVERSITY FOR PSYCHOACTIVE DOSES OF KETAMINE, LSD AND PSILOCYBIN, SCI. REP. (2017), <https://www.nature.com/articles/srep46421.pdf> (reporting that ketamine, psilocybin, and LSD may produce similar effects on consciousness as reflected by changes on magnetoencephalography (MEG), a form of functional neuroimaging that measures changes in magnetic fields, which reflect altered neuronal activity).

a useful model for future treatment centers that administer other psychedelic drugs.

It is with some reluctance that I adopt the term “psychedelic” in this article because it still carries the stigma associated with recreational drug use and the counterculture of the 1960s. However, it is an appropriate term derived from the Greek words *psykhe*, which means mind, and *deloun*, which means to manifest or make visible.³⁶ The name is fitting because some patients claim that psychedelics allow them to access thoughts and feelings that have long been repressed or unavailable to them. In theory, the medications allow them to manifest portions of their minds that have been repressed or held captive by mental illness. Painful memories and traumas bubble to the surface where they can be consciously processed and resolved.³⁷

In the United States, all psychedelics are controlled substances, which means their manufacture, sale, and use are heavily regulated by the DEA. Controlled substances are categorized into five tiers or “schedules” based largely on their potential for abuse and dependence and the risks they pose to public health.³⁸ This scheduling system was created by the Controlled Substances Act of 1970 (the “CSA”), which granted the U.S. Attorney General the power to categorize and recategorize drugs.³⁹ Since the formation of the DEA in 1973, the Attorney General has typically delegated his or her scheduling power to the agency. Substances that the DEA deems to have no currently accepted medical use and a “high potential for abuse and dependence” are placed in Schedule I, which includes marijuana, psilocybin, LSD, 3,4-Methylenedioxymethamphetamine (MDMA), and heroin.⁴⁰ Schedule I substances are the most heavily restricted and the most difficult to research legally.⁴¹ Schedule II drugs have currently accepted medical uses and are believed to have “high potential for abuse and depen-

36. *Psychedelic*, ONLINE ETYMOLOGY DICTIONARY, <http://www.etymonline.com/index.php?term=psychedelic> (last visited Aug. 21, 2017) (explaining that the term psychedelic originated in a 1956 letter from psychiatrist Humphry Osmond to Aldous Huxley).

37. Shaunacy Ferro, *Why Doctors Can't Give You LSD (But Maybe They Should)*, POPULAR SCI., <http://www.popsci.com/science/article/2013-04/new-science-lsd-therapy> (last visited Aug. 14, 2017) (noting that LSD was seen as having the potential to break down barriers, freeing the mind so patients could open up during psychotherapy).

38. 21 U.S.C. § 811(c) (1970).

39. *Id.* § 811(b).

40. *Id.* § 812(b)(1); see also *Drug Schedules*, U.S. DRUG ENF'T ADMIN., <http://www.dea.gov/druginfo/ds.shtml> (last visited Aug. 14, 2017).

41. Mason Marks, *Legal Barriers to Research on Schedule I Controlled Substances*, YOUTUBE (Dec. 21, 2017), <https://www.youtube.com/watch?v=SLrtixosxGk>.

dence.”⁴² Examples of Schedule II drugs include cocaine, fentanyl, and methamphetamine.⁴³ Schedule III drugs have accepted medical uses and are considered by the DEA to have “moderate to low potential for physical and psychological dependence.” Ketamine falls into this category.⁴⁴

C. *Brief Discussion of Psychedelic Agents and Their Clinical Applications*

1. LSD

The Swiss chemist Albert Hofmann first synthesized LSD in 1938. Five years later, he accidentally absorbed some of the compound through his skin and discovered its unusual properties after being induced into a dream-like state.⁴⁵ He reported perceiving “an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors.”⁴⁶ Hofmann and his employer Sandoz began testing the compound on animals, and before long, it became apparent that the drug could be useful for modeling and treating psychiatric illness. It is estimated that between 1950 and 1963, LSD may have been tested on up to 40,000 research subjects.⁴⁷ However, despite some initial progress, research on LSD came to a halt in the 1960s and 1970s.⁴⁸ It is only recently that clinical research into the drug has been reinitiated.

In 2014, a paper described as “the first controlled study of LSD-assisted psychotherapy in more than 40 years” reported the results of using LSD to treat anxiety in ten patients with life-threatening diseases.⁴⁹ Participants experienced a 77.8% reduction in anxiety and a 66.7% rise in quality of life, which persisted for up to one year.⁵⁰ Furthermore, recent neuroimaging studies suggest LSD could help re-

42. 21 U.S.C. § 812(b)(2).

43. *Drug Schedules*, U.S. DRUG ENF'T ADMIN., *supra* note 40.

44. *Id.*

45. Tom Shroder, ‘Apparently Useless’: *The Accidental Discovery of LSD*, ATLANTIC (Sept. 9, 2014), <https://www.theatlantic.com/health/archive/2014/09/the-accidental-discovery-of-lsd/379564/>.

46. ALBERT HOFMANN, *LSD—MY PROBLEM CHILD: REFLECTIONS ON SACRED DRUGS, MYSTICISM, AND SCIENCE* 15 (Jonathan Ott trans., J.P. Tarcher, Inc. 1983) (1979).

47. Ferro, *supra* note 37; Vollenweider & Kometer, *supra* note 28, at 642.

48. *See* Ferro, *supra* note 37 (explaining that once LSD was placed in Schedule I, research became severely restricted and funding was difficult to receive).

49. Peter Gasser et al., *Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated with Life-Threatening Diseases*, 202 J. NERVOUS MENTAL DISEASES 513, 513 (2014).

50. *Id.* at 513.

veal the biochemical bases for mental illness and improve our understanding of consciousness.⁵¹

2. *Psilocybin*

Several wild mushroom species contain psilocybin, which produces hallucinogenic effects similar to those of LSD.⁵² Preliminary studies suggest the drug is safe and may be useful for treating psychiatric illnesses such as depression, OCD, and anxiety associated with advanced-stage cancer.⁵³ In 2006, Roland Griffiths, Professor of Psychiatry and Behavioral Sciences at Johns Hopkins University, reported the results of a double-blind study in which he administered psilocybin to thirty healthy volunteers with no prior history of hallucinogen use. Griffiths concluded that when psilocybin is administered under controlled and supportive conditions, it can create spontaneous mystical experiences characterized by feelings of unity, a “deeply felt positive mood,” and “transcendence of time and space.”⁵⁴ Griffiths measured these phenomena with a set of widely used questionnaires including the Hallucinogen Rating Scale (HRS). The HRS was developed to measure subjective experiences induced by classic hallucinogens.⁵⁵ In its original form, introduced in 1994, the scale consists of 126 questions from six categories: (1) somaesthesia, which relates to one’s perception of bodily sensations such as pain and touch; (2) affect, which involves changes in a subject’s emotional state; (3) perception, which includes auditory, visual, olfactory, and gustatory sensations; (4) cognition, which pertains to alterations in the content or patterns of thought; (5) volition, which involves changes in one’s desire to interact with oneself, the environment, or the aspects of the

51. See generally Robin L. Carhart-Harris et al., *Neural Correlates of the LSD Experience Revealed By Multimodal Neuroimaging*, 113 *PROC. NAT’L ACAD. SCI.* 4853, 4857 (2016) (explaining that the neurobiology of psychedelic-induced ego-dissolution can inform on the neurobiology of the “self” or “ego”).

52. Charles S. Grob et al., *Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced-Stage Cancer*, 68 *ARCHIVES GEN. PSYCHIATRY* 71, 72 (2011).

53. See *id.*; see also R. R. Griffiths et al., *Psilocybin Can Occasion Mystical-Type Experiences Having Substantial and Sustained Personal Meaning and Spiritual Significance*, 187 *J. PSYCHOPHARMACOLOGY* 268 (2006); Francisco A. Moreno et al., *Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients with Obsessive Compulsive Disorder*, 67 *J. CLINICAL PSYCHIATRY* 1735 (2006).

54. Griffiths et al., *supra* note 53, at 272.

55. Frederick S. Barrett, *The Challenging Experience Questionnaire: Characterization of Challenging Experiences with Psilocybin Mushrooms*, 30 *J. PSYCHOPHARMACOLOGY* 1279, 1280 (2017).

treatment experience; and (6) intensity, which measures the strength of certain aspects of the treatment experience.⁵⁶

In Griffith's 2006 study, two-thirds of the participants ranked their psilocybin-induced experiences among the top five most meaningful events of their lives, a belief that persisted in most subjects when they were polled again fourteen months later.⁵⁷ The therapy appeared to create persistent personality changes. Specifically, the subjects became happier and more optimistic. These qualities are notably absent in depression, which is characterized by feelings of hopelessness, numbness, isolation, and sadness.

Francisco Moreno, Professor of Psychiatry at the University of Arizona, reported the effects of psilocybin on nine patients with OCD. The drug produced a marked decrease in symptoms, as reflected by scores on the Yale-Brown OCD scale, in patients who had previously failed to respond to treatment.⁵⁸ The greatest improvements were achieved two hours after peak psychedelic effects, and the benefits persisted for up to twenty-four hours.⁵⁹ Although the benefits were short-lived in this study, with further research, the effects could potentially be extended, and a drug for daily use could be developed.

In 2010, Professor Charles Grob, Director of the Division of Child and Adolescent Psychiatry at Harbor-UCLA Medical Center, administered psilocybin to twelve patients with terminal cancer. These subjects carried multiple diagnoses including generalized anxiety disorder. After administering modest doses of psilocybin, Grob observed a significant decrease in anxiety that persisted for several months in some cases.⁶⁰ In 2016, Roland Griffiths published a larger, randomized double-blind study on the use of psilocybin for treating depression and anxiety in fifty-one cancer patients.⁶¹ He reported no serious adverse events attributed to psilocybin and found that high doses of the drug produced significant reductions in anxiety and depressed mood that endured for over six months.

56. Rick J. Strassman et al., *Dose-Response Study of N,N-Dimethyltryptamine in Humans: II. Subjective Effects and Preliminary Results of a New Rating Scale*, 51 ARCHIVES GEN. PSYCHIATRY 98, 99 (1994).

57. Roland R. Griffiths et al., *Mystical-type Experiences Occasioned by Psilocybin Mediate the Attribution of Personal Meaning and Spiritual Significance 14 Months Later*, 22 J. PSYCHOPHARMACOLOGY 621 (2008).

58. Moreno et al., *supra* note 53, at 1735.

59. *Id.*

60. Grob et al., *supra* note 52.

61. Roland R. Griffiths et al., *Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial*, 30 J. PSYCHOPHARMACOLOGY 1181 (2016).

Admittedly, these psilocybin studies have their shortcomings. Most of the studies had small sample sizes, and the positive effects were sometimes fleeting. However, they suggest that administering the drug to mentally ill patients in controlled settings is safe and potentially therapeutic. Any shortcomings underscore the importance of conducting additional research, which remains challenging under existing federal regulations. If the obstacles to psilocybin research were reduced, larger studies with more clinical endpoints could be conducted, treatment protocols could be refined, and clinical benefits could likely be improved.

3. *Ayahuasca*

Ayahuasca is consumed as a tea derived from vines and shrubs of the Amazon rainforest, including *Banisteriopsis caapi* and *Psychotria viridis*.⁶² The active ingredient is DMT, which is a Schedule I substance in the United States. There is a growing trend in which Western travelers visit South America to consume ayahuasca. Each year thousands of tourists participate in rituals led by Amazonian shaman that prepare and administer the tea. To capitalize on this trend, many ayahuasca retreat centers have opened in the area surrounding Iquitos, Peru.⁶³

Despite its restricted status in the United States, two groups are permitted to use DMT. The Brazilian churches Centro Espírita Beneficente União do Vegetal (the “UDV”) and Santo Daime have won religious exemptions to the CSA, which allow them to consume DMT as part of their religious rituals.⁶⁴ Scientists observed the use of ayahuasca by the UDV and found its members to be in good physical health.⁶⁵ Several studies suggest that ayahuasca could help treat mental illness and substance use disorders.⁶⁶ In one observational

62. Paulo Cesar Ribeiro Barbosa et al., *Health Status of Ayahuasca Users*, 4 DRUG TESTING ANALYSIS 601, 605 (2012).

63. David Hill, *Peru’s Ayahuasca Industry Booms As Westerners Search for Alternative Healing*, GUARDIAN (June 7, 2016, 1:30 PM), <https://www.theguardian.com/travel/2016/jun/07/peru-ayahuasca-drink-boom-amazon-spirituality-healing>.

64. *Gonzales v. O Centro Espírita Beneficente União do Vegetal*, 546 U.S. 418 (2006); *Church of the Holy Light of the Queen v. Mukasey*, 615 F.2d 1210 (D. Or. 2009), *vacated sub nom.* *Church of the Holy Light of the Queen v. Holder*, 443 F. App’x 301 (9th Cir. 2001).

65. See, e.g., Evelyn Doering-Silveira et al., *Report on Psychoactive Drug Use Among Adolescents Using Ayahuasca Within a Religious Context*, 37 J. PSYCHOACTIVE DRUGS 141 (2011).

66. Ede Frecska, Petra Bokor & Michael Winkelman, *The Therapeutic Potentials of Ayahuasca: Possible Effects Against Various Diseases of Civilization*, 7 FRONTIERS PHARMACOLOGY 35 (2016); Michael Winkelman, *Psychedelics as Medicines for Sub-*

study on ayahuasca-assisted therapy for substance use disorders, the authors observed statistically significant improvements in several factors associated with substance use including quality of life and hopefulness.⁶⁷ Study participants reported reduced consumption of alcohol, tobacco, and cocaine.⁶⁸ Though there is some evidence for the therapeutic use of ayahuasca, much of it remains anecdotal, and more rigorous experimental studies would be beneficial.

4. *Ketamine*

Ketamine has traditionally been used as an anesthetic and an analgesic primarily in pediatric populations. Unlike the other psychedelics discussed in this article, ketamine is a Schedule III drug that can technically be prescribed by any licensed physician in the United States. It is listed as an anesthetic on the World Health Organization's (WHO) List of Essential Medications for children and adults.⁶⁹ Ketamine has proven useful in a variety of settings including the emergency room, the operating theater, the battlefield, in rural medicine, and in the midst of natural disasters.⁷⁰ The drug has a good safety profile and is easy to administer requiring little equipment.

Because ketamine is FDA-approved for some conditions, physicians may prescribe it at their discretion for any use they see fit. When a doctor prescribes a drug for a purpose that is not FDA-approved, it is said to be prescribed "off-label." However, many physicians are hesitant to prescribe ketamine due to its lack of FDA approval for treating mental illness, its reputation as a club drug, and a lack of safety data

stance Abuse Rehabilitation: Evaluating Treatments with LSD, Peyote, Ibogaine and Ayahuasca, 7 CURRENT DRUG ABUSE REV. 101 (2014).

67. Gerald Thomas et al., *Ayahuasca-Assisted Therapy for Addiction: Results from a Preliminary Observational Study in Canada*, 6 CURRENT DRUG ABUSE REV. 30 (2013).

68. *Id.*

69. Tony Kirby, *Ketamine for Depression: The Highs and Lows*, 2 LANCET PSYCHIATRY 783, 784 (2015); WORLD HEALTH ORG., WHO MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN (2017), http://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017_FINAL_amendedAug2017.pdf?ua=1; WORLD HEALTH ORG., WHO MODEL LIST OF ESSENTIAL MEDICINES (2017), www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1.

70. Itamar Ashkenazi et al., *Prehospital Management of Earthquake Casualties Buried Under Rubble*, 20 PREHOSPITAL DISASTER MED. 122 (2005); Madhuri S. Kurdi, Kaushic A. Theerth & Radhika S. Deva, *Ketamine: Current Applications in Anesthesia, Pain, and Critical Care*, 8 ANESTHESIA ESSAYS RES. 283 (2014); Bisola Obembe, *Not Just a Party Drug: No Ketamine Means No Surgery in Some Developing Countries*, GUARDIAN (Mar. 3, 2016, 5:47 PM), <https://www.theguardian.com/global-development-professionals-network/2016/mar/03/not-just-a-party-drug-no-ketamine-means-no-surgery-in-some-developing-countries>.

regarding long-term use. Psychiatry Professor George Sanacora, Director of the Yale Depression Research Program, estimates that over 3000 people have been treated with ketamine for symptoms of depression, yet he finds many of his colleagues reluctant to prescribe it. His response to ketamine detractors is simple: “If you have patients that are likely to seriously injure themselves or kill themselves within a short period of time, and they’ve tried the standard treatments, how do you not offer this treatment?”⁷¹

Though there is resistance to prescribing ketamine off-label, a growing number of providers are willing to prescribe it for the treatment of mood and anxiety disorders. Ketamine clinics are cropping up across the country.⁷² They are usually staffed by anesthesiologists, who have experience administering anesthetics, or psychiatrists, who have experience treating mental illness. However, ketamine therapy can be prohibitively expensive. A single dose may cost up to \$1000, and a series of treatments is often recommended.⁷³ Because health insurance does not cover the use of ketamine in psychiatry, patients must pay out of pocket, which puts the drug out of reach for many.

5. MDMA

MDMA is sold illegally under the street name “ecstasy.” Originally patented in 1912, its euphoria-inducing properties were not discovered until the 1970s.⁷⁴ It was introduced into therapy practices on the West Coast in late 1976.⁷⁵ At the time, some researchers believed it could aid in the treatment of drug and alcohol use disorders, enhance emotional intimacy, and facilitate communication in the therapeutic setting. However, before clinical trials could get off the ground, the DEA placed MDMA on its list of Schedule I drugs in 1985, which prevented further study.⁷⁶ Recently, there has been a global resurgence of MDMA research. Studies in Israel, Canada, Switzerland, and the

71. Jon Hamilton, *Ketamine for Severe Depression: ‘How Do You Not Offer This Drug to People?’*, NAT’L PUB. RADIO: HEALTH SHOTS (Mar. 20, 2017, 3:19 PM), <http://www.npr.org/sections/health-shots/2017/03/20/520169959/ketamine-for-severe-depression-how-do-you-not-offer-this-drug-to-people>.

72. Mandy Oaklander, *New Hope for Depression*, TIME, Aug. 7, 2017.

73. Kirby, *supra* note 69, at 783.

74. Alexander T. Shulgin, *History of MDMA*, in ECSTASY: THE CLINICAL, PHARMACOLOGICAL AND NEUROTOXICOLOGICAL EFFECTS OF THE DRUG MDMA 2 (Stephen J. Peroutka ed., 1990).

75. David M. McDowell & Herbert D. Kleber, *MDMA: Its History and Pharmacology*, 24 PSYCHIATRIC ANNALS 127, 127–28 (1994).

76. *See id.* at 128.

United States have investigated the use of MDMA-assisted psychotherapy for treating PTSD.⁷⁷

6. *Ibogaine*

Ibogaine is a psychedelic compound derived from the roots of *Tabernanthe iboga*, a Central-West African shrub.⁷⁸ In Gabon, the plant is consumed by adherents of the Bwiti religion who believe it helps them connect with their ancestral spirits. In the late 1980s and early 1990s, ibogaine was shown to inhibit the self-administration of morphine, cocaine, and alcohol in rats.⁷⁹ More recently, it has been established as a potential agent for opioid detoxification.⁸⁰ As a result, it has the potential to help combat the current opioid epidemic. Ibogaine became a U.S. Schedule I drug in 1970.⁸¹ However, it is less tightly controlled in other countries such as Canada, Brazil, and South Africa.⁸² In New Zealand, ibogaine is available by prescription despite lack of approval from the New Zealand Medicines and Medical Devices Safety Authority (“Medsafe”).⁸³ A recent study conducted there, which was co-sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), reported that single doses of ibogaine reduced opioid withdrawal symptoms and achieved abstinence or re-

77. *MDMA-Assisted Psychotherapy for PTSD—Phase 3 Trials: FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Psychotherapy for PTSD, Agrees on Special Protocol Assessment*, MULTIDISCIPLINARY ASS’N PSYCHEDELIC STUD., <http://www.maps.org/research/mdma> (last visited Aug. 21, 2017) (stating that MDMA-assisted psychotherapy is also under investigation for treating social anxiety in autistic adults and anxiety associated with life-threatening illness).

78. Piotr Popik et al., *100 Years of Ibogaine: Neurochemical and Pharmacological Actions of a Putative Anti-Addictive Drug*, 46 *PHARMACOLOGY REV.* 235, 236 (1995).

79. See, e.g., S.D. Glick, *Effects and Aftereffects of Ibogaine on Morphine Self-administration in Rats*, 195 *EUR. J. PHARMACOLOGY* 341, 342–44 (1991); see also Susanne L.T. Cappendijk & Michailo R. Dzoljic, *Inhibitory Effects of Ibogaine on Cocaine Self-administration in Rats*, 241 *EUR. J. PHARMACOLOGY* 261, 261 (1993); Amir H. Rezvani et al., *Attenuation of Alcohol Intake by Ibogaine in Three Strains of Alcohol-preferring Rats*, 52 *PHARMACOLOGY BIOCHEMISTRY BEHAV.* 615, 615 (1995).

80. Thomas Kingsley Brown & Kenneth Alper, *Treatment of Opioid Use Disorder with Ibogaine: Detoxification and Drug Use Outcomes*, 44 *AM. J. DRUG & ALCOHOL ABUSE* 24, 24 (2017).

81. Brian Vastag, *Addiction Treatment Strives for Legitimacy*, 288 *JAMA* 3096, 3101 (2002).

82. Elizabeth Llorente, *Many Ex-Opioid Addicts Credit ‘Ibogaine’ with Cure, But It’s Illegal in US*, FOX NEWS (Oct. 11, 2017), <http://www.foxnews.com/health/2017/10/11/many-ex-opioid-addicts-credit-ibogaine-with-cure-but-its-illegal-in-us.html>.

83. See *id.*; see also Geoffrey E. Noller et al., *Ibogaine Treatment Outcomes for Opioid Dependence from a Twelve-Month Follow-Up Observational Study*, *AM. J. DRUG & ALCOHOL ABUSE* 1, 2 (2017).

duced opioid use in fourteen individuals over a twelve-month period.⁸⁴

Due to the current lack of availability of ibogaine in the United States, Americans with opioid use problems sometimes travel abroad for ibogaine therapy at centers, such as Liberty Root in British Columbia or Clear Sky Recovery on the island of Saint Kitts, where a ten-day course of treatment can cost over \$7000.⁸⁵

II.

HURDLES TO RESEARCH AND CLINICAL USE

If psychedelic medications show so much promise for treating psychiatric illness, then why are they not in widespread use or at least being vigorously studied? There are a variety of explanations for why research on these drugs has been inhibited and why their power to treat mental illness is only just beginning to be understood. This section discusses regulatory and social obstacles that inhibit progress on psychedelics research and clinical use. These factors include legislation rooted in the U.S. War on Drugs of the 1960s and 1970s; stigma against psychedelics held by physicians, employers, insurance companies, and patients; safety concerns; the risk of medical malpractice litigation; and a general lack of incentives for psychedelics research and development.

A. *The U.S. War on Drugs and the Controlled Substances Act of 1970*

During the 1960s and 1970s, psychedelic drugs became associated with hedonism and cultural rebellion.⁸⁶ Simultaneously, a wave of new drug legislation was passed globally. In 1961, many countries, including the United States, signed the United Nations Single Convention on Narcotic Drugs (the “Single Convention”), which regulated cannabis, opium, and the coca plant. It replaced previous multilateral treaties with a single document and brought drug control into the post-war era.⁸⁷ Though its roots can be traced back to treaties of the early twentieth century, the Single Convention can be viewed as a turning

84. Noller et al., *supra* note 83.

85. Llorente, *supra* note 82; see also CLEAR SKY RECOVERY, <https://clearskyibogaine.com/> (last visited Nov. 3, 2017); Trevor Millar, *Ibogaine FAQ*, LIBERTY ROOT, <http://libertyroot.net/ibogaine-faq/> (last visited Nov. 3, 2017).

86. See, e.g., Vollenweider & Kometer, *supra* note 28, at 642.

87. See David Bewley-Taylor & Martin Jelsma, *Fifty Years of the 1961 Single Convention on Narcotic Drugs: A Reinterpretation*, 12 SERIES LEGIS. REFORM DRUG POL'YS 1, 1 (2011).

point in international drug law. Prior to its implementation, the approach toward the non-medical use of drugs was rarely punitive. When measures to reduce non-medical use were implemented, they usually took the form of limits on production and efforts to minimize diversion of drugs from legitimate channels. With the introduction of the Single Convention, the focus shifted from an approach that emphasized the control of drugs as mere commodities to a prohibitionist approach toward the non-medical use of some drugs. This change in philosophy is evident in the preamble to the Single Convention, which declares that narcotics use “[c]onstitutes a serious evil for the individual and is fraught with social and economic danger to mankind.”⁸⁸

In 1970, Congress passed the CSA, which represented a major expansion of federal drug regulation.⁸⁹ Just as the Single Convention is viewed as a turning point in international drug law, the CSA is a landmark in the history of U.S. drug enforcement. Prior to the 1960s and 1970s there was a patchwork of drug laws and enforcement agencies in the United States. The DEA had not yet been established, and an act of Congress was required to regulate drugs. The CSA was intended to modernize U.S. drug laws, harmonize the disparate agencies responsible for drug control, and create an administrative structure that could regulate drugs without congressional intervention.⁹⁰ As discussed previously, the CSA gave the Attorney General the power to categorize substances into one of five schedules.⁹¹ Three years after the law was implemented, President Nixon issued an executive order that created the DEA.⁹² Subsequent amendments to the CSA expanded the power of the DEA and increased criminal penalties for drug offenses.⁹³ The amended CSA became the foundation of the U.S. War on Drugs.⁹⁴ In its original incarnation, the CSA balanced law enforcement and public health concerns. However, according to historian David Courtwright, over the course of several decades, amended forms of the CSA became more politically charged to favor the concerns of the Justice Department, namely cracking down on criminals, over the promotion of public health. In Courtwright’s words, “[n]o

88. Single Convention on Narcotic Drugs, preamble, Mar. 30, 1961, 520 U.N.T.S. 151.

89. Robert A. Mikos, *Preemption Under the Controlled Substances Act*, 16 J. HEALTH CARE L. & POL’Y 5, 10 (2013) [hereinafter Mikos, *Preemption Under the Controlled Substances Act*].

90. Marks, *supra* note 41.

91. 21 U.S.C. § 811(b).

92. JOHN SCHEB & JOHN SCHEB, II, *CRIMINAL LAW* 238 (5th ed. 2009).

93. David T. Courtwright, *The Controlled Substance Act: How a “Big Tent” Reform Became a Punitive Drug Law*, 76 DRUG & ALCOHOL DEPENDENCE 9, 10 (2004).

94. *Id.*

one looking at the bill in its current form should assume that its framers anticipated that it would operate in such an inflexible way, or serve such punitive ends.”⁹⁵

In 1971, one year after the CSA was passed, the United Nations Convention on Psychotropic Substances was signed. Unlike the Single Convention, it put LSD, psilocybin, and DMT under stricter international control.⁹⁶ That same year, President Nixon declared a war on drugs when he proclaimed that drug use was America’s “public enemy number one.”⁹⁷ In 1978, Congress passed the Psychotropic Substances Act, which amended previous U.S. drug legislation to comply with the Convention on Psychotropic Substances.⁹⁸

By the end of the 1970s, many psychedelics were heavily restricted or outright banned in the United States and internationally. Researchers conducting experiments on these medications had to close up shop. As a result, many questions regarding the therapeutic application of these drugs remain unanswered. Even today, conducting clinical research on psychedelics can be daunting because the drugs are heavily regulated. Obtaining permission from the federal government can be slow and requires a special license from the DEA.⁹⁹ Furthermore, complying with regulatory requirements may be prohibitively expensive and onerous.¹⁰⁰ These obstacles raise the cost of manufacturing and administering psychedelic drugs. In recent years, the number of active licenses has declined. In 2010 there were 550 scientists with DEA licenses to study Schedule I substances. The number of licenses decreased by 36.5% to 349 by 2013.¹⁰¹

The War on Drugs has been so pervasive and so deeply ingrained in our culture that even the label “controlled substance” has taken on an aura of its own. Ask any physician to prescribe a controlled substance for all but the gravest conditions, and he may become notice-

95. *Id.*

96. Convention on Psychotropic Substances, List of Substances in Schedule I, Feb. 21, 1971, 1019 U.N.T.S. 261.

97. Peter J. Boettke, *Keep Off the Grass: The Economics of Prohibition and U.S. Drug Policy*, 91 OR. L. REV. 1069, 1075 (2013).

98. 21 U.S.C. § 801 (1978).

99. See Terrance Woodworth, *How Will DEA Affect Your Clinical Study?*, 7 J. CLINICAL RES. BEST PRACTICES 1, 1 (2011) (explaining the licensing guidelines, import export controls, quotas, security measures, and record-keeping requirements associated with studying controlled substances); see also Ferro, *supra* note 37 (reporting that the DEA estimates it takes nine months to receive a license to study Schedule I substances, but researchers are skeptical of this estimate).

100. *Id.*

101. Ferro, *supra* note 37 (suggesting that the recent decrease in Schedule I licenses could be due to increased DEA scrutiny of existing licenses).

ably defensive. Concerns regarding these drugs are rising due to the growing opioid use problem in the United States.¹⁰² Regardless, controlled substances, including those in Schedule I, should not be universally condemned. As discussed above in Part I, despite their Schedule I status, psychedelics are proving to have legitimate medical uses. Though not a psychedelic, marijuana is also a stigmatized Schedule I substance. Despite growing evidence for legitimate medical applications, attempts to remove marijuana from Schedule I have failed to meet DEA and common law requirements for rescheduling, which are discussed further in Part III. Lessons can be learned from efforts to reschedule marijuana, to regulate it, and to develop it into FDA-approved medications. In other words, it serves as a useful model for the development and regulation of psychedelic drugs.

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive compound in marijuana. The United States Adopted Name, or generic drug name, for THC is dronabinol. It is the sole active ingredient in two FDA-approved medications. One of these drugs is Marinol, which is produced by the American pharmaceutical company AbbVie and is FDA-approved for treating AIDS-associated appetite loss and nausea and vomiting associated with cancer chemotherapy.¹⁰³ It consists primarily of dronabinol, sesame oil, and food dyes suspended in a gelatin capsule.¹⁰⁴ Though its sole active ingredient is dronabinol, a schedule I drug with no currently accepted medical uses, the DEA lists Marinol as a Schedule III compound that may be prescribed by any physician.¹⁰⁵

The second FDA-approved drug based on dronabinol is Syndros. On May 24, 2017, Insys Therapeutics announced final FDA approval of Syndros for clinical indications similar to those of Marinol.¹⁰⁶ Syn-

102. Richard C. Dart et al., *Trends in Opioid Analgesic Abuse and Mortality*, 372 *NEW ENG. J. MED.* 241, 242 (2015) (describing an observed rise in overuse of prescription drugs including opioid analgesics).

103. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: MARINOL (DRONABINOL) CAPSULES FOR ORAL USE 18–19 (2017), https://www.access-data.fda.gov/drugsatfda_docs/label/2017/018651s0291bl.pdf.

104. *Id.* at 19.

105. U.S. DRUG ENF'T ADMIN., CONTROLLED SUBSTANCES—ALPHABETICAL ORDER 8 (2018) [hereinafter U.S. DRUG ENF'T ADMIN., CONTROLLED SUBSTANCES], https://www.deaiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf.

106. Press Release, Insys Therapeutics, Inc., Insys Therapeutics, Inc. Announces FDA Final Product Label for Syndros (Aug. 2017), <http://investors.insysrx.com/phoenix.zhtml?c=115949&p=irol-newsArticle&ID=2276177>.

dros consists of an oral solution containing little more than dronabinol, alcohol, sucralose, and water that is administered by syringe.¹⁰⁷

THC-based drugs are also being approved internationally.¹⁰⁸ Sativex is a cannabis-derived oral spray produced by the British drug maker GW Pharmaceuticals; it contains both THC and its non-psychoactive counterpart cannabidiol (CBD), which is also derived from marijuana.¹⁰⁹ Sativex can treat spasticity in multiple sclerosis and is approved for medical use in thirty countries.¹¹⁰

Notwithstanding the growing medical uses for marijuana and its chemical derivatives such as dronabinol, all attempts to remove it from Schedule I have failed. On July 19, 2016, the DEA denied two petitions to reschedule marijuana. In a written response to the petitioners, Acting DEA Administrator Chuck Rosenberg explained that the denials were based primarily on a lack of scientific evidence proving efficacy.¹¹¹ According to the DEA, well-controlled clinical trials, conducted in collaboration with the FDA, are the “most appropriate way” to establish legitimate medical uses for marijuana and its constituents.¹¹²

There seems to be inconsistent reasoning given to explain why these drugs remain listed in Schedule I. Despite the FDA approval of Marinol and Syndros, which consist of little more than THC, and in spite of European approval of Sativex, which contains little more than THC and CBD, isolated THC, dronabinol, and botanical marijuana remain in Schedule I. Although the FDA has not approved the botanical form of marijuana for any clinical use, its primary psychoactive

107. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: SYNDROS (DRONABINOL) ORAL SOLUTION 3, 12 (2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205525s000lbl.pdf.

108. E.g., Michal Tzadok et al., *CBD-Enriched Medical Cannabis for Intractable Pediatric Epilepsy: The Current Israeli Experience*, 35 SEIZURE 41, 44 (2016) (explaining that the Israeli Ministry of Health has approved drug products containing THC).

109. Nick Thompson, *There is Legal Marijuana in the UK, So Why Is It Hard to Get Hold Of?*, Independent (Apr. 26, 2017, 8:00 PM), <https://www.independent.co.uk/life-style/health-and-families/legal-marijuana-medical-uk-availability-law-a7699056.html>.

110. Derick T. Wade et al., *Meta-Analysis of the Efficacy and Safety of Sativex (Nabiximols), on Spasticity in People with Multiple Sclerosis*, 16 MULTIPLE SCLEROSIS 707 (2010); see also *Sativex*, GW PHARMACEUTICALS, <https://www.gwpharm.com/products-pipeline/sativex-delta-9-tetrahydrocannabinol-and-cannabidiol> (last visited Apr. 9, 2018).

111. Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 81 Fed. Reg. 53,688 (Aug. 12, 2016) (to be codified at 21 C.F.R. pt. 1301).

112. *DEA Announces Actions Related to Marijuana and Industrial Hemp*, U.S. DRUG ENFORCEMENT ADMIN. (Aug. 11, 2016), <https://www.dea.gov/divisions/hq/2016/hq081116.shtml>.

component, THC, has undergone extensive clinical testing in the United States and abroad. Currently, the CSA makes no distinction between THC and the botanical form of marijuana.¹¹³ However, according to the DEA, in its isolated form, THC has no legitimate medical uses and a “high potential for abuse.”¹¹⁴ Yet, when suspended in sesame oil and gelatin or dissolved in alcohol solution, then THC has legitimate medical uses and a “low potential for abuse and dependence.”¹¹⁵

Can purified THC be said to have no legitimate medical uses when it is the sole active ingredient in two FDA approved medications? Since THC is the primary psychoactive ingredient in marijuana, can marijuana be said to have no accepted medical uses when it is the source of THC? From the perspective of the DEA, the Department of Health and Human Services (HHS), and the FDA, the answer is yes. However, for the medical community, and a growing number of states, the answer may be no. This apparent contradiction reflects the growing tension between opinions of healthcare providers and those of the regulatory community.

Essentially, dronabinol is listed in three different schedules depending on whether it is purified, dissolved in alcohol, or suspended in sesame oil and gelatin. The fact that a single substance is listed in multiple schedules depending on how it is formulated highlights inconsistencies in the current scheduling methodology. One might ask whether it is logical for two oral formulations of a single Schedule I compound to be listed in Schedules II and III.

Jerry Avorn, a Harvard Medical School Professor and drug policy expert, has referred to the dismissal of the therapeutic benefits of marijuana as an “example of the FDA making pronouncements that seem to be driven more by ideology than by science.”¹¹⁶ Based on numerous FDA approvals for the medical use of cannabinoids, American and international clinical trial results,¹¹⁷ a recent landmark public

113. 21 U.S.C. § 802 (2011) (“The term ‘marihuana’ means all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.”).

114. U.S. DRUG ENF’T ADMIN., CONTROLLED SUBSTANCES, *supra* note 105, at 15 (listing dronabinol (THC) in Schedule I).

115. *Id.* at 8 (listing dronabinol (THC) in Schedules II and II).

116. Gardiner Harris, *F.D.A. Dismisses Medical Benefit from Marijuana*, N.Y. TIMES, Apr. 21, 2006, at A1.

117. See Donald Abrams et al., *Cannabis in Painful HIV-Associated Sensory Neuropathy*, 68 NEUROLOGY 515 (2007) (reporting that smoked cannabis is superior to placebo for treating pain in HIV-associated sensory neuropathy); Ronald J. Ellis et al., *Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover*

health study,¹¹⁸ and countless doctors who recommend marijuana to patients every day, it may no longer be reasonable to claim that marijuana and its derivatives have no acceptable medical uses. The evidence for the medical use of psychedelics may be even greater than the evidence for using medical marijuana. Multiple Phase 2 clinical trials have been conducted in the United States and abroad. As mentioned previously, at least one Schedule I psychedelic, ibogaine, has been prescribed for medical use in other countries.¹¹⁹

In light of these developments, it may be time for lawmakers and administrators to reevaluate the current U.S. drug scheduling system, an aging relic of the War on Drugs. Because marijuana and most psychedelics are categorized as Schedule I substances, research into their medical uses is significantly impaired. The following section describes how the restricted status of Schedule I substances drives up the cost of producing these compounds, restricts access to clinical trials, and perpetuates the stigma associated with psychedelic medicines.

B. Stigma Associated with the Use of Psychedelic Compounds

Doctors, insurance companies, universities, and employers contribute to the stigma associated with psychedelic medications. A patient who uses psychedelics or enrolls in a clinical trial to evaluate them could face discrimination from any of these groups. The fact that most psychedelics are Schedule I controlled substances contributes to the stigma. It may inhibit physicians from learning about or discussing psychedelics and it could prevent patients from enrolling in legitimate research programs. Unfortunately, despite great advances made in securing accommodations for people with disabilities, patients with

Clinical Trial, 34 NEUROPSYCHOPHARMACOLOGY 672 (2009) (reporting that smoked cannabis is superior to placebo for treating neuropathic pain associated with HIV); Mark A. Ware et al., *Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial*, 182 CANADIAN MED. ASS'N J. 694 (2010) (explaining that inhaled herbal cannabis was well-tolerated and reduced pain and improved sleep in adults with chronic neuropathic pain); John Zajicek et al., *Cannabinoids for Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis (CAMS Study): Multicentre Randomised Placebo-Controlled Trial*, 362 LANCET 1517 (2003) (reporting that whole cannabis extract and isolated THC are equally effective at improving walk time and patient perception of spasticity in multiple sclerosis).

118. NAT'L ACADEMIES OF SCIENCES, ENG'G & MED., *THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH* 13 (2017) (reporting that evidence supports the use of cannabis for treating chronic pain in adults).

119. See Noller et al., *supra* note 83, at 2.

mental illness still experience discrimination in society.¹²⁰ They can face negative attitudes from employers, universities, and even their treatment providers. As a result, they can have difficulty finding and maintaining employment, completing their educations, or receiving adequate medical care.¹²¹ Evidence shows that physicians can harbor negative attitudes toward both the mentally ill and individuals who consume illicit substances.¹²² If physicians remain critical of using psychedelic medicines, then the stigma associated with mental illness could be compounded by the stigma associated with psychedelics.

1. *Stigma Perpetuated by Physicians*

Doctors are trained to view controlled substances with skepticism and to monitor patients closely for signs of substance use disorders and drug-seeking behavior. As a result, many physicians harbor negative attitudes toward patients who suffer from substance use disorders.¹²³ These biases may affect their views of patients who seek psychedelics for legitimate medical uses. If a patient visits his doctor and requests a prescription for ketamine, a red flag goes up in the doctor's mind, and she will likely react with a mix of confusion and consternation. Yet in reality, given the current research on ketamine for treating depression, asking for the drug may be a reasonable request. A patient inquiry about LSD, psilocybin, or ayahuasca may elicit a harsher response and possibly a lecture on the dangers of drug use. Physicians understandably fear opening themselves up to medical malpractice liability. From a physicians's perspective, discussing

120. See, e.g., Bernice A. Pescosolido, *The Public Stigma of Mental Illness, What Do We Think; What Do We Know; What Can We Prove?*, 54 J. HEALTH & SOC. BEHAV. 1 (2013).

121. See Lynne M. Harris et al., *Perspectives on Barriers to Employment for Job Seekers with Mental Illness and Additional Substance-Use Problems*, 22 HEALTH & SOC. CARE COMMUNITY 67 (2014); see also Annica Brannlund, Mattias Strandh & Karina Nilsson, *Mental-Health and Educational Achievement: The Link Between Poor Mental-Health and Upper Secondary School Completion and Grades*, 26 J. MENTAL HEALTH 318 (2016) (reporting that mental health problems during childhood are associated with negative educational outcomes).

122. Andriyka Papish et al., *Reducing the Stigma of Mental Illness in Undergraduate Medical Education: A Randomized Controlled Trial*, 13 BMC MED. EDUC. 141 (2013) (explaining that the attitudes toward mental illness held by medical professionals are often more negative than those held by the general public); see also Leonieke C. van Boekel, *Stigma Among Health Professionals Towards Patients with Substance Use Disorders and Its Consequences for Healthcare Delivery: Systematic Review*, 131 DRUG & ALCOHOL DEPENDENCE 23, 32–33 (2013) (explaining that healthcare providers' negative views of patients with substance use disorders can negatively impact the quality of clinical care).

123. See van Boekel, *supra* note 122, at 26, 29.

psychedelics with patients could expose doctors to risk if patients subsequently use the drugs and are harmed. In addition, doctors may fear sanctions from the federal government and state medical licensing boards for recommending Schedule I controlled substances.¹²⁴ However, instead of shutting down the conversation, a more constructive approach might be to look for ongoing research programs to which the patient might be referred. For example, nonprofit organizations such as MAPS have ongoing trials to evaluate the use of psychedelics for treating mental illness and substance use disorders.¹²⁵

Oftentimes, to be on the cutting edge of science, we must look back and reevaluate older technologies that were overlooked or shunned by previous generations. We should also examine our perspectives for flaws. Only a few decades ago, many healthcare providers would have looked down upon complementary medicine modalities such as meditation, acupuncture, and yoga.¹²⁶ Though these practices have been used in some form for millennia, until recently the Western medical establishment viewed them as fringe activities. Today, healthcare providers routinely recommend them, and some insurance companies will even reimburse patients for their use.¹²⁷ Perhaps the use of psychedelic medications will follow a similar trajectory.

Like psychedelics, mental illnesses are stigmatized by society and healthcare providers. Some of the stigma may stem from physician perceptions that mental illnesses are untreatable.¹²⁸ These views are reinforced by the relative ineffectiveness of traditional antidepressants. Non-pharmacologic treatments such as ECT, psychosurgery, and DBS have their own associated stigma. Though it is counterproductive for patients to feel stigmatized by the treatments they seek to cope with mental illness, negative views of psychiatric disorders

124. See ROBERT A. MIKOS, MARIJUANA LAW, POLICY, AND AUTHORITY 602 (2017) (explaining that, in the early days of state marijuana reforms, the DEA attempted to discourage California physicians from recommending medical marijuana by threatening to revoke their DEA licenses).

125. MDMA-Assisted Psychotherapy, MULTIDISCIPLINARY ASS'N PSYCHEDELIC STUD., <https://www.maps.org/research> (last visited Jan. 26, 2018).

126. See Eliot Marshall, *Bastions of Tradition Adapt to Alternative Medicine*, 288 SCIENCE 1571 (2000) (citing physician-critics of complementary medicine).

127. Kenneth R. Pelletier, *Current Trends in the Integration and Reimbursement of Complementary and Alternative Medicine by Managed Care, Insurance Carriers, and Hospital Providers*, 12 AM. J. HEALTH PROMOTION 112 (1997).

128. See Colleen L. Barry et al., *Stigma, Discrimination, Treatment Effectiveness, and Policy: Public Views About Drug Addiction and Mental Illness*, 65 PSYCHIATRIC SERVICES 1269, 1271 (2014) (explaining that stigma associated with HIV was reduced after increasing public recognition that AIDS is a treatable condition and proposing that reframing mental illness as treatable could reduce associated stigma).

and controlled substances persist in the medical profession. These perceptions hinder potentially life-saving uses for psychedelic medicines.

2. *Employment Discrimination*

In addition to facing the negative attitudes of healthcare providers, patients who use psychedelics may fear discrimination from their employers. People tend to fear what they do not understand, and psychedelic substances and mental illness are both poorly understood in our society. Research suggests that employers may discriminate against people with disabilities when making hiring decisions, and they may be less likely to hire individuals with mental illnesses than those with physical disabilities.¹²⁹ As a result, if a person's use of psychedelics to treat mental illness becomes known to employers, it could adversely affect a hiring decision. If people with mental illness are employed, and their use of psychedelics is revealed to superiors or co-workers, they could be chastised, demoted, moved to a new position, or fired.

3. *The Influence of Religion*

It is possible that organized religion has played a role in stigmatizing psychedelic medications. These substances can induce powerful spiritual experiences in patients, and this power may be threatening to some religious institutions. In the 1960s, psychiatrist Stanislav Grof administered LSD to patients in his clinical practice. He believed the mystical experiences made possible by psychedelics threatened America's moral values.¹³⁰ Describing the introduction of psychedelics to industrialized nations, Grof wrote: "Western culture was unprepared to accept and incorporate the extraordinary mind-altering properties and power of psychedelics. The sudden invasion of the Dionysian elements from the depths of the unconscious and the heights of the superconscious was too threatening for the Puritanical values of our society."¹³¹ According to Grof, psychedelic experiences challenge the very foundations of Western thought and materialist sci-

129. See, e.g., Song Ju et al., *Employer Attitudes Toward Workers with Disabilities: A Review of Research in the Past Decade*, J. VOCATIONAL REHABILITATION 113, 119 (2013) (reporting that employers are "less likely to endorse the hiring of people with disabilities when compared to those without disabilities" and that employers view employees with physical disabilities more positively than people with intellectual disabilities).

130. Michael Pollan, *The Trip Treatment*, NEW YORKER (Feb. 9, 2015), <https://www.newyorker.com/magazine/2015/02/09/trip-treatment>.

131. MYRON J. STOLAROFF, THE SECRET CHIEF REVEALED 13 (rev. ed. 2004).

ence.¹³² Similar observations have been made in Mexico, where the use of psychedelic mushrooms is thought to have been suppressed by Spanish colonials who viewed them as instruments of paganism.¹³³

4. *Negative Attitudes Held by University Administrators and Scientists*

Finally, scientists may harbor prejudices against the study of psychedelics. A researcher may not want to risk tarnishing his reputation by being branded a psychedelics researcher. According to David Nichols, Professor Emeritus of Pharmacology at Purdue University, “[i]f you wanted to kill your research career in academics [during the 1970s], you did research on psychedelics.”¹³⁴ Since the early 1990s, and particularly in the last fifteen years, attitudes towards the academic study of psychedelics have slowly begun to shift. However, psychedelics research remains a challenging field to break into due to regulatory hurdles, federal limits on the amount of the drugs that may be produced each year, and the reluctance of universities and scientists to take on the risk associated with studying Schedule I substances.

5. *The Stigma Associated with Psychedelics May Be Decreasing*

There is some evidence that the stigma associated with psychedelics is decreasing. For example, celebrities and public intellectuals are speaking openly about the potential benefits of the drugs. Author Sam Harris, comedian Joe Rogan, and clinical psychologist Jordan Peterson have openly discussed their personal use of psychedelics.¹³⁵ Each of them reaches millions of listeners per month through lectures and podcasts released on social media. The public also appears more receptive to learning about psychedelics, as evidenced by a growing tourism industry in South America that caters to

132. *Id.*

133. Gaston Guzman, *Hallucinogenic Mushrooms in Mexico: An Overview*, 62 *ECON. BOTANY* 404, 410 (2008).

134. *See* Ferro, *supra* note 37.

135. *See* Big Think, *Sam Harris: Can Psychedelics Help You Expand Your Mind?*, YOUTUBE (Oct. 30, 2014), <https://www.youtube.com/watch?v=XOET9n8wnmo>; Bite-Sized Philosophy, *Jordan Peterson—The Mystery of DMT and Psilocybin*, YOUTUBE (May 17, 2017), <https://www.youtube.com/watch?v=GoI5sPM073k>; Erik Hede-gaard, *How Joe Rogan Went from UFC Announcer to 21st-Century Timothy Leary*, ROLLING STONE (Oct. 22, 2015), <https://www.rollingstone.com/sports/features/how-joe-rogan-went-from-ufc-announcer-to-21st-century-timothy-leary-20151022>; *see also* Christian Chensvold, *YouTube’s New Father Figure*, NAT’L REV. (June 17, 2017, 4:00 AM), <http://www.nationalreview.com/article/448714/jordan-b-peterson-self-help-guru-father-figure> (explaining the rise of Jordan Peterson as a YouTube sensation with over 300,000 regular subscribers).

Western travelers who wish to consume ayahuasca.¹³⁶ Popular books and articles about psychedelics have been published, and ongoing clinical trials have received regular attention in the mainstream media.¹³⁷ However, one might ask whether the culture is changing rapidly enough to have a substantial impact on the epidemic of mental illness. The cost of doing nothing is high. Suicide, drug overdose, economic losses, and the emotional suffering of patients and those around them, take a heavy toll on society. With few traditional psychiatric drugs in the development pipeline, psychedelics could be one of the best options for improving mental health. However, to realize their potential, the stigma associated with their use must be reduced.

C. *Safety Concerns*

Any consideration of administering psychedelics in humans should include a discussion of the associated risks. Most safety concerns fall into the following categories: risk of adverse events, drug misuse, dependence, and diversion of legitimate supplies of drugs to illegitimate channels.¹³⁸ Even though there are potential dangers, the risks must be balanced against the possible benefits to individual patients and public health. When it comes to safety, not all psychedelics are the same. Some psychedelics—such as ketamine, psilocybin, and LSD—are believed to be relatively safe while others—including MDMA and ibogaine—may require further research.

As discussed above, ketamine is a well-studied drug used primarily in surgery and pain management. It is thought to be extremely safe at the doses used in psychiatry, which are many times lower than those used for anesthesia and analgesia. However, even at low doses, some patients experience headache, dizziness, and nausea during ketamine infusion. These symptoms are usually benign and resolve shortly after stopping a treatment. Chronic overuse of ketamine has been associated

136. See Hill, *supra* note 63.

137. See, e.g., AYELET WALDMAN, *A REALLY GOOD DAY: HOW MICRODOSING MADE A MEGA DIFFERENCE IN MY MOOD, MY MARRIAGE, AND MY LIFE* (2017) (discussing the author's use of LSD microdosing in which small doses of the drug are consumed on a semi-regular basis); see also Dave Philipps, *F.D.A. Agrees to New Trials for Ecstasy to Help Soothe Post-Traumatic Stress*, N.Y. TIMES, Nov. 30, 2016, at A11.

138. See generally Rick Doblin, *THE PSYCHEDELIC POLICY QUAGMIRE: HEALTH, LAW, FREEDOM, AND SOCIETY* 365 (J. Harold Ellens & Thomas B. Roberts eds., 2015) (describing four major areas of risk including "misuse, abuse, diversion, and the potential negative effects of information about approved medical use on nonmedical use patterns").

with more serious side effects such as bladder disease and urinary dysfunction.¹³⁹

The classic hallucinogens LSD and psilocybin are also believed to be relatively safe.¹⁴⁰ They are thought to have low toxicity and no potential for dependence or symptoms of withdrawal. Nevertheless, perceptual and emotional disturbances can cause transient anxiety and paranoia, which some people find distressing. These effects are usually temporary and resolve completely in a matter of hours.¹⁴¹ There have been scattered reports of anxiety escalating to aggressive behavior toward oneself and others. Prolonged psychotic episodes lasting days or months have also been reported. However, these reactions are believed to be uncommon, and the risk of harm can be reduced by administering psychedelics in safe environments under appropriate supervision.¹⁴² In exceptionally rare cases, individuals have reported consuming hallucinogens and experiencing perceptual disturbances for months or years after ceasing to use the drugs. This phenomenon is referred to as Hallucinogen Persisting Perception Disorder (HPPD).¹⁴³

Like the classic hallucinogens, ayahuasca is reported to be relatively safe and to produce no cognitive or psychological problems following long term use. Nausea and vomiting are the most common side effects. Less frequently, ayahuasca may cause transient psychotic epi-

139. Natalie Katalinic et al., *Ketamine as a New Treatment for Depression: A Review of Its Efficacy and Adverse Effects*, 47 AUSTL. & N.Z. J. PSYCHIATRY 710, 722 (2013); Shu-Huei Shen & Jia-Hwia Wang, *Imaging Diagnosis of Ketamine-Induced Uropathy*, 26 UROLOGICAL SCI. 160, 160 (2015).

140. Jan Van Amsterdam, Antoon Opperhuizen & Wim Van Den Brink, *Harm Potential of Magic Mushroom Use: A Review*, 59 REG. TOXICOLOGY PHARMACOLOGY 423 (2011) (presenting the results of a 2007 study commissioned by the Dutch Minister of Health to evaluate the potential harm of consuming mushrooms that contain psilocybin. The report summarized the scientific literature and concluded there is little potential for psychological or physical dependence and low potential for toxicity from chronic use. The study reported that magic mushrooms presented few risks to the individual or public health).

141. Jeffrey A. Lieberman & Daniel Shalev, *Back to the Future: Research Renewed on the Clinical Utility of Psychedelic Drugs*, 1 J. PSYCHOPHARMACOLOGY 1198, 1199 (2016).

142. MW Johnson, WA Richards & RR Griffiths, *Human Hallucinogen Research: Guidelines and Safety*, 22 J. PSYCHOPHARMACOLOGY 603, 607 (2008).

143. Leo Hermle et al., *Hallucinogen-Persisting Perception Disorder*, 2 THERAPEUTIC ADVANCES PSYCHOPHARMACOLOGY 199 (2012) (describing one case in which a thirty-three-year-old woman reported perceptual disturbances that persisted for thirteen years after consuming LSD); see also John H. Halpern, *Hallucinogen Persisting Perception Disorder: What Do We Know After 50 Years?*, 69 DRUG & ALCOHOL DEPENDENCE 109 (2003); Fabida Noushad et al., *25 Years of Hallucinogen Persisting Perception Disorder—A Diagnostic Challenge*, 8 BRITISH J. MED. PRACTITIONERS 805 (2015).

sodes. However, these events may be due to preexisting bipolar disorder, a history of psychosis, or concomitant use of other drugs.¹⁴⁴

MDMA exhibits some neurotoxicity at high doses in laboratory animals. Nonetheless, some psychedelics researchers believe it is safe at the therapeutic doses used in humans.¹⁴⁵ The Phase 1 and 2 trials completed by MAPS support this conclusion, and the upcoming Phase 3 trial will yield more information.¹⁴⁶ However, adverse events including hyperthermia, renal failure, and pulmonary edema, have been reported in the literature.¹⁴⁷ It is worth noting that the MDMA consumed in these case reports was manufactured illegally under unknown conditions, and it may not be possible to rule out contamination as the precipitating factor.

Case reports have linked ibogaine to cardiac arrhythmias and sudden cardiac arrest.¹⁴⁸ One study reported that there were nineteen fatalities recorded following ibogaine ingestion between 1990 and 2008.¹⁴⁹ However, the authors concluded that detailed post-mortem information is available for only fourteen of those cases, and twelve of the fourteen are likely attributable to preexisting conditions such as severe cardiovascular disease or concurrent substance use disorders.¹⁵⁰

144. Rafael G. dos Santos, Jose Carlos Bouso & Jaime E.C. Hallak, *Ayahuasca Dimethyltryptamine and Psychosis: A Systematic Review of Human Studies*, 7 THERAPEUTIC ADVANCES PSYCHOPHARMACOLOGY 141 (2017); see also Rafael Guimarães dos Santos, *Safety and Side Effects of Ayahuasca in Humans—An Overview Focusing on Developmental Toxicology*, 45 J. PSYCHOACTIVE DRUGS 68 (2013).

145. See Johnson, Richards & Griffiths, *supra* note 142, at 606.

146. *A Phase 3 Program of MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder (PTSD)*, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUD., <http://www.maps.org/research/mdma/ptsd/phase3> (last visited Dec. 27, 2017).

147. See, e.g., K.J. Dar & M.E. McBrien, *MDMA Induced Hyperthermia: Report of a Fatality and Review of Current Therapy*, 22 INTENSIVE CARE MED. 995, 995 (1996); Astrid Haaland et al., *Isolated Non-Cardiogenic Pulmonary Edema—A Rare Complication of MDMA Toxicity*, AM. J. EMERGENCY MED. 3 (2017); Ravi K. Narang et al., *A Case of MDMA Toxicity with Unusual Clinical and Neuroradiological Features*, 15 INTENSIVE CARE SOC'Y 70 (2014).

148. E.g., RP Litjens & TM Brunt, *How Toxic is Ibogaine?*, 54 CLINICAL TOXICOLOGY 297 (2016); X. Koenig et al., *Anti-Addiction Drug Ibogaine Inhibits hERG Channels: A Cardiac Arrhythmia Risk*, 2 ADDICTION BIOLOGY 237 (2014); Stavroula A. Papadodima et al., *Ibogaine Related Sudden Death: A Case Report*, 20 J. FORENSIC & L. MED. 809 (2013) (reporting the death of a fifty-two-year-old man with a history of alcoholism and liver cirrhosis that could be linked to ibogaine consumption); L.J. Schep et al., *Ibogaine For Treating Drug Dependence. What is a Safe Dose?*, 166 DRUG & ALCOHOL DEPENDENCE 1 (2016).

149. Noller, *supra* note 83, at 8.

150. *Id.*

Several cases of mania have also been reported.¹⁵¹ These events could be due to underlying medical conditions. Additional research is necessary, and ongoing studies should provide additional safety information. If ibogaine therapy is implemented in the United States, protocols should be developed to screen for individuals with cardiovascular disease and other risk factors.

Another safety concern associated with psychedelics is the diversion of drugs from research labs or medical facilities to illicit channels.¹⁵² Drug and alcohol use disorders are very real concerns, and doctors understandably fear contributing to these vexing problems. They could face lawsuits or penalties from state licensing boards if patients use psychedelics inappropriately and harm themselves or others. However, current evidence suggests that psychedelics are not addictive.¹⁵³ Furthermore, the risk of diversion is likely exaggerated.¹⁵⁴ In one article by authorities in psychopharmacology, the authors report finding no significant examples of Schedule I drugs being diverted from research labs into the recreational market.¹⁵⁵ Concerns regarding diversion and substance use disorders can also be minimized by administering psychedelics in controlled settings under the supervision of medical professionals. As with other medical procedures, doctors can minimize their potential liability by being open and transparent about the risks and benefits of treatment, and by obtaining full informed consent from patients.

Some psychedelics are being studied to treat substance use disorders involving alcohol, opioids, and tobacco.¹⁵⁶ These three substances have risks that are far more serious and well-established than the dangers associated with psychedelics. Tobacco smoke and alcohol are among the most dangerous substances that can legally be consumed. According to the Centers for Disease Control and Prevention

151. Cole J. Marta et al., *Mania Following Use of Ibogaine: A Case Series*, 24 AM. J. ADDICTIONS 203 (2015).

152. See Alex Kreit, *Controlled Substances, Uncontrolled Law*, 6 ALBANY GOV. L. REV. 355 (2013).

153. Teri Suzanne Krebs, *Protecting the Human Rights of People Who Use Psychedelics*, 2 LANCET 294 (2015).

154. See Kreit, *supra* note 152, at 356.

155. David J. Nutt, Leslie A. King & David E. Nichols, *Effects of Schedule I Drug Laws on Neuroscience Research and Treatment Innovation*, 14 NATURE REV. NEUROSCIENCE 577, 579 (2013).

156. See, e.g., Matthew W. Johnson et al., *Pilot Study of the 5-HT_{2A}R Agonist Psilocybin in the Treatment of Tobacco Addiction*, 28 J. PSYCHOPHARMACOLOGY 983 (2014); see also Michael P. Bogenschutz et al., *Psilocybin-Assisted Treatment for Alcohol Dependence: A Proof-of-Concept Study*, 29 J. PSYCHOPHARMACOLOGY 289 (2015); Brown & Alper, *supra* note 80.

(CDC), smoking tobacco “harms nearly every organ of the body.”¹⁵⁷ Each year, cigarettes cause over 480,000 deaths in the US,¹⁵⁸ and excessive alcohol consumption results in approximately 88,000 deaths per year.¹⁵⁹ Drinking alcohol is associated with increased risk of developing heart disease and cancer of the mouth, throat, esophagus, liver, colon, and breast.¹⁶⁰ Cigarettes and alcohol have no legitimate medical uses and impose significant costs on society far greater than those attributed to psychedelics. Yet they can be purchased by anyone of legal age at nearly any convenience store.

Unlike alcohol and tobacco, opioids have legitimate medical uses; however, the potential for overuse, dependence, and harm is well-documented. According to recent estimates, about one hundred Americans die each day from opioid overdose.¹⁶¹ In many cases, the recommended treatment for opioid use disorder is another opioid, such as methadone, which itself can result in fatal overdose.¹⁶² Psychedelic medicines could break this trend of treating opioid use disorders with other drugs in the same class.

Some might argue that psychedelic drugs should be banned entirely because the risks of harm are too great. However, though there are some legitimate risks, they must be balanced against the potential public health benefits. Moreover, when evaluating the dangers posed by psychedelic drugs, one must consider that patients are also exposed to significant risks when using traditional therapies for mental illness. For example, the risks associated with antidepressants are well-established. SSRIs commonly cause sexual dysfunction, weight gain, and

157. *Smoking & Tobacco Use: Fast Facts*, CTNS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm (last updated Dec. 27, 2017).

158. *Id.*

159. *Alcohol & Public Health: Fact Sheets—Alcohol Use and Your Health*, CTNS. FOR DISEASE CONTROL & PREVENTION (last updated Jan. 3, 2018), <https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm>.

160. *Id.*

161. Christopher Ingram, *White House Opioid Commission to Trump: ‘Declare A National Emergency’ on Drug Abuse*, WASH. POST (July 31, 2017), https://www.washingtonpost.com/news/wonk/wp/2017/07/31/white-house-opioid-commission-to-trump-declare-a-national-emergency-on-drug-overdoses/?utm_term=.ea33c0b62c0f (citing a draft report by the President’s Commission on Combating Drug Addiction and the Opioid Crisis, which states that 142 Americans are killed daily by opioids); *Opioid Overdose: Understanding the Epidemic*, CTNS. FOR DISEASE CONTROL & PREVENTION (last updated Dec. 27, 2017), <https://www.cdc.gov/drugoverdose/epidemic/index.html> (reporting that there are ninety-one deaths each day due opioid overdose).

162. See Mark Faul, Michele Boh & Caleb Alexander, *Methadone Prescribing and Overdose and the Association with Medicaid Preferred Drug List Policies—United States, 2007–2014*, 66 MORBIDITY & MORTALITY WKLY. REP. 320 (2017).

sleep disturbances.¹⁶³ If they are discontinued abruptly, they can cause lethargy, dizziness, anxiety, and agitation. In rare cases, they may increase suicidal behavior.¹⁶⁴ Tricyclic antidepressants, such as imipramine and amitriptyline, which are still prescribed but have been largely supplanted by SSRIs, can cause seizures, cardiac arrhythmias, and death.¹⁶⁵ Atypical antipsychotics, such as risperidone and olanzapine, which are often used to augment the effects of traditional antidepressants, have caused cardiac conduction abnormalities, myocarditis, permanent neurologic dysfunction, and death.¹⁶⁶

Even though administering psychedelics raises understandable safety concerns, there are also significant risks associated with not adequately treating the mentally ill. Every year, 38,000 Americans die of suicide, which translates to 105 suicide deaths per day (or one suicide every thirteen minutes).¹⁶⁷ It has been estimated that twenty-two veterans commit suicide daily.¹⁶⁸ Even if these statistics overestimate the true suicide rate, they would be no less disturbing. The economic cost of suicide is equally troubling. In 2015, the CDC estimated that suicide cost the United States \$51 billion in medical and work-related costs.¹⁶⁹

A drug like ketamine, which has proven safe and effective in patients who have failed to respond to traditional antidepressants, could help reduce suicide rates. Unlike traditional antidepressants, it acts quickly and is generally considered safe at doses much higher than those of drugs currently used to treat depression.¹⁷⁰ However, even though ketamine may be legally prescribed in the United States for this purpose, there are many obstacles in the way of patients who hope

163. Christina M. Dording et al., *The Pharmacologic Management of SSRI-Induced Side Effects: A Survey Of Psychiatrists*, 14 ANNALS CLINICAL PSYCHIATRY 143 (2002).

164. See, e.g., David Gunnell & Deborah Ashby, *Antidepressants and Suicide: What Is the Balance of Benefit and Harm*, 329 BMJ 34 (2004).

165. James M. Ferguson, *SSRI Antidepressant Medications: Adverse Effects and Tolerability*, 3 PRIMARY CARE COMPANION J. CLINICAL PSYCHIATRY 22 (2001).

166. Peter M. Haddad & Sonu G. Sharma, *Adverse Effects of Atypical Antipsychotics: Differential Risk and Clinical Implications*, 21 CNS DRUGS 911, 912 (2007).

167. *Suicide Facts*, SUICIDE AWARENESS VOICES EDUC., http://www.save.org/index.cfm?fuseaction=home.viewPage&page_id=705D5DF4-055B-F1EC-3F66462866FCB4E6 (last visited Aug. 16 2017).

168. Moni Basu, *Why Suicide Rate Among Veterans May Be More Than 22 a Day*, CNN (Nov. 14, 2013), <http://www.cnn.com/2013/09/21/us/22-veteran-suicides-a-day/>.

169. CTRS. FOR DISEASE CONTROL & PREVENTION, *SUICIDE: FACTS AT A GLANCE I* (2015), <https://www.cdc.gov/violenceprevention/pdf/suicide-datasheet-a.pdf>.

170. Rodrigo Machado-Vieira et al., *Ketamine and the Next Generation of Antidepressants with a Rapid Onset of Action*, 123 PHARMACOLOGY & THERAPEUTICS 143 (2009).

to receive it. While these hurdles to effective treatments remain in place, thousands of patients with treatment refractory mental illness will continue to suffer and die each year, costing the economy billions of dollars and taking an incalculable emotional toll on society.

The death toll from drug overdose rivals that of suicide and has more than tripled since 1999.¹⁷¹ In 2016, more than 64,000 deaths in the United States were attributed to drug overdose. Most of these deaths were due to opioids.¹⁷² Even methadone, which is commonly used to treat opioid use disorder, was implicated in 3314 deaths in the United States in 2016.¹⁷³ One possible alternative is the psychedelic drug ibogaine. Though it may carry some risk of cardiotoxicity, it could be useful in treating opioid use disorder. If a person is hopelessly addicted to opioids, and the likely outcome is an imminent drug-induced death, then taking some calculated risk may be warranted. Risks are already taken with methadone and other forms of medication assisted treatment for opioid use disorder. Implementing proper screening, counseling, and safety precautions could reduce or eliminate the risks associated with ibogaine.

When a patient fails to respond to SSRIs and other classic psychiatric drugs, he may be subjected to therapies with substantial risks of death and disability. Some patients with mental illness have electrodes implanted in their brains or portions of their brains removed. These procedures carry a risk of hemorrhage, seizure, stroke, infection, and loss of speech and motor function.¹⁷⁴ A patient facing these treatment options should be given the opportunity to try a drug that has the potential to be effective, even if it carries potentially serious or even lethal risks.

D. Lack of Incentives for Research and Development

The U.S. psychiatric drug industry is large, with sales exceeding \$70 billion in 2010.¹⁷⁵ Despite high sales volume and growing demand due to the widespread nature of mental illness, many drug com-

171. See *Overdose Death Rates*, NAT'L INST. ON DRUG ABUSE, *supra* note 10 (providing data illustrating that national drug overdose deaths more than tripled from less than 20,000 in 1999 to over 64,000 in 2016).

172. *Id.*

173. *Id.*

174. See Aleksander Beric et al., *Complications of Deep Brain Stimulation Surgery*, 77 STEREOTACTIC FUNCTIONAL NEUROSURGERY 73, 75 (2001); Albert J. Fenoy & Richard K. Simpson, Jr., *Risks of Common Complications in Deep Brain Stimulation Surgery: Management and Avoidance*, 120 J. NEUROSURGERY 132, 134–36 (2014).

175. Gary Greenberg, *The Psychiatric Drug Crisis*, NEW YORKER (Sept. 3, 2013), <http://www.newyorker.com/tech/elements/the-psychiatric-drug-crisis>.

panies have scaled back funding for research on psychiatric drugs.¹⁷⁶ Others have pulled out all together.¹⁷⁷ One explanation for decreased investment is the relative unpredictability of psychiatric drug discovery compared to other fields in medicine. The nervous system is extremely complex, and the causes of mental illness are poorly defined.¹⁷⁸ Furthermore, in the past, many psychiatric drugs were discovered through serendipitous events rather than well-planned research, and the reasons for their effectiveness are often unclear.¹⁷⁹ As a result, the mechanism of action of antidepressants has changed little in the half century since they were introduced. It is unclear where to go from here.¹⁸⁰ The drugs used to treat substance use disorders have also changed little in the past fifty years. For instance, Naloxone, a drug used to treat opioid dependence, was invented over fifty years ago,¹⁸¹ and disulfiram, which is used to treat alcoholism, was discovered in 1945.¹⁸²

Drug makers may have little interest in commercializing psychedelic drugs. One explanation is that existing psychedelics cannot be patented.¹⁸³ In order to be patent eligible, a drug must be new and cannot already be in public use.¹⁸⁴ Synthetic psychedelics have been produced and used for decades, and naturally occurring psychedelics have been grown and consumed for hundreds or thousands of years. Therefore, they lack novelty and are not eligible for patent protection. Furthermore, because they are naturally occurring, psychedelics derived from plants or animals fall into one of three judicially created exceptions to patent-eligible subject matter.¹⁸⁵ Under U.S. patent law, inventors cannot patent laws of nature, natural

176. Steven E. Hyman, *Psychiatric Drug Development: Diagnosing a Crisis*, CEREBRUM, Mar.–Apr. 2013, at 2.

177. *Id.*

178. See Editorial, *Psychiatric Drug Discovery on the Couch*, 6 NATURE REV. DRUG DISCOVERY 171 (2007).

179. Thomas A. Ban, *The Role of Serendipity in Drug Discovery*, 8 DIALOGUES CLINICAL NEUROSCIENCE 335 (2006).

180. Greenberg, *supra* note 175.

181. William Yardley, *Jack Fishman Dies at 83; Saved Many from Overdose*, N.Y. TIMES, Dec. 15, 2013, at A30.

182. Helge Kragh, *From Disulfiram to Antabuse: The Invention of a Drug*, 33 BULL. FOR HIST. CHEMISTRY 82, 82 (2008).

183. Ferro, *supra* note 37.

184. JANICE M. MUELLER, PATENT LAW 174 (4th ed. 2013).

185. Joshua D. Sarnoff, *Patent-Eligible Inventions After Bilski: History and Theory*, 63 HASTINGS L.J. 53 (2011); see also Guisepe Colangelo, *Still Anything Under the Sun? Patent-Eligibility After Bilski*, 1 COMP. L. REV. 1, 3 (2010) (discussing how U.S. Supreme Court precedent excludes laws of nature, natural phenomena, and abstract ideas from patent eligibility).

phenomena, or abstract ideas. Naturally occurring psychedelics such as psilocybin, DMT, and ibogaine would be deemed patent-ineligible products of nature.

Drug makers may also be hesitant to invest in psychedelics because they would compete with their existing products.¹⁸⁶ Instead of investing in new classes of medications, drug companies often modify pre-existing compounds and release them under new trade names. The process of patenting subtle improvements on a drug is called evergreening. It helps drug makers ensure a continued stream of revenue when the patents on their drugs expire.¹⁸⁷ Evergreening can be achieved by patenting a close structural relative of the previously patented molecule, patenting a new formulation of the compound, or patenting a new application of the drug.¹⁸⁸ One famous example of evergreening in psychiatry is the patenting of escitalopram (trade name Lexapro), the “left-handed” mirror image or isomer of citalopram, which is marketed as Celexa by Forest Laboratories.¹⁸⁹ In one French review of escitalopram prescribing habits, the authors conclude that the clinical benefits of escitalopram over citalopram are not well established. Yet, at the time of the study, the overall cost burden of reimbursements for escitalopram were substantially higher than those for citalopram.¹⁹⁰ These data suggest that even though escitalopram may not be more effective than its mirror image citalopram, more money was being spent to treat patients with the newer, patented drug escitalopram. If pharmaceutical companies can profit by evergreening preexisting classes of drugs, their incentives to invest in novel compounds may be reduced. Historically, this lack of incentives has been an obstacle to research and development on psychedelic drugs.

III.

OVERCOMING REGULATORY OBSTACLES TO PSYCHEDELICS RESEARCH AND CLINICAL USE

This section introduces five paths around the regulatory obstacles to researching and administering psychedelic medicines. These options range from working within the existing federal regulatory framework to reforming existing drug laws and creating state-governed

186. See Ferro, *supra* note 37.

187. Andrew W. Hitchings, Emma H. Baker & Teck K. Khong, *Making Medicines Evergreen*, 345 *BMJ* 1, 2 (2012).

188. See *id.*

189. *Id.*

190. Ali A. Alkhafaji et al., *Impact of Evergreening on Patients and Health Insurance: A Meta Analysis and Reimbursement Cost Analysis of Citalopram/Escitalopram Antidepressants*, 10 *BMC MED.* 142, 145 (2012).

systems for regulating psychedelics. State regulatory systems could be found to conflict with the CSA and could consequently be preempted by federal law. When it comes to state laws governing psychedelics, the marijuana laws of U.S. states serve as useful models. Ultimately, systems in which state and federal entities collaborate may be most likely to succeed.

A. *Conduct FDA-Sanctioned Clinical Trials*

One option for developing psychedelic medicines is to work within the federal regulatory framework rather than opposing it. Organizations interested in studying or administering psychedelics can collaborate with the FDA to conduct well-controlled clinical trials and prove the safety and efficacy of these drugs. This approach is promoted by the DEA and FDA and is the path taken by MAPS to seek FDA approval for using smoked marijuana and MDMA-assisted psychotherapy to treat PTSD.¹⁹¹

Clinical trials are divided into four phases. Phase 1 trials evaluate the safety of new drugs in small groups of healthy volunteers. They are often the first time a drug is tested in humans. Before Phase 1 trials can commence, the entities seeking FDA approval, known as the drug sponsors, must submit an Investigational New Drug application (the “IND”). If the IND is approved by the FDA and local Institutional Review Boards (IRBs), then the sponsors can begin clinical testing.¹⁹² At this stage, the emphasis is on establishing safety rather than efficacy, and one goal is to determine which doses can be administered without producing serious side effects.¹⁹³ Phase 1 studies typically contain twenty to eighty participants and can last several months.¹⁹⁴

Phase 2 studies are longer, involve more participants, and evaluate drugs for clinical effectiveness in addition to safety.¹⁹⁵ They can include several hundred participants with the disease or condition to be treated, and they typically last between several months and two

191. *Marijuana for Symptoms of PTSD in U.S. Veterans*, MULTIDISCIPLINARY ASS’N FOR PSYCHEDELIC STUD., <http://www.maps.org/research/mmj/marijuana-us> (last visited Aug. 17, 2017).

192. *The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN. [hereinafter *FDA’s Drug Review Process*], <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last visited Aug. 21, 2017).

193. STUART J. POCOCK, CLINICAL TRIALS: A PRACTICAL APPROACH 1–3 (1983); see also *Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/forpatients/approvals/drugs/ucm405622.htm> (last updated Jan. 4, 2018).

194. *FDA’s Drug Review Process*, *supra* note 192.

195. *Id.*

years.¹⁹⁶ If a drug proves safe and effective in Phase 2, then it may advance to the next stage. Phase 3 clinical trials are much larger, often involving between 300 and 3000 people,¹⁹⁷ and usually include a control group to compare the effects of the drug against a placebo.¹⁹⁸ The study population is also monitored for adverse drug reactions. Phase 3 trials are larger, considerably more expensive, and significantly longer than previous phases. According to the FDA, a Phase 3 trial may last between one and four years.¹⁹⁹ Phase 4 of the process consists of post-market surveillance, also called confirmatory trials, which monitor thousands of volunteers who take the drug for its FDA-approved clinical indication.²⁰⁰

One drawback of the clinical trials process is the length of time required for a drug to complete the first three phases. Estimates of the time have been decreasing since the 1960s and 1970s, when the standard process took approximately eight years. It is thought to have decreased by about six months in the 1980s and 1990s.²⁰¹ Though the FDA has been criticized for approving drugs too slowly, since 2000, it has approved drugs more quickly than its counterpart organizations in Canada and Europe.²⁰² Nevertheless, when Schedule I drugs are involved, there can be significant delays between FDA acceptance of study protocols and the enrollment of participants. According to MAPS, its protocol for dispensing marijuana to patients with PTSD was initially accepted by the FDA on April 28, 2011. However, the first study participant did not receive treatment until February 6, 2017.²⁰³ In this case, the time between initial acceptance of the study protocol and commencement of the study was nearly as long as the entire Phase 1 through Phase 3 trial process for less-strictly-regulated drugs. Future clinical trials with psychedelics could experience similar delays.

A second drawback to working within the existing regulatory framework is the associated expense. The cost of clinical trials using

196. *Id.*

197. *Id.*

198. *Id.*

199. *Id.*

200. *See id.*; *see also Step 5: FDA Post-Market Drug Safety Monitoring*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405579.htm> (last updated Jan. 4, 2018).

201. Erin E. Kepplinger, *FDA's Expedited Approval Mechanisms for New Drug Products*, 34 BIOTECH. L. REP. 15, 21 (2015).

202. Jonathan J. Darrow et al., *New FDA Breakthrough-Drug Category—Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1253 (2014).

203. *See Marijuana for Symptoms of PTSD in U.S. Veterans*, *supra* note 191 (describing the timeline of MAPS marijuana research).

psychedelics is particularly high because their Schedule I status drives up the cost of their manufacture, storage, and administration. For example, a Schedule I controlled substance can only be manufactured in limited quantities by labs with proper DEA licenses. The resulting high costs of manufacturing and administering psychedelics can be prohibitively expensive. David Nutt, a psychiatrist and neuropharmacologist at Imperial College London, estimates the cost of research on Schedule I drugs to be about ten times higher than research on less-restricted substances.²⁰⁴

MAPS contracts with DEA-licensed labs to synthesize psychedelic compounds and works with the FDA to conduct clinical trials. However, current drug regulation severely limits how far the funds raised by MAPS can go. In 1999, MAPS obtained a quote for the synthesis of one gram of psilocybin for use in a study on treating OCD. A DEA-licensed lab agreed to produce the gram for \$10,000.²⁰⁵ More recently, in preparation for its upcoming MDMA trial, MAPS will obtain one kilogram of MDMA for about \$400,000. According to MAPS, half the price is attributable to manufacturing costs, and the other half is associated with licensing fees and regulatory compliance.²⁰⁶ MAPS predicts the cost of conducting two MDMA trials, one in the United States and one in Europe, to be between \$25 million and \$33 million over the course of five years.²⁰⁷

Existing drug laws and the high cost of production and regulatory compliance create a catch-22 for psychedelics researchers. The DEA will not change the scheduling of psychedelic drugs without scientific evidence of efficacy obtained from large, well-controlled clinical trials. However, the current DEA classification of psychedelic compounds makes it challenging to obtain adequate amounts of psychedelics for completing such trials. Nevertheless, as conventional drug manufacturers pull out psychiatric research, nonprofit organizations like MAPS, the Heffter Research Institute, and the Beckley

204. David Nutt, *Illegal Drug Laws: Clearing a 50-Year-Old Obstacle to Research*, 13 PLOS BIOLOGY 1, 4 (2015).

205. Francisco Moreno, *Progress Report: The Psilocybin/Obsessive-Compulsive Disorder (OCD) Study Obtains Final FDA Approval!*, 11 MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUD. 15, 16 (2001).

206. Gigen Mammoser, *A Nonprofit is Raising \$400,000 for a Kilo of MDMA by Hosting "Psychedelic Dinner" Parties*, VICE: THUMP (Mar. 1, 2016, 2:50 PM), https://thump.vice.com/en_ca/article/ez7vja/a-nonprofit-is-raising-400000-for-a-kilo-of-mdma-by-hosting-psychedelic-dinner-parties.

207. *FDA Receives Protocol for Phase 3 Trials of MDMA-Assisted Psychotherapy for PTSD*, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUD. (Jan. 23, 2017), <http://www.maps.org/research/mdma/ptsd/6561-fda-receives-protocol-for-phase-3-trials-of-mdma-assisted-psychotherapy-for-ptsd>.

Foundation are picking up the slack.²⁰⁸ These organizations raise funds for psychedelics research and sponsor clinical trials on substances that are of little interest to universities and traditional pharmaceutical firms due to the associated stigma, relative lack of available patent protection, and potential to compete with existing drug products.²⁰⁹ However, nonprofits like MAPS lack the revenue of established pharmaceutical companies. Instead, they rely on donor contributions to support their work. The high cost of synthesizing psychedelics and running large clinical trials may not pose a significant barrier to pharmaceutical companies, which have large financial reserves. However, it is a significant barrier to nonprofits and smaller startups entering the drug market. Essentially, conducting FDA-sanctioned clinical trials remains out of reach to all but the most well-organized and well-funded groups.

1. *Petition the FDA for Expedited Approval of Psychedelics*

One approach to reducing the time and cost associated with psychedelics trials is to apply for one of the accelerated approval pathways offered by the FDA. The trend of expediting clinical testing and approval emerged within the context of the AIDS epidemic of the 1980s.²¹⁰ The AIDS community demanded quicker access to therapies and pressured the FDA to reform its approval process.²¹¹ Today, there are four pathways for expediting FDA approval that are designed to facilitate the development of drugs that address the unmet needs of people with serious or life-threatening conditions: priority review, accelerated approval, fast track designation, and breakthrough therapy designation. These programs differ based on the standards of review and the type of evidence required to support approval.²¹²

Priority review does not actually decrease the time required to complete clinical trials. Instead, it decreases the period between submitting a New Drug Application (NDA), which occurs after clinical trials have been completed, and receiving FDA approval to market a

208. Jeneen Interlandi, *The Scientists Who Revived Magic Mushroom Research*, NEWSWEEK (July 1, 2008), <http://www.newsweek.com/scientists-who-revived-magic-mushroom-research-92731>.

209. *Id.*; Ferro, *supra* note 37.

210. Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503, 503 (1995).

211. Mary Dunbar, *Shaking Up the Status Quo: How AIDS Activists Have Challenged Drug Development and Approval Procedures*, 46 FOOD & DRUG COSMETIC L. J. 673, 689–90 (1991).

212. Kepplinger, *supra* note 201.

drug. In order to qualify, a drug must be a significant improvement over previous treatments.²¹³ Priority review can reduce the NDA processing time from ten months to six months.²¹⁴

Fast track designation, accelerated approval, and the breakthrough therapy designation could each be used to reduce the duration of clinical trials with psychedelics. The fast track designation was introduced in 1988 and was designed to speed development of new therapies for serious, life-threatening conditions.²¹⁵ It was inspired by the clinical evaluation and approval of zidovudine, an antiretroviral designed to treat AIDS. Zidovudine was tested and approved in only two years with a single Phase 2 trial.²¹⁶ A drug can receive the fast track designation if it treats a serious condition and shows potential to address an unmet medical need. The potential to address an unmet need can be demonstrated by pre-clinical data if a drug is in the early development process.²¹⁷ Fast track designation does not change the legal standard required to approve a drug, and clinical effectiveness and acceptable levels of risk must still be demonstrated. However, this pathway modifies the nature and quantity of evidence required to meet the legal standard.²¹⁸ It has reduced the mean duration of clinical development from 8.9 to 6.2 years.²¹⁹

Accelerated approval was implemented in 1992 to improve access to drugs that treat serious conditions and offer “a meaningful therapeutic benefit over existing treatments.”²²⁰ Unlike the fast track designation, accelerated approval allows the submission of surrogate endpoints to establish drug efficacy if they are “reasonably likely to predict clinical benefit.”²²¹ For example, a drug maker could submit lab measurements, radiologic images, or other data that are thought to reflect clinical benefit but are not direct measurements of clinical im-

213. *Priority Review*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm> (last updated Jan. 4, 2018).

214. SUSAN THAUL, CONG. RESEARCH SERV., RS22814, FDA FAST TRACK AND PRIORITY REVIEW PROGRAMS 3 (2008); *see also* *Priority Review*, *supra* note 213.

215. Aaron S. Kesselheim et al., *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987–2014: Cohort Study*, 351 *BMJ* 1 (2015).

216. *See* Darrow et al., *supra* note 202, at 1253.

217. BUREAU OF HEALTH CARE SAFETY & QUALITY, COMMONWEALTH OF MASS., GUIDANCE FOR PHYSICIANS REGARDING THE MEDICAL USE OF MARIJUANA 9 (2015), <http://www.mass.gov/eohhs/docs/dph/quality/medical-marijuana/physician-guidance-2015-06-09.pdf>.

218. *See* Darrow et al., *supra* note 202, at 1254.

219. *Id.*

220. *See* Elizabeth A. Richey et al., *Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe and Ineffective Drugs*, 27 *J. CLINICAL ONCOLOGY* 4398, 4398 (2009).

221. *See* THAUL, *supra* note 214, at 2.

provement. Ordinarily, using surrogate endpoints can shorten the clinical investigation period allowing drugs to be approved more quickly. However, there are drawbacks to using surrogate endpoints to show efficacy for psychiatric drugs. Improvement in mental illness is measured using tests that ask people to report their subjective levels of anxiety, depression, or other symptoms. Surrogate measures of these subjective states are not easily identified, which could make accelerated approval a difficult path for approving psychedelics. Despite these differences, some surrogate markers have been proposed for mental illness. For example, the inhibition of rapid eye movement sleep has been presented as a potential surrogate for antidepressant activity, and abnormal responses on electroencephalography have been proposed as surrogate markers of schizophrenia.²²² Ultimately, approval could be used to reduce the clinical investigation period of psychedelics if they are used to treat serious conditions (e.g., major depression with suicidal ideation), offer a meaningful benefit over traditional therapies, and can be shown to affect standard or surrogate markers of mental illness.²²³ However, at least so far, no psychiatric drugs have received accelerated approval.²²⁴

The breakthrough therapy designation was introduced in July 2012 with passage of the FDA Safety and Innovation Act.²²⁵ It provides for expedited review of therapies for serious conditions that have an unmet need.²²⁶ Though approval can be expedited, drugs in this pathway must still undergo clinical testing, and the “FDA expects preliminary evidence to come from Phase 1 or 2 clinical trials.”²²⁷ However, similar to the fast track pathway, the breakthrough therapy designation reduces the quantity of clinical evidence required.²²⁸ Drugs in this program have an average approval time of 4.2 years.²²⁹

222. Luc Staner, *Surrogate Outcomes in Neurology, Psychiatry, and Psychopharmacology*, 8 *DIALOGUES CLINICAL NEUROSCIENCE* 345, 347 (2006).

223. Thomas R. Fleming, *Surrogate Endpoints and FDA's Accelerated Approval Process*, 24 *HEALTH AFF.* 67 (2005); see also Thomas R. Fleming & John H. Powers, *Biomarkers and Surrogate Endpoints in Clinical Trials*, 31 *STAT. MED.* 2973 (2012).

224. U.S. FOOD & DRUG ADMIN., CDER DRUG AND BIOLOGIC ACCELERATED AND RESTRICTED APPROVALS AS OF DECEMBER 31, 2017, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM404466.pdf>.

225. Rachel E. Sherman, *Expedited Drug Development—The FDA's New “Breakthrough Therapy” Designation*, 369 *NEW ENG. J. MED.* 1877 (2013).

226. Rachel R. Chizkov et al., *Trends in Breakthrough Therapy Designation*, 14 *DRUG DISCOVERY* 597 (2015).

227. See *FDA's Drug Review Process*, *supra* note 192, at 11.

228. See Darrow et al., *supra* note 202, at 1254.

229. See *id.* at 1253.

In 2013, Johnson & Johnson obtained breakthrough status for an intranasal preparation of its drug esketamine, the molecular mirror image of ketamine, for use in treatment-resistant depression.²³⁰ In 2016, the company obtained the breakthrough status for esketamine in the treatment of depressive disorder with imminent risk for suicide.²³¹ These successes prove that mental illnesses can satisfy the FDA's definition of an "unmet medical need" and pave the way for obtaining breakthrough status for future treatments based on psychedelic compounds.

In 2017, MAPS petitioned the FDA to obtain breakthrough therapy designation for MDMA-assisted psychotherapy in the treatment of PTSD.²³² In a historic decision, the FDA granted the request and approved the design of two Phase 3 clinical trials to be sponsored by MAPS.²³³ In the wake of this development, it seems possible that the FDA could grant breakthrough therapy status to other Schedule I psychedelic compounds for treating anxiety disorders, depression, and substance use disorder.

2. *Collaborate with the FDA to Implement Risk Mitigation Strategies*

The FDA Amendments Act of 2007 enables the FDA to require certain drug sponsors to provide a risk evaluation and mitigation strategy (REMS).²³⁴ A REMS can take many forms such as package inserts, which warn patients of potential risks, or communication plans for disseminating safety information to healthcare providers. In some cases, if a drug is associated with serious side effects that cannot be adequately addressed by these measures, the FDA will implement increased restrictions. It may require additional elements to assure safe

230. Sara Reardon, *Rave Drug Holds Promise for Treating Depression*, 517 NATURE 130, 131 (2015).

231. Press Release, Johnson & Johnson, Esketamine Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for Major Depressive Disorder with Imminent Risk for Suicide (Aug. 16, 2016), <https://www.jnj.com/media-center/press-releases/esketamine-reeives-breakthrough-therapy-designation-from-us-food-and-drug-administration-for-major-depressive-disorder-with-imminent-risk-of-suicide>.

232. Bryce Montgomery, *MAPS Submits Breakthrough Therapy Designation Application to FDA for Phase 3 Trials of MDMA-Assisted Psychotherapy for PTSD*, MULTIDISCIPLINARY ASS'N FOR PSYCHEDELIC STUD. (July 28, 2017), <http://www.maps.org/news/update/6748-newsletter-july-2017>.

233. Kai Kupferschmidt, *All Clear for the Decisive Trial of Ecstasy in PTSD Patients*, SCIENCE (Aug. 26, 2017, 6:30 PM), <http://www.sciencemag.org/news/2017/08/all-clear-decisive-trial-ecstasy-ptsd-patients>.

234. 21 U.S.C. § 355-1(a)(1) (2012).

use (ETASU), which can include monitoring patients while they receive the drug or requiring prescribers to have specific levels of training and experience.²³⁵

During the FDA approval process, drug sponsors can propose the voluntary implementation of REMS and ETASU. Pledging to implement risk mitigation strategies could help psychedelics receive FDA approval. It demonstrates a commitment by drug sponsors to ensure the safe administration of their drugs. Rick Doblin, the founder and executive director of MAPS, believes this collaborative approach is the best way to realize the medical benefits of psychedelics while minimizing their risks.²³⁶ The FDA approval of MDMA-assisted psychotherapy, which is sponsored by MAPS, would be contingent upon implementation of the following ETASU: treatment will only be administered by certified therapists who complete training with MAPS; therapy will only be provided in certified treatment centers; patients will be prohibited from driving for five MDMA half-lives; the lifetime doses of MDMA received by patients will not exceed ten to twelve; a patient registry will be created; and MDMA will be dispensed by a centralized pharmacy.²³⁷

Additional measures could be mutually agreed upon to facilitate FDA approval of psychedelics. For example, drug sponsors could promise to immediately implement Phase 4 trials after receiving approval.²³⁸ These confirmatory trials are important to establish safety in the post-market period; however, they are sometimes delayed until many years after a drug is approved.²³⁹ Phase 4 trials are mandated for drugs that receive accelerated approval, and the FDA can withdraw approval or impose financial penalties if they are not conducted diligently.²⁴⁰ A voluntary commitment to start Phase 4 trials immediately

235. U.S. FOOD & DRUG ADMIN., FDA'S APPLICATION OF STATUTORY FACTORS IN DETERMINING WHEN A REMS IS NECESSARY: GUIDANCE FOR INDUSTRY (DRAFT GUIDANCE) (2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM521504.pdf>.

236. See Doblin, *supra* note 138, at 370.

237. Yale Undergraduate Think Tank, *Dr. Rick Doblin on MDMA-Assisted Psychotherapy*, YouTube (June 9, 2017), <https://www.youtube.com/watch?v=5GhRzPL8fmQ>.

238. See Doblin, *supra* note 138, at 372.

239. Walid F. Gellad & Aaron S. Kesselheim, *Accelerated Approval and Expensive Drugs—A Challenging Combination*, 376 NEW ENG. J. MED. 2001, 2003 (2017) (reporting that confirmatory trials are sometimes delayed by five to ten years and calling for commencement of confirmatory trials within three months of FDA approval).

240. See *id.*

would be mutually beneficial regardless of whether the drug is a candidate for the accelerated pathway.²⁴¹

*B. Petition the DEA to Change the Federal
Scheduling of Psychedelics*

Instead of working within the existing regulatory framework that governs psychedelic drugs, researchers can attempt to reform it. One such path involves rescheduling psychedelics at the federal level.²⁴² There are two avenues for rescheduling a controlled substance: legislative or administrative action.²⁴³ On the legislative side, Congress can initiate a change either by enacting legislation that directly reschedules a substance or by amending relevant sections of the CSA.²⁴⁴ Since 1981, a series of bills have been introduced to reschedule marijuana, and none have been successful.²⁴⁵

Alternatively, a change can be initiated at the administrative level. The administrative rescheduling of drugs is a complex process involving multiple federal agencies. The Attorney General can initiate a change unilaterally by asking HHS to open a scientific and medical review of a controlled substance.²⁴⁶ The Secretary of HHS, or any interested party from outside the government, can also petition for a change in scheduling.²⁴⁷ The Attorney General reviews all petitions and has the discretion to forward them to HHS for evaluation. Regardless of where a request to reschedule originates, if it is approved by the Attorney General, it is forwarded to HHS, and the FDA investi-

241. See Doblin, *supra* note 138, at 372.

242. See generally Nutt, *supra* note 204.

243. John Hudak & Grace Wallack, *How To Reschedule Marijuana, and Why It's Unlikely Anytime Soon*, BROOKINGS, <https://www.brookings.edu/blog/fixgov/2015/02/13/how-to-reschedule-marijuana-and-why-its-unlikely-anytime-soon/> (last visited Aug. 21, 2017).

244. *Id.*

245. *E.g.*, Legitimate Use of Medicinal Marijuana Act (LUMMA), H.R. 4498, 113th Cong. (2014); Ending Federal Marijuana Prohibition Act of 2013, H.R. 499, 113th Cong. (2013); see also Elizabeth Flock, *Congress Is About to Introduce Legislation to Decriminalize Marijuana*, U.S. NEWS (Feb. 5, 2013, 11:57 AM), <https://www.usnews.com/news/blogs/washington-whispers/2013/02/05/congress-is-about-to-introduce-legislation-to-decriminalize-marijuana> (discussing H.R. 499); Tom Jackman, *Va. Rep. Griffith Introduces Federal 'Legitimate Use of Medicinal Marijuana Act'*, WASH. POST (Apr. 30, 2014), https://www.washingtonpost.com/blogs/local/wp/2014/04/30/va-rep-griffith-introduces-federal-legitimate-use-of-medicinal-marijuana-act/?utm_term=.07a9cd396aa3 (discussing H.R. 4498).

246. See Mikos, *supra* note 124, at 197, 272 (2017) (explaining that the Attorney General is empowered by the CSA to reschedule or deschedule drugs; however, when making scheduling decisions, the Attorney General and the DEA must defer to the medical and scientific opinions of HHS).

247. 21 U.S.C. § 811 (2012).

gates whether the petition has merit.²⁴⁸ The Office of the Attorney General conducts its own parallel investigation, usually through the DEA, to determine whether the drug should be reclassified. In reaching a conclusion, the Attorney General considers eight factors laid out in the CSA:

(1) [i]ts actual or relative potential for abuse; (2) [s]cientific evidence of its pharmacological effect, if known; (3) [t]he state of current scientific knowledge regarding the drug or other substance; (4) [i]ts history and current pattern of abuse; (5) [t]he scope, duration, and significance of abuse; (6) [w]hat, if any, risk there is to the public health; (7) [i]ts psychic or physiological dependence liability; (8) [w]hether the substance is an immediate precursor of a substance already controlled under this subchapter.²⁴⁹

The DEA changes its categorization of Schedule I substances relatively infrequently. The DEA has moved a substance from Schedule I to Schedule II only five times in over forty years, and it has entirely removed a Schedule I drug from the list of scheduled substances only twice.²⁵⁰ On May 25, 1984, the drug Sufentanil, a synthetic opioid estimated to be five to ten times stronger than fentanyl, was moved from Schedule I to Schedule II.²⁵¹ On May 13, 1986, Abbvie's THC drug Marinol was moved from Schedule I to Schedule II.²⁵² Thirteen years later, in 1999, it was moved a second time to Schedule III.²⁵³

1. *Establishing a Currently Accepted Medical Use for Psychedelics*

Marinol's most recent rescheduling originated in 1995 when UNIMED Pharmaceuticals, the original producer of the drug, petitioned the DEA to move it from Schedule II to Schedule III.²⁵⁴ There have been several unsuccessful attempts to compel the rescheduling of marijuana in its botanical form. In 1994, the Alliance for Cannabis Therapeutics (ACT) argued in the U.S. Court of Appeals for the Dis-

248. *Id.*

249. *Id.* § 811(c).

250. See *Scheduling Actions: Chronological Order*, in U.S. DRUG ENF'T ADMIN., LISTS OF SCHEDULING ACTIONS, CONTROLLED SUBSTANCES, REGULATED CHEMICALS (2018), <https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf>.

251. *Id.* at 5.

252. Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(-)-D9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule II to Schedule III, 64 Fed. Reg. 35,928, 35,928–30 (July 2, 1999) (to be codified at 21 C.F.R. pts. 1308 & 1312).

253. *Id.*

254. The Petition to Reschedule Marinol, 64 Fed. Reg. 35,928 (July 2, 1999).

trict of Columbia that marijuana should be moved from Schedule I to a less restrictive category because it has medicinal purposes. ACT had previously petitioned the DEA to reschedule botanical marijuana, and the DEA Administrator denied the request.²⁵⁵ ACT contended that the Administrator's denial turned on an incorrect interpretation of the phrase "currently accepted medical use," which originates from the CSA's definition of Schedule I substances.²⁵⁶ In its opinion, the Court adopted a five-part test for "currently accepted medical use." It included the following criteria: (1) the drug's chemistry must be known and reproducible; (2) there must be adequate safety studies; (3) there must be adequate and well-controlled studies proving efficacy; (4) the drug must be accepted by qualified experts; and (5) the scientific evidence must be widely available.²⁵⁷

The court concluded that it would be possible for a Schedule I substance to meet all of these requirements.²⁵⁸ It pointed out that the Administrator relied on the opinions of medical experts in his final order denying ACT's petition. In contrast, ACT relied primarily on anecdotal testimony from patients. The court concluded that anecdotal evidence could not prove a "currently accepted medical use," even when it is provided by patients' respected physicians, and subsequently upheld the Administrator's denial of ACT's petition.²⁵⁹

The *Alliance for Cannabis Therapeutics v. Drug Enforcement Administration* decision highlights the need for persuasive expert testimony and objective scientific evidence to prove currently accepted use. The five-factor test adopted by the court is the barrier that must be overcome if psychedelic drugs are to be rescheduled. The first factor could be an obstacle for advocates of rescheduling the plant-based psychedelics or the botanical forms of marijuana. Because these plants contain thousands of chemicals and exhibit wide compositional variety, it could be difficult to establish that their chemistry is "known and reproducible" under factor one. Satisfying this criterion would be much easier to do for isolated compounds than for the plants that produce them. In other words, attempting to reschedule THC, CBD, or another compound produced by marijuana could be far less challenging than rescheduling the entire plant. Similarly, it could be easier to reschedule one of the compounds found in psychedelic plants, such as

255. *All. for Cannabis Therapeutics v. Drug Enf't Admin.*, 15 F.3d 1131, 1133–34 (D.C. Cir. 1994).

256. *Id.* at 1134.

257. *Id.* at 1135.

258. *Id.*

259. *Id.* at 1137.

psilocybin or ibogaine, rather than a whole mushroom or *Tabernanthe iboga* plant.

A more recent case further defined what constitutes an adequate scientific basis for proving the medical efficacy of a Schedule I controlled substance, and thereby satisfying the third criterion of the five-factor test. Instead of using anecdotal reports like the petitioners in *Alliance for Cannabis Therapeutics*, the petitioners in *Americans for Safe Access v. Drug Enforcement Administration* relied on peer-reviewed scientific literature.²⁶⁰ They asserted that “numerous peer-reviewed scientific studies could demonstrate that marijuana is effective in treating various medical conditions, but the DEA simply ignores them to conclude that marijuana should remain in Schedule I.”²⁶¹ Thus, the petitioners claimed, the DEA’s refusal to reschedule marijuana was arbitrary and capricious. They relied heavily on an Institute of Medicine (IOM) report from 1999, which stated that marijuana could offer relief to AIDS patients and people receiving chemotherapy.²⁶² However, the court accepted the DEA’s interpretation of the IOM report as a call for additional studies on marijuana rather than an endorsement of its medical uses.²⁶³ Furthermore, it held that the studies provided by the petitioners fell short of the “adequate and well-controlled studies proving efficacy” required by the five-part test outlined in *Alliance for Cannabis Therapeutics*.²⁶⁴ Consequently, it decided the case in favor of the DEA.²⁶⁵

The *Alliance for Cannabis Therapeutics* and *Americans for Safe Access* cases suggest that in order to successfully compel rescheduling of a Schedule I substance, it is not sufficient to rely on anecdotal evidence such as case reports and the testimony of patients and their doctors. Nor is it sufficient to present scientific literature that is merely peer-reviewed or that lacks clear evidence for medical use from “adequate and well-controlled studies proving efficacy.” However, the phrase “adequate and well-controlled studies proving efficacy” remains open to interpretation because the explanation offered by the DEA in *Americans for Safe Access* is vague. According to the DEA, “to establish accepted medical use, the effectiveness of a drug must be established in well-controlled, well-designed, well-conducted, and

260. *Ams. for Safe Access v. Drug Enf’t Admin.*, 706 F.3d 438, 440, 442 (D.C. Cir. 2013).

261. *Id.* at 440.

262. *Id.* at 450.

263. *Id.* at 451.

264. *Id.* at 450.

265. *Id.* at 442 (quoting Denial of Petition to Initiate Proceedings to Reschedule Marijuana, 76 Fed. Reg. 40,552, 40,579 (July 8, 2011)).

well-documented scientific studies, including studies performed in a large number of patients.”²⁶⁶ It is unclear what is meant by the terms “well-controlled, well-designed, well-conducted, and well-documented.” For example, must the study have been conducted under the supervision of the FDA? Must the trials have been conducted in the United States, or can well-controlled studies from other countries be determinative? How many people must participate in a trial for it to be considered large?

A Phase 2 trial can include several dozen to several hundred participants, and a Phase 3 trial could involve several thousand.²⁶⁷ Depending on the standard adopted to determine what makes a trial “large,” the range of numbers deemed sufficient could be quite considerable. Must a full-scale Phase 3, double-blind, randomized controlled trial (RCT) be conducted for the study to be considered well-controlled or is a Phase 2 clinical trial adequate? As evidence for the therapeutic use of marijuana and psychedelics grows, these questions will need to be answered.

Thomas Frieden, a former head of the CDC, argues persuasively against blind devotion to RCTs as the sole basis for health decision-making.²⁶⁸ Though RCTs have clear strengths, they also have substantial limitations. For example, they explore the use of a drug in a limited population (i.e., the study population). Consequently, the results are not always generalizable to individuals with characteristics that differ from those of the study population. In addition, RCTs are rarely of sufficient duration to fully assess a drug for unusual but serious side effects that may not manifest until a drug has already been approved. Rare side effects are often detected following FDA approval, during the period of post-marketing surveillance. According to Frieden, the high cost, time constraints, and long planning stages of clinical trials can prevent them from keeping up with the pace of healthcare innovation.²⁶⁹ As a result, new treatments and standards of care can arrive between the inception and completion of a clinical trial.²⁷⁰ Frieden points out that there are several other valid sources of evidence on which to base medical and public health decisions: “Elevating RCTs at the expense of other potentially highly valuable sources of data is

266. *See id.*

267. *See The Drug Development Process: Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm> (last updated Jan. 4, 2018).

268. Thomas Frieden, *Evidence for Health Decision Making—Beyond Randomized, Controlled Trials*, 377 *NEW ENG. J. MED.* 465 (2017).

269. *Id.* at 465.

270. *Id.*

counterproductive. . . . [T]here is no single, best approach to the study of health interventions; clinical and public health decisions are almost always made with imperfect data.”²⁷¹

There are many substances used in medical practice, such as penicillin, epinephrine, and aspirin, that were not subjected to RCTs before gaining widespread use.²⁷² This is not to say that clinical testing and RCTs are unimportant. However, they should not be the sole source of clinically useful information on which doctors base their decisions. Similarly, they should not be the determining factor in concluding whether drugs have currently accepted uses.

2. *Currently Accepted Medical Use Should Be Defined Broadly and Flexibly*

Future petitions to reschedule marijuana or psychedelics will have to meet the bar for currently accepted medical use established in *Americans for Safe Access*. In this case, the court adopted the DEA’s conclusion that marijuana has no accepted medical use because no Phase 2 or 3 trials conducted under the FDA have proven its medical efficacy.²⁷³ This interpretation of accepted medical use is extremely narrow. It does not reflect the evidence on which practicing physicians base their decisions or the flexibility employed by the FDA when evaluating drugs that treat serious illnesses.

Doctors treat the patients sitting in front of them and not the study population from an RCT. According to Dr. Louis Lasagna, who wrote the modern Hippocratic Oath taken by medical students, an individual patient “does not care if a drug is safe and effective for others if it fails so to perform for him.”²⁷⁴ Because all patients are unique, doctors consider what is best for each patient individually. They rely on patient feedback, suggestions from colleagues, and a variety of studies found in the scientific literature including case reports, observational studies, meta-analyses, and RCTs. Therefore, courts and the DEA should consider all of these sources of evidence in determining whether a substance has an accepted medical use. At the very least, because their current test for accepted medical use is heavily inspired by the FDA’s requirements for proving efficacy, the test should be

271. *Id.* at 469–72.

272. See Doblin, *supra* note 138, at 367; see also Louis Lasagna, *Clinical Trials in the Natural Environment*, in *DRUGS BETWEEN RESEARCH AND REGULATIONS* 45, 46 (C. Steichele et al. eds., 1985).

273. *Ams. for Safe Access v. Drug Enf’t Admin.*, 706 F.3d 438, 451 (D.C. Cir. 2013).

274. See Lasagna, *supra* note 272, at 47.

applied with the same flexibility employed by the FDA when a drug is intended to treat serious or life-threatening illnesses.

Courts and the DEA should recognize that, in granting breakthrough therapy designation, the FDA accepts preliminary evidence from Phase 1 and 2 clinical trials to show efficacy. As described above, these phases are smaller and have different requirements than Phase 3 trials. In evaluating future rescheduling petitions, courts and the DEA should consider whether each drug can meet the requirements for breakthrough status. If so, then the bar for demonstrating accepted medical use should reflect the reduced clinical evidence requirements of the FDA. Similarly, if a drug would be capable of meeting the requirements for fast-track or accelerated-approval, then the standard for accepted medical use should be lowered. According to experts on pharmaceutical regulation at Harvard Medical School, “[a]lthough neither the fast-track nor the accelerated-approval pathways changed the legal standard for approval—which is still effectiveness with acceptable risk—they reduced the quantity of evidence needed to meet this standard and altered the nature of that evidence.”²⁷⁵ When drugs show promise for safely treating serious illnesses, the FDA reduces the requirements to show efficacy. Courts and the DEA should do the same when contemplating whether a drug meets the third factor of the *Americans for Safe Access* test for accepted medical use.

3. *Determining Who Decides When a Medical Use is “Currently Accepted”*

When a court considers whether a treatment falls under “currently accepted medical use,” it is important to ask by whom must the treatment be accepted? Should the reference point be practicing physicians, legislators, administrators, or all of the above? There may be no right answer, and it could depend on who you ask. However, the choice could have profound impacts on public health. Consider the case of medical marijuana. Well over half of all U.S. states allow doctors to prescribe marijuana and regulate its cultivation, manufacturing, distribution, and sale.²⁷⁶ Thousands of doctors in these states prescribe marijuana every day, which suggests that it has achieved a non-trivial degree of accepted medical use. These doctors and their patients believe marijuana eases the suffering associated with debilitating condi-

275. See Darrow et al., *supra* note 202, at 1254.

276. *Medical Marijuana*, NORML, <http://norml.org/legal/medical-marijuana-2> (last visited Dec. 26, 2017).

tions.²⁷⁷ Many doctors and officials from these states will likely agree that marijuana has currently accepted medical uses.

Groups of professionals, such as doctors, can be thought of as knowledge communities.²⁷⁸ They share common knowledge and experience, solve similar problems, and have shared mechanisms for establishing safety and validity.²⁷⁹ In general, individuals seek advice from professionals because, unlike the individual, professionals have access to both specialized knowledge and the training and experience to interpret it.²⁸⁰ Specifically, patients seek advice from physicians because doctors serve as information conduits between the patient and the accumulated knowledge of the medical community. In our current information age, patients can find substantial medical information on websites and mobile health apps. However, physicians have years of training that allows them to interpret this information and tailor treatment to the patient.²⁸¹

States influence medical professionals through licensing requirements, standards for medical education, and medical malpractice regulations.²⁸² Problems can arise when state regulation becomes incompatible with the views of the medical community.²⁸³ For example, when the boundaries of medical knowledge are expanded, there is a tipping point at which emergent knowledge, once at the fringe of the community's base, becomes accepted as part of its core knowledge.²⁸⁴ State regulation can inhibit this integration of emergent knowledge with the community's core beliefs,²⁸⁵ and the case of medical marijuana serves as a useful example.²⁸⁶ In recent years, attitudes of the medical community towards marijuana have shifted.²⁸⁷ The drug has changed from a fringe medical therapy accepted by a small number of physicians in California to a widely accepted treatment used in twenty-nine U.S. states, the District of Columbia, and several foreign

277. Christopher Ingraham, *92% of Patients Say Medical Marijuana Works*, WASH. POST (Oct. 1, 2014), https://www.washingtonpost.com/news/wonk/wp/2014/10/01/92-of-patients-say-medical-marijuana-works/?utm_term=.31e6c77f2081.

278. Claudia Haupt, *Unprofessional Advice*, 19 U. PA. J. CONST. L. 671, 679–80 (2017) (defining “knowledge communities”).

279. *See id.* at 680.

280. *See id.*

281. *See id.* at 678.

282. *See id.* at 679.

283. *See id.*

284. *See id.* at 721.

285. *See id.*

286. *See id.* at 721–22.

287. *Id.*

countries such as Canada, Australia, and Germany.²⁸⁸ Yet the U.S. federal government continues to see marijuana as a drug that lies beyond the fringe of what is considered acceptable medical treatment.²⁸⁹ This view shapes the practices of the medical community through federal regulation, which inhibits marijuana from gaining universal acceptance. The tension between medical and federal attitudes toward marijuana has real-world consequences. In states where medical use remains illegal, patients with debilitating and life-threatening illnesses are denied access to drugs which could significantly improve their quality of life. Similarly, when it comes to psychedelics, the federal prohibition prevents millions of Americans with treatment refractory mental illness from trying potentially effective therapies.

Society must ask who is best qualified to determine whether a medical use is currently accepted.²⁹⁰ In other words, who is in the best position to decide when emergent knowledge has moved beyond the tipping point to become something more than a fringe belief or practice?²⁹¹ Perhaps the best way to evaluate current acceptance is to look to the most relevant knowledge community itself, in this case health-care providers, instead of outside actors such as federal agencies. It may be easier to look to the FDA and DEA for quick answers regarding currently accepted use instead of engaging in the more difficult, nuanced work of weighing all the evidence. However, when agencies are asked to make public health decisions, they may base their decision on moral or political ideology rather than accurate interpretations of scientific evidence and the best interest of the public.²⁹²

As an example, consider the President's Commission on Combating Drug Addiction and the Opioid Crisis (the "Commission"). On March 29, 2017, President Trump issued an executive order to create the Commission and nominated then-New Jersey Governor Chris Christie to lead it.²⁹³ The remaining members included three politi-

288. *See id.* at 722–23; *see also* Allison L. Bergstrom, *Medical Use of Marijuana: A Look at Federal & State Responses to California's Compassionate Use Act*, 2 DEPAUL J. HEALTH CARE L. 155, 156 (1997); Meera Senthilingam, *Germany Joins the Global Experiment on Marijuana Legalization*, CNN (Mar. 6, 2017, 9:05 AM), <http://www.cnn.com/2016/12/29/health/global-marijuana-cannabis-laws/index.html>.

289. *See* Haupt, *supra* note 278, at 721.

290. *See id.*

291. *See id.*

292. *See* Mason Marks, *The Opioid Crisis Requires Evidence-Based Solutions, Part I: How the President's Commission on Combating Drug Addiction Misinterpreted Scientific Studies*, HARV. L.: BILL HEALTH (Dec. 18, 2017), blogs.harvard.edu/bill-of-health/2017/12/18/the-opioid-crisis-requires-solutions-backed-by-evidence-and-reason-part-1/.

293. *Id.*

cians, a state attorney general, and a professor of psychobiology; only one has scientific expertise and none have medical training.²⁹⁴ Perhaps as a result of its composition, the Commission misinterpreted numerous scientific studies and disregarded the growing body of evidence supporting the use of psychedelics to treat substance use disorders.²⁹⁵ Moreover, the Commission disregarded thousands of public comments urging it to consider all options for combatting pain and the opioid crisis including marijuana, ibogaine, and kratom (an unscheduled plant that the DEA may soon categorize in Schedule I).²⁹⁶ In this case, the Commission had some specialized scientific knowledge stemming from the experience of its PhD-trained scientist. Yet it apparently lacked the knowledge, experience, or motivation to accurately interpret existing medical literature.

Like the medical community, federal agencies and panels such as the Commission can be thought of as knowledge communities because their members share knowledge, training, and experience.²⁹⁷ For instance, politicians and agency officials possess skills that most medical professionals lack; the former may have experience drafting and enforcing rules and navigating the American political system. Similarly, healthcare providers have training and experience that is unfamiliar to most government officials. Though there is some overlap between the goals, training, and experience of government agencies and the medical community, for example, employees of the FDA may have medical or scientific backgrounds, agencies and medical professionals serve different functions. These groups are also subject to different motives and pressures, which can influence how they interpret data and make decisions.

Administrative agencies such as the DEA and FDA may not be the most qualified group to determine what constitutes currently accepted medical use. Healthcare professionals, the knowledge community that treats illness every day, could be a better choice.

4. *The Shortcomings of Rescheduling*

Controlled substances are regulated by both the CSA, which governs scheduling, and by the Food Drug and Cosmetics Act (FDCA),

294. *Id.*

295. *Id.*

296. Mason Marks, *The Opioid Crisis Requires Evidence-Based Solutions, Part II: How the President's Commission on Combating Drug Addiction Ignored Promising Medical Treatments*, HARV. L.: BILL HEALTH (Dec. 20, 2017), blogs.harvard.edu/billofhealth/2017/12/20/opioid-crisis-requires-evidence-based-solutions-part-2/.

297. See Haupt, *supra* note 278, at 680.

which controls federal approval of medical products.²⁹⁸ Because these laws are distinct and serve different functions, successfully moving psychedelics from Schedule I to Schedule II, which could be accomplished by amending the CSA, will not automatically allow psychedelics to be marketed by pharmaceutical companies and prescribed by physicians. If a drug is moved from Schedule I to Schedule II, it can be marketed and prescribed only after being incorporated into FDA-approved medications as required by the FDCA.²⁹⁹

In addition to being rescheduled, a psychedelic would have to go through the FDA approval process including clinical trials to be marketed and prescribed in the United States.³⁰⁰ Individual states would also have to decide whether to reschedule the drug under state law.³⁰¹ Most states have laws that mirror the scheduling system of the CSA.³⁰² Therefore, physicians will not be permitted to prescribe psychedelics unless they are rescheduled under both state and federal law. Because some states might resist rescheduling, there could be delays between federal rescheduling and the availability of psychedelics in individual states.³⁰³

Though federal rescheduling alone may not allow psychedelics to be prescribed, it could

reduce some of the obstacles to clinical research. For instance, the cost of manufacturing and administering psychedelics for research could be lowered. As discussed previously, the Schedule I status of psychedelics raises economic barriers to production and use because labs that supply them must be licensed by the DEA and researchers must meet costly and burdensome regulatory requirements. Rescheduling would also diminish the stigma associated with psychedelics research, which might stimulate interest at universities and lower the bar for IRB approval. However, federal rescheduling is not the only way in which barriers to psychedelics research could be reduced.

298. 21 U.S.C. § 505 (1938).

299. Kevin A. Sabet, *Much Ado About Nothing: Why Rescheduling Won't Solve Advocates' Medical Marijuana Problem*, 58 WAYNE L. REV. 81, 86 (2013).

300. *Id.* at 91.

301. *See* Doblin, *supra* note 138, at 369.

302. *See id.*

303. *Id.*

C. *Petition the DEA to Reduce Restrictions
on Psychedelics Research*

For many years, the cultivation of marijuana for research purposes has been limited to a University of Mississippi lab run by the National Institute on Drug Abuse (NIDA).³⁰⁴ On August 11, 2016, the DEA announced plans to accept applications from other organizations to grow marijuana for research.³⁰⁵ Theoretically, the DEA could implement a similar reduction of restrictions on the manufacturing and clinical testing of psychedelics while maintaining their Schedule I status. This change would allow research organizations to apply for licenses to cultivate mushrooms containing psilocybin or Amazonian vines that produce ibogaine.

However, since their implementation in 2016, the reduced restrictions on marijuana research have produced no results.³⁰⁶ As of February 8, 2018, twenty-five applications to grow marijuana for research had been received by the DEA. However, none of them had progressed beyond the application stage.³⁰⁷ Eighteen months after the DEA announced expansion of its marijuana cultivation program, NIDA remained the only federally sanctioned producer of marijuana because the Department of Justice had not approved any of the applications received by the DEA.³⁰⁸ The limited amount and variety of marijuana available from NIDA can serve as a bottleneck for the supply of plant material for legitimate research.³⁰⁹ Furthermore, even though the DEA purports to have relaxed restrictions on growing marijuana, if no applications are approved by the Department of Justice,

304. Evan Halper, *DEA Ends Its Monopoly on Marijuana Growing for Medical Research*, L.A. TIMES (Aug. 11, 2016, 2:45 PM), <http://www.latimes.com/politics/la-na-marijuana-dea-20160811-snap-story.html>.

305. *Id.*

306. Eric Killelea, *Why Is It So Hard To Study Pot?*, ROLLING STONE (Feb. 8, 2018), <https://www.rollingstone.com/culture/features/why-is-it-so-hard-to-study-pot-w516486>.

307. *Id.*; see also Brooke Edwards Staggs, *The DEA Said It Would End Its Monopoly on Research Marijuana. Was It Just Smoke and Mirrors?*, CANNABIST (July 5, 2017, 2:27 PM), <http://www.thecannabist.co/2017/07/05/dea-marijuana-monopoly-research-mississippi-nida/83118/>; Alicia Wallace, *DEA Plans to Reduce Quota of Government-Grown Marijuana for Research in 2018*, CANNABIST (Aug. 8, 2017, 7:37 AM), <http://www.thecannabist.co/2017/08/08/dea-marijuana-research-quota-2018-nida/85321/>.

308. See Matt Zaposky & Devlin Barrett, *Justice Department at Odds with DEA on Marijuana Research, MS-13*, WASH. POST (Aug. 15, 2017), https://www.washingtonpost.com/world/national-security/justice-department-at-odds-with-dea-on-marijuana-research-ms-13/2017/08/15/ffa12cd4-7eb9-11e7-a669-b400c5c7e1cc_story.html?utm_term=.b8e28da2447c.

309. See Killelea *supra* note 306 (describing how the limited availability of marijuana from NIDA has reduced the quantity and quality of marijuana research).

then the reduction in restrictions on marijuana research is merely theoretical. Therefore, even if the DEA decreased restrictions on research with psychedelics, it is unclear whether barriers to research would actually be reduced. The approval of research applications could be delayed indefinitely, as they are now with respect to marijuana research, and without a concurrent change in scheduling, the financial, regulatory, and social barriers to psychedelics research would persist. For instance, the recordkeeping, security, and monitoring requirements keep the cost of doing psychedelics research very high. Even if new organizations receive DEA approval to cultivate marijuana, the cost of complying with federal requirements limits the number of researchers that can enter the field. Moreover, even though universities can technically apply to grow their own supplies of marijuana for research, the stigma associated with its Schedule I status may prevent them from launching their own research programs. Similarly, even if federal restrictions on psychedelics research are relaxed, if psychedelics remain listed on Schedule I, university-based researchers could have trouble funding their research and obtaining the blessings of their IRBs.

On October 26, 2017, President Trump announced he would direct HHS to declare the opioid epidemic a public health emergency.³¹⁰ The following month, his Commission issued its final recommendations.³¹¹ The Commission acknowledged the limitations of current treatments for opioid dependence including methadone, buprenorphine, and naltrexone.³¹² It called on Congress to provide additional resources for the development of new medication-assisted treatments (MAT) for opioid dependence.³¹³ Few specific recommendations were made, and several options including psychedelics were conspicuously absent from consideration.

Interestingly, one member of the President's Commission, Harvard psychobiologist Bertha Madras, studied the pharmacology of psychedelics in the 1960s.³¹⁴ In a 2016 interview with the Washington Post, Dr. Madras expressed concerns about using psilocybin in a therapeutic context: "We are already seeing a national epidemic of opioid

310. Julie Hirschfield Davis, *Trump Declares Opioid Crisis a 'Health Emergency' but Requests No Funds* (Oct. 26, 2017), <https://www.nytimes.com/2017/10/26/us/politics/trump-opioid-crisis.html>.

311. THE PRESIDENT'S COMMISSION ON COMBATING DRUG ADDICTION AND THE OPIOID CRISIS, FINAL RECOMMENDATIONS (2017).

312. *Id.* at 87.

313. *Id.*

314. *Bertha K. Madras*, MCLEAN HOSPITAL, <http://www.mcleanhospital.org/biography/bertha-madras> (last visited Nov. 8, 2017).

overdose deaths, [a]nd if we medicalize another group of drugs, one has to weigh the cost-benefit equation to society. Will people think this is a safe drug . . . but will it, in fact, be a plague on society?"³¹⁵ Yet the scientific literature offers little support for these concerns. As discussed above, multiple studies indicate that psilocybin and other psychedelics can be administered safely under professional supervision.³¹⁶

In light of the rising opioid-related death toll, the Commission's failure to consider psychedelics as potential treatments for substance use disorders is a missed opportunity with potentially serious consequences for public health. The Commission could have urged the President to compel the DEA to ease restrictions on psychedelics research and reduce limits on their synthesis paving the way for much needed drug innovation. Current MAT for opioid dependence, such as methadone, carry significant risks including overdose and death.³¹⁷ Psychedelics could be safe and effective adjuncts or alternatives to existing MAT.³¹⁸ However, unless restrictions on research are reduced, the potential of psychedelic medicines for treating substance use disorders may not be fully realized or understood.

D. Implement State Regulation Governing Psychedelics

Another option for facilitating psychedelics research and development requires state involvement. State-governed systems could take many forms and could work either within the existing federal regulatory framework or in opposition to it. However, because psychedelics are Schedule I drugs, state-run programs could be challenged in court and, if found to conflict with the CSA, they could be preempted by federal law.

The U.S. Constitution declares federal law the supreme law of the land.³¹⁹ Accordingly, when states and the federal government regulate the same activity, federal laws will override state legislation to

315. Laurie McGinley, *Key Ingredient in "Magic Mushrooms" Eased Cancer Patients' Fear of Death*, WASH. POST (Dec. 1, 2016), https://www.washingtonpost.com/national/health-science/hallucinogenic-drugs-relieved-cancer-patients-of-existential-distress/2016/11/30/fed60968-b1ab-11e6-8616-52b15787add0_story.html?utm_term=.4bce0b862030.

316. *E.g.*, Gasser et al., *supra* note 50; *see also* Griffiths et al., *supra* note 53; Grob et al., *supra* note 52; Moreno et al., *supra* note 53.

317. NAT'L INST. ON DRUG ABUSE, *supra* note 10 (reporting that in 2016 there were 3314 deaths associated with the use of methadone).

318. Marks, *supra* note 296.

319. U.S. CONST. art. VI, § 2.

the extent that they overlap.³²⁰ In addition, if Congress chooses to preempt state laws, it need only express the intent to do so.³²¹ In other words, if a bill passed by Congress explicitly states its intention to preempt state law, then no additional analysis is required; state law will be preempted. However, when the intention to preempt state law is not clearly stated, courts can infer it if certain standards are met.³²² The Supreme Court has established criteria for determining congressional intent to preempt state law.³²³ First, in so-called field preemption, if Congress creates a pervasive regulatory framework that leaves no room for state regulation, then courts will conclude that Congress intended to preempt state laws. Second, if state laws are found to conflict with federal regulation, then courts are likely to find state laws preempted.³²⁴

In Section 903 of the CSA, Congress explicitly states its lack of intent to “occupy the field” in which the CSA operates.³²⁵ Therefore, if states pass laws regulating psychedelics, they are unlikely to be subject to field preemption. However, courts could still find that state laws governing psychedelics are invalid if they conflict with provisions of the CSA. There are two ways in which tension can arise between state and federal law. First, if a state law makes it impossible to simultaneously comply with state and federal regulations, then the state law is subject to direct preemption. For example, imagine that a state law requires pharmacists to supply psilocybin to all patients holding a doctor’s recommendation. It would be physically impossible for pharmacists to comply with the law without violating the federal ban on psilocybin. Supplying it to patients, even if legal under state law, would conflict with the CSA, making it impossible to comply with both laws at once. Alternatively, a state law can be found to conflict with federal law through obstacle preemption. If a state law serves as a barrier to the complete achievement of Congress’s purposes and objectives, as embodied in a federal statute, then the state law can be preempted. The requirements for obstacle preemption are broader than those of direct preemption. One can imagine many scena-

320. Stephen A. Gardbaum, *The Nature of Preemption*, 79 CORNELL L. REV. 767, 770 (1994).

321. See Mikos, *Preemption Under the Controlled Substances Act*, *supra* note 89, at 106.

322. *See id.*

323. *Id.*

324. *Id.*

325. See Mikos, *supra* note 89 at 108 (“Section 903 [of the CSA] is clear in at least one important respect: it rejects any inference that Congress wanted to preempt the field of drug regulation.”). However, Professor Mikos notes that there is a lack of known legislative history that could support this interpretation of Section 903. *Id.*

rios in which a state law governing psychedelics could be found to frustrate Congress' objectives. For example, suppose a state bill prohibits professional licensing boards from sanctioning physicians who recommend MDMA to patients. To comply with the law, licensing boards would not have to violate federal law directly. They need only refrain from instituting sanctions, which amounts to doing nothing; in this case, taking no action would not directly violate the CSA. However, it could be argued that refusing to act interferes with the CSA's goal of preventing substance use disorders because it protects doctors who endorse the use of a Schedule I drug. Under this analysis, courts could find the state law invalid even though it requires licensing officials to take no action.

Currently, at least twenty-nine U.S. states and the District of Columbia regulate marijuana for medical use.³²⁶ Most states have elaborate systems governing the cultivation, manufacturing, testing, distribution, and sale of medical marijuana. These regulatory frameworks may conflict with the CSA. However, direct regulation is not the only option for facilitating psychedelics research and development. This section discusses several alternatives that fall along a continuum that ranges from hands-off approaches like decriminalization to comprehensive laws establishing state regulation of psychedelics. The extent to which they could be successful may depend, at least in part, on the degree to which they are likely to conflict with the CSA. Approaches that promote cooperation between state and federal government are least likely to frustrate congressional objectives and most likely to facilitate the development of psychedelic medicines.

1. Decriminalize or "Legalize" the Medical Use of Psychedelics

A middle-of-the-road option for promoting psychedelics research and development involves state decriminalization. This approach would reduce or eliminate criminal penalties for medical use and would help combat the stigma associated with psychedelics, which could stimulate interest in research. If penalties are completely eliminated, then decriminalization would effectively make psychedelics legal under state law. Additionally, state legalization of psychedelics would not necessarily be in conflict with federal objectives.

Professor Robert Mikos distinguishes between state legalization of marijuana and state regulation of marijuana.³²⁷ According to Pro-

326. *West Virginia Becomes 30th State to Legalize Medical Cannabis*, MARIJUANA BUS. DAILY (Apr. 19, 2017), <https://mjbizdaily.com/west-virginia-governor-signs-bill-legalizing-medical-cannabis/>.

327. MIKOS, *supra* note 124, at 112.

fessor Mikos, “[w]hen a state legalizes marijuana, it simply chooses to leave marijuana-related activities to the vagaries of private market forces and federal regulation.”³²⁸ In contrast, regulation involves state participation in marijuana related activities³²⁹ such as business licensing, taxation, and patient registration. Under the anti-commandeering rule, established by the Supreme Court in 1992, Congress cannot compel a state to enforce federal drug laws.³³⁰ In other words, the federal government cannot oblige state law enforcement to uphold the CSA.³³¹ As a result, the mere legalization of marijuana or psychedelic drugs by a state should not be preempted by federal law. Mere legalization amounts to taking no legislative action, and states cannot be forced to implement anti-drug regulation.³³² This example is distinguishable from the state licensing board scenario mentioned previously because in that hypothetical case, the state passed a law that amounted to indirect participation in drug-related activities, whereas, in the case of legalization, no laws need be passed.

Despite the anti-commandeering rule, some courts and officials have failed to recognize the difference between legalization and regulation.³³³ Nevertheless, if a state wishes to legalize psychedelics for medical use, it could eliminate state penalties for manufacturing, possessing, distributing, or consuming them. By taking a hands-off approach, the state would not be regulating psychedelics directly. Instead, it would merely be leaving the investigation, prosecution, and sentencing for psychedelics offenses to the Department of Justice. That is, individuals who possess psychedelics would not be detained by state law enforcement or prosecuted in state courts; however, they could be arrested by federal agents and tried in federal court.

On August 16, 2017, Oregon Governor Kate Brown took a half-step in the direction of legalization when she signed a bill that reduced state criminal penalties for possession of Schedule I drugs including

328. *Id.*

329. *Id.*

330. *Id.* at 113 (“This means that Congress could not force the states to enact a marijuana ban. Neither, logically could it force the states to keep bans already enacted but no longer wanted.”); see also Andrew B. Coan, *Commandeering, Coercion, and the Deep Structure of American Federalism*, 95 BOS. U. L. REV. 1, 3 (2015).

331. See Coan, *supra* note 330, at 29.

332. Robert A. Mikos, *On the Limits of Supremacy: Medical Marijuana and the States’ Overlooked Power to Legalize Federal Crime*, 62 VAND. L. REV. 1422, 1453 (2009); see also Mikos, *Preemption Under the Controlled Substances Act*, *supra* note 89, at 113.

333. Mikos, *Preemption Under the Controlled Substances Act*, *supra* note 89, at 113.

MDMA, psilocybin, and LSD.³³⁴ Though the measure falls short of full legalization, it downgrades first-time possession of small amounts of psychedelics from a felony to a misdemeanor.³³⁵ Nevertheless, the law has received criticism for not going far enough to reduce penalties for drug possession.³³⁶ Countries such as Portugal and Norway have made efforts to decriminalize all drugs, and some U.S. states have downgraded marijuana possession offenses from misdemeanors to civil penalties carrying no possibility of jail time.³³⁷ Nevertheless, Oregon is the first state to reduce criminal penalties for possessing psychedelics, and its new law could diminish the stigma associated with these drugs.

States could also pass laws prohibiting discrimination and retaliation against professionals, employees, or patients who research, recommend, administer, or consume psychedelics for medical purposes. These protections could reduce stigma and stimulate research. In fact, some states have written similar safeguards into their medical marijuana laws.³³⁸ In the past, such protections could have been at high risk for preemption challenges, as evidenced by several state courts that have invalidated them in part due to concerns over federal preemption.³³⁹ However, there seems to be a slow trend indicating a shift

334. H.B. 2355, 2017 Leg. § 9, 79th Sess. (Or. 2017). Under previous Oregon drug laws, possession of MDMA was a Class B felony carrying a penalty of up to ten years in prison. Under the new law, if a person possesses less than one gram of MDMA, or fewer than five pills, then the offense is a Class A misdemeanor with a penalty of up to one year in prison. Similar changes were implemented for psilocybin and LSD. H.B. 2355; see also Nick Wing, *Drug Possession Is No Longer a Felony Offense in Oregon*, HUFFINGTON POST (Aug. 18, 2017, 10:31 AM), http://www.huffingtonpost.com/entry/oregon-defelonizing-drug-possession_us_5963b4a4e4b03f144e2c85d5.

335. Wing, *supra* note 334.

336. Mike Adams, *Oregon Is Not Decriminalizing All Drugs, But It Should*, HIGH TIMES (July 11, 2017), <http://hightimes.com/news/oregon-is-not-decriminalizing-all-drugs-but-it-should/> (explaining that complete decriminalization of drugs in Portugal has had a positive effect on the country, evidenced by increased access to treatment programs and reduced overdose rates).

337. See *id.*; Rebecca Flood, *Norway Becomes First Scandinavian Country to Decriminalise Drugs in Historic Vote*, INDEP. (Dec. 15, 2017, 9:43 AM), <http://www.independent.co.uk/news/health/norway-parliament-drugs-decriminalise-recreational-cocaine-heroin-marijuana-a8111761.html>; *States That Have Decriminalized*, NORML, <http://norml.org/aboutmarijuana/item/states-that-have-decriminalized> (last visited Aug. 22, 2017) (listing twenty-two states that reduced or eliminated criminal penalties for marijuana possession).

338. MASS. GEN. LAWS ch. 369, §§ 4–5 (2012) (protecting marijuana patients and their personal caregivers from prosecution, penalization, and loss of rights or privileges; and shielding dispensary agents from prosecution).

339. *E.g.*, Washburn v. Columbia Forest Prods., Inc., 134 P.3d 161, 166 (Or. 2006) (Kistler, J., concurring) (arguing that federal law “would preempt plaintiff’s claim that his employer must accommodate his medical use of marijuana”); Emerald Steel

away from this mentality. For example, Massachusetts recently upheld laws protecting employees from being fired for using medical marijuana.³⁴⁰ Furthermore, a recent decision in the District of Connecticut could make federal preemption of state protections more challenging. In *Noffsinger v. SSC Niantic Operating Company, LLC*, the district court denied the defendant's motion to dismiss on the ground that Connecticut marijuana laws are preempted by the CSA.³⁴¹ In the ruling, Judge Jeffrey Meyer discussed obstacle preemption and what constitutes a "sufficient obstacle" to invoke it. Citing an earlier case, he held that "the conflict between state law and federal policy must be a sharp one."³⁴² He concluded that the tension between the CSA and Connecticut's law protecting marijuana patients from employment discrimination does not "rise to the level of the 'sharp' conflict required to establish obstacle preemption under the case law."³⁴³ *Noffsinger* could be the first of many decisions to defend a state's ability to protect residents who use or research Schedule I drugs in accordance with state laws. However, its analysis of obstacle preemption is somewhat cursory and foregoes discussion of counterarguments such as why Congress might wish to preempt state laws that protect employees.³⁴⁴ If Congress's intent to preempt such laws could be established, then state laws protecting employees who use or administer marijuana and other Schedule I drugs could be preempted.

A lack of clear guidelines regarding discrimination and retaliation for the use of psychedelics could have far-reaching consequences for professionals, employees, and patients. For example, without state protections in place, attorneys may be unwilling to represent clients engaged in psychedelics research out of fear of being sanctioned. In the early days of the medical marijuana industry, attorneys were hesitant to represent marijuana-related clients out of concern for being dis-

Fabricators, Inc. v. Bureau of Labor & Indus., 230 P.3d 518, 523–28 (2010) (holding that the federal Controlled Substances Act preempted an Oregon state law authorizing medical marijuana use).

340. *Barbuto v. Advantage Sales & Mktg., LLC*, 78 N.E.3d 37 (Mass. 2017).

341. *Noffsinger v. SSC Niantic Operating Co.*, 237 F. Supp. 3d 326, 336 (D. Conn. 2017).

342. *Id.* at 333 (quoting *Marsh v. Rosenbloom*, 499 F.3d 165, 178 (2d Cir. 2007)).

343. *Id.* at 336.

344. Robert Mikos, *Federal District Court Finds Connecticut Law Barring Employment Discrimination Against Medical Marijuana Users Is NOT Preempted*, VAND. UNIV. L. SCH.: MARIJUANA L., POL'Y & AUTHORITY (Aug. 15, 2017), <https://my.vanderbilt.edu/marijuanalaw/2017/08/14/7/>.

barred or subjected to federal criminal liability.³⁴⁵ Similarly, patients may hesitate to enroll in clinical trials due to social stigma or concerns about employment or insurance discrimination. Researchers may be reluctant to propose clinical research out of fear of losing employment or tarnishing their reputations. State protections like those instituted for marijuana patients could shield attorneys, physicians, patients, and scientists from such discrimination.

Decriminalization, legalization, and state protections may reduce the stigma associated with psychedelics, which could stimulate interest in research. However, they may do little to directly affect the availability of psychedelics to people with mental illness. Without state infrastructure to provide a safe and steady supply of psychedelics for research and clinical use, people may turn to illicit channels to obtain these drugs.

2. *Regulate the Medical Use of Psychedelics*

A more radical option for facilitating psychedelics research and clinical use is for states to take a hands-on approach and regulate these activities directly. As discussed above, state regulation of psychedelics is unlikely to be subject to field preemption because, when it comes to drug regulation, Congress expressed its lack of intent to preempt the field in Section 903 of the CSA.³⁴⁶ However, state regulation of psychedelics would still conflict with the CSA because it involves active state participation in psychedelics-related activities. As a result, courts could invoke direct or obstacle preemption to invalidate it.

Despite this risk, the regulation of psychedelics remains an option available to states. The medical marijuana movement, which has swept across much of the United States, began in California with the passage of the Compassionate Use Act of 1996.³⁴⁷ The Act allowed California physicians to recommend marijuana for medical uses they deemed appropriate. This move provoked significant pushback from the federal government. The U.S. Attorney General threatened to retaliate against doctors who recommend marijuana by revoking their DEA registration and access to Medicare and Medicaid programs.³⁴⁸

345. *Conflicting State and Federal Marijuana Laws Create Ethical Complications for Lawyers*, AM. BAR ASS'N (Apr. 2014), <https://www.americanbar.org/newsletter/publications/youraba/201404article06.html>.

346. See Mikos, *Preemption Under the Controlled Substances Act*, *supra* note 89, at 11.

347. Patrick Stack & Claire Suddath, *Medical Marijuana*, TIME (Oct. 21, 2009), <http://content.time.com/time/health/article/0,8599,1931247,00.html>.

348. George J. Annas, *Reefer Madness—The Federal Response to California's Medical-Marijuana Law*, 337 NEW ENG. J. MED. 435, 436–37 (1997).

In response, a group of physicians successfully sued the government and established their First Amendment right to recommend marijuana to patients.³⁴⁹ State legalization of psychedelics could have a similar origin and follow a similar trajectory.

If states decide to actively regulate psychedelics, physicians could face retaliation from the current administration. Though it has tolerated medical marijuana laws, the federal government could view the implementation of state psychedelics programs as a step beyond the pale. Regardless, one advocacy group in Oregon is contemplating a state ballot initiative in 2020 to regulate the medical use of psilocybin.³⁵⁰ The proposed bill would differ from marijuana legislation in several important ways.³⁵¹ Unlike some marijuana laws, it would not allow personal cultivation, meaning that patients seeking psilocybin treatment would not be able to grow their own supply. Nor would patients be able to buy it from retail dispensaries. Instead, patients would be required to visit treatment centers where they could receive psilocybin under close professional supervision.³⁵² The restriction of treatment to licensed centers is one example in which psychedelics regulation could be tailored to address the safety concerns raised in Section II.C of this article.

On August 25, 2017, a more radical psilocybin initiative was filed with the office of California's Attorney General.³⁵³ The initiative proposes to decriminalize psilocybin use for all California adults age twenty-one and older.³⁵⁴ More specifically, the possession, sale, and cultivation of psilocybin would no longer be prohibited by the state's Health and Safety Codes.³⁵⁵ Unlike the proposed Oregon bill, California's initiative would allow people to grow their own psilocybin containing mushrooms and use them for any purpose without supervision.³⁵⁶ It remains to be seen whether the initiative's supporters

349. *See* Conant v. McCaffrey, 172 F.R.D. 681, 685 (N.D. Cal. 2017).

350. Ben Wofford, *Why Psychedelics Might Be Legalized Sooner Than You Think*, ROLLING STONE (Nov. 8, 2016), <http://www.rollingstone.com/culture/news/why-psychedelics-might-be-legalized-sooner-than-you-think-w449133>.

351. Aaron Kase, *Shrooms Could Be Legalized Sooner Than You Think*, VICE (July 11, 2017, 5:32 PM), https://www.vice.com/en_us/article/mba3m3/shrooms-could-be-legalized-sooner-than-you-think.

352. *Id.*

353. Letter from Kevin P. Saunders to Initiative Coordinator, Office of the Atty. Gen. of Cal. 1 (Aug. 22, 2017), https://oag.ca.gov/system/files/initiatives/pdfs/17-0024%20%28Legalize%20Psilocybin%29_0.pdf.

354. *Id.*

355. *Id.*

356. *Id.*

can collect over 365,000 valid signatures to place it on the ballot.³⁵⁷ Frankly, a bill allowing unrestricted access to psilocybin could be a tough sell to voters. The Oregon model in which psilocybin is administered only in licensed treatment centers may be more palatable to the average voter.

As discussed above, ketamine treatment for mental illness is usually administered in single doses in a doctor's office. This practice reduces the risk of adverse reactions, diversion of drugs from legitimate channels, and development of substance use disorders. Requiring other psychedelics such as psilocybin to be dispensed only in state-licensed facilities would also minimize these risks. Furthermore, additional safeguards could be implemented, such as state-mandated educational standards for psychedelics prescribers.³⁵⁸ Physicians that dispense ketamine for mental illness are usually psychiatrists who are trained to treat mental illness and to de-escalate acute mental health crises, or anesthesiologists who are experienced with altered states of consciousness, physiologic monitoring, and resuscitation. These specialists have unique skills that make them better qualified than the other physicians to deal with the potential risks of ketamine. State psychedelics laws could require treatment providers to be board-certified psychiatrists, anesthesiologists, or other physicians who receive adequate training in relevant treatment and safety procedures.

To minimize the risk of diversion, a state registry could be created to track the use of psychedelics by individual patients.³⁵⁹ Substance use disorders could further be addressed by limiting advertising for psychedelic medicines and restricting the use of psychedelics to certain patient populations.³⁶⁰ However, a state registry would raise privacy concerns that could discourage doctors from prescribing psychedelic treatments.³⁶¹ A registry could also inhibit patients from seeking treatment and encourage them to obtain psychedelics on the black market instead. Restricting therapy to certain patient populations may also be problematic because it can arbitrarily deny treatment to

357. Reid Wilson, *California Initiative Would Legalize Psychedelic Mushrooms*, HILL (Aug. 30, 2017, 4:10 PM), <http://thehill.com/homenews/state-watch/348607-california-initiative-would-legalize-psychedelic-mushrooms>.

358. *See* Doblin, *supra* note 138, at 369 (describing the skills required of psychedelics-assisted psychotherapy providers).

359. *See id.* at 379 (describing the potential benefits of a patient registry for psychedelic therapy sessions).

360. *See id.* at 370–71 (explaining the potential link between advertising in support of approving the medical use of psychedelics and their nonmedical use of the drugs).

361. *Id.* (explaining how a state registry would likely inhibit some medically-appropriate prescriptions for psychedelic therapies).

people who could benefit from these drugs. Massachusetts' guidance is a good example of how legislation can be structured with enough flexibility and inclusiveness to ensure that all patients who need the treatment can access it. Physicians in Massachusetts can prescribe marijuana for any "debilitating medical condition."³⁶² The statute provides examples of debilitating conditions while leaving the term open to interpretation by physicians. Thus, many medical conditions can qualify. Still, other states such as Connecticut and Florida take a more restrictive approach.³⁶³ They limit medical marijuana to patients with specific conditions, and physicians have little discretion to determine whether a condition qualifies for treatment.³⁶⁴

Regardless of the form the regulation takes, state psychedelics laws will be controversial. They could also be counterproductive. On one hand, state legalization creates a path for additional research on psychedelics and treatment of a state's mentally ill population. On the other hand, the potential federal backlash could undermine gains made by MAPS and other non-profits to turn psychedelics into FDA-approved medicines. As discussed previously, MAPS is working within the existing federal regulatory framework to develop FDA-approved treatments that utilize psychedelics. If states legalize psychedelics for medical or recreational use, the federal government could respond by tightening restrictions on psychedelics research, which would frustrate the efforts of MAPS and similar situated nonprofits.

3. *Sponsor Clinical Research on Psychedelics*

The proposed Oregon ballot initiative to regulate psilocybin would not be the first time states have considered making psychedelics available to their residents. New York and Vermont have contemplated using ibogaine to combat substance use disorders involving opioids and other drugs.³⁶⁵ However, unlike the proposed Oregon law, these bills would have created state-sponsored clinical trials conducted in collaboration with the FDA. In other words, instead of regulating ibogaine in a manner that could conflict with the CSA, the

362. MASS. BUREAU OF HEALTH CARE SAFETY & QUALITY, GUIDANCE FOR PHYSICIANS REGARDING THE MEDICAL USE OF MARIJUANA 1 (2015).

363. Lucia Graves, *Medical Marijuana States Add Number 17, Connecticut*, HUFFPOST (Jun. 1, 2012), https://www.huffingtonpost.com/2012/06/01/medical-marijuana-connecticut-17th-state_n_1563206.html; Maureen Meehan, *Florida's MMJ Bill More Restrictive Than Before Legalization*, HIGH TIMES (Mar. 9, 2017), <https://high-times.com/news/floridas-mmj-bill-more-restrictive-than-before-legalization/>.

364. *Id.*

365. *See* H. 741, 2016 Leg., Reg. Sess. (Vt. 2016); Assemb. 8356, 2015–16 Assemb., Reg. Sess. (N.Y. 2015).

proposed laws would allocate or raise funds to study ibogaine therapy while simultaneously addressing the opioid crises in these states and collecting data to propel ibogaine through the FDA approval process. This approach to research on Schedule I drugs has been done before.

In 1999, the California legislature introduced a bill to create a state-governed marijuana research program.³⁶⁶ The Marijuana Research Act of 1999 commissioned research on the safety and efficacy of medical marijuana,³⁶⁷ appropriating \$9 million to fund the program.³⁶⁸ According to the DEA, the California Marijuana Research Program (CMRP) is likely responsible for the largest spike in U.S. marijuana research.³⁶⁹ In the five years following its introduction, the “DEA received applications for registration in connection with at least 17 State-sponsored pre-clinical or clinical studies of marijuana (all of which DEA granted).”³⁷⁰ The CMRP can serve as a model for similar state efforts to promote psychedelics research.

If a similar state-sponsored program was implemented for psychedelics, it could accelerate the pace of clinical research. As discussed previously, cost is a significant barrier to research with Schedule I compounds. Setting aside state funding would help overcome the financial burdens that are now shouldered by nonprofit organizations. Additional benefits of a collaborative approach between state and federal government include avoiding the risk of federal preemption of state laws, making psychedelic drugs available to some state residents prior to FDA approval, and decreasing the stigma associated with psychedelics research and clinical use.

Many states have strong interests in funding solutions to the opioid crisis. In 2014, Massachusetts Governor Deval Patrick declared a state public health emergency to address the opioid crisis. Governor Patrick allocated \$20 million to bolster the state’s substance use disorder treatment programs.³⁷¹ Similar emergency declarations have been made in five other states.³⁷² To help combat the opioid crisis, a por-

366. S.B. 847, 1999 Leg., Reg. Sess. (Ca. 1999).

367. *Id.*

368. Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States, 81 Fed. Reg. 53,846, 53,846 n.2 (Aug. 12, 2016) (to be codified at 21 C.F.R. pt. 1301).

369. *Id.*

370. *Id.*

371. Rebecca Haffajee et al., *What Is A Public Health Emergency?*, 371 NEW ENG. J. MED. 986, 986 (2014).

372. Allen, *supra* note 12 (reporting that Massachusetts, Virginia, Maryland, Florida, Arizona, and Alaska have declared state opioid crises).

tion of these emergency funds could be allocated to establishing state-sponsored psychedelics trials.

All the same, state-sponsored research does have some drawbacks. If done in collaboration with the FDA, it could suffer from the same limitations as traditional trials involving Schedule I drugs. For example, the acceptance of study protocols could be delayed and federal limits on the production of Schedule I drugs could restrict the number of study participants.

CONCLUSION

This article has introduced several approaches to increasing research and development on psychedelic medicines. As stated, there are many social and legal obstacles that must be overcome. Yet, the need for new mental health treatments has never been greater, and these drugs represent an opportunity to provide relief from several debilitating conditions. Admittedly, psychedelics are not a perfect solution to these problems. There are risks to taking psychedelics and additional research is needed to refine treatment protocols. Yet there are dangers linked to current treatments for mental illness, and doing nothing to create new therapies is associated with the greatest risk of all; hundreds of people will continue to die every day from suicide and drug overdose. Therefore, it is incumbent on physicians, scientists, and regulators to reduce social and legal obstacles to unlocking the therapeutic potential of psychedelics.

Millions of Americans suffer from debilitating mood, anxiety, and substance use disorders. These conditions affect social and occupational functioning and cost the U.S. economy billions of dollars each year. Meanwhile, deaths from suicide and substance use are rising. Traditional therapies such as SSRIs, psychosurgery, and deep brain stimulation have limited effectiveness, and new approaches are urgently needed. Psychedelic medicines show promise for filling this void, and the ongoing mental health and opioid crises demand further exploration of these drugs. However, their Schedule I status creates barriers to legitimate research and development. Key obstacles include social stigma, the financial burden of synthesizing and dispensing psychedelics, and strict federal regulation stemming from the War on Drugs.

There are several approaches to surmounting these hurdles. Collaborating with the FDA to expedite clinical trials is the most conservative approach to developing psychedelic drugs. Yet it suffers from several drawbacks including potential delays and high cost. More radical solutions include state legalization and regulation. The

former may not directly increase access for patients, and the latter runs the risk of being preempted by the federal Controlled Substances Act.

A more moderate approach involves petitioning the DEA to remove psychedelics from Schedule I or reduce federal restrictions on psychedelics research. However, this seems unlikely given that efforts to reschedule or reduce restrictions on studying marijuana have failed because petitioners could not meet the criteria for currently accepted medical use elaborated in *Alliance for Cannabis Therapeutics*. Similar efforts on behalf of psychedelics may have limited success unless courts broaden these criteria. This article argues that the current standard is too narrow and proposes a broader, more flexible approach, which more accurately reflects the way the FDA approves drugs and how doctors integrate emergent knowledge into clinical practice.

Approaches that involve cooperation between state and federal government could be most likely to facilitate the development of psychedelic medicines. Specifically, a hybrid program combining elements of state regulation and FDA-sanctioned clinical trials would address the current mental health crisis and avoid problems of federal preemption. States can allocate funds to make psychedelics available to residents while developing them into FDA approved drugs.

Regardless of the path chosen, overcoming obstacles to developing psychedelic medicines may offer new hope for millions of people who are non-responsive to traditional therapies.